

The Journal of
**Supportive
ONCOLOGY**

Quality of Life • Symptoms/Side Effects • Palliative Care

Editor-in-Chief

Michael J. Fisch, MD, MPH, FACP

Associate Editors

David Cella, PhD

Thomas Strouse, MD

Debra Barton, PhD, RN, AOCN, FAAN

Review

Radiopharmaceuticals: When and How to Use Them to Treat Metastatic Bone Pain

Fabio M. Paes, Vinicius Ernani, Peter Hosein, and Aldo N. Serafini

PEER VIEWPOINTS

Radiopharmaceuticals: Present and Future

Bradley J. Atkinson and Shi-Ming Tu

Radiopharmaceuticals for Painful Bone Metastases: Perspective from Radiation Oncology

Elizabeth A. Barnes

How We Do It

Coordination of Care in Breast Cancer Survivors: An Overview

Kimberly S. Peairs, Antonio C. Wolff, Sharon J. Olsen, Elissa T. Bantug, Lillie Shockney, Melinda E. Kantsiper, Elisabeth Carrino-Tamasi, and Claire F. Snyder

Original Research

Documenting the Symptom Experience of Cancer Patients

Teresa L. Deshields, Patricia Potter, Sarah Olsen, Jingxia Liu, and Linh Dye

Efficacy and Safety of Fentanyl Pectin Nasal Spray Compared With Immediate-Release Morphine Sulphate Tablets in the Treatment of Breakthrough Cancer Pain: A Multicentre, Randomised, Controlled, Double-Blind, Double-Dummy Multiple-Crossover Study

Marie Fallon, Carlo Reale, Andrew Davies, A. Eberhard Lux, Kirushna Kumar, Andrzej Stachowiak, and Rafael Galvez, on behalf of the Fentanyl Nasal Spray Study 044 Investigators Group

Observations

Highlights from the 2011 Annual Meeting of the American Society of Clinical Oncology





Michael J. Fisch



David Cella



Thomas Strouse



Debra Barton

The Journal of Supportive Oncology is published by:



Elsevier Oncology
60B Columbia Road
Morristown, NJ 07960
(973) 290-8200 tel
(631) 424-8905 fax

Editorial Director
Mary Jo M. Dales

Managing Editor
Susan D. Hite

Production Manager
Yvonne Evans

National Accounts Manager
Devin Gregorie

National Sales Manager
Adam Sansolo

President and Publisher
Alan J. Imhoff

Editor-in-Chief

Michael J. Fisch, MD, MPH, FACP
The University of Texas
M. D. Anderson Cancer Center
Houston, Texas

Associate Editors

David Cella, PhD
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University
Chicago, Illinois

Thomas Strouse, MD
David Geffen UCLA School of Medicine
Departments of Psychiatry and
Palliative Medicine
Los Angeles, California

Debra Barton, PhD, RN, AOCN, FAAN
Mayo Clinic
Rochester, Minnesota

Editorial Board

Janet L. Abraham, MD
Dana-Farber Cancer Institute
Harvard Medical School
Boston, Massachusetts

Betty R. Ferrell, PhD, FAAN
City of Hope National Medical Center
Duarte, California

Steven D. Passik, PhD
Vanderbilt University Medical Center
Nashville, Tennessee

Donald Abrams, MD
UCSF School of Medicine
San Francisco, California

John A. Glaspy, MD, MPH
UCLA School of Medicine
Los Angeles, California

Russell K. Portenoy, MD
Beth Israel Medical Center
New York, New York

Anthony Back, MD
University of Washington
Seattle, Washington

Steven M. Grunberg, MD
University of Vermont College of
Medicine
Burlington, Vermont

Lidia Schapira, MD
Massachusetts General Hospital
Cancer Center
Boston, Massachusetts
Section Editor, How We Say It

Walter Baile, MD
The University of Texas
M. D. Anderson Cancer Center
Houston, Texas

Paul R. Helft, MD
Indiana University School of Medicine
Indianapolis, Indiana

Lee S. Schwartzberg, MD, FACP
The West Clinic
Memphis, Tennessee

Ann M. Berger, MSN, MD
National Institutes of Health
Clinical Center
Bethesda, Maryland

Paul J. Hesketh, MD
Lahey Clinic Medical Center
Burlington, Massachusetts

Charles L. Shapiro, MD
Ohio State University Comprehensive
Cancer Center
Columbus, Ohio

Diane Blum, MSW
Lymphoma Research Foundation
New York, New York

Jimmie Holland, MD
Memorial Sloan-Kettering
Cancer Center
New York, New York

Neal E. Slatkin, MD, DABPM
City of Hope National Medical Center
Duarte, California

Robert Buckman, MD, PhD
Princess Margaret Hospital
Toronto, Ontario

Mark G. Kris, MD
Memorial Sloan-Kettering
Cancer Center
New York, New York

Stephen T. Sonis, DMD, DMSc
Brigham and Women's Hospital
Boston, Massachusetts

Barrie R. Cassileth, PhD
Memorial Sloan-Kettering
Cancer Center
New York, New York

**D. Andrew Loblaw, BSc, MD, MSc,
FRCPC, CIP**
Odette Cancer Centre
Toronto, Ontario

N. Simon Tchekmedyian, MD
Pacific Shores Medical Group
UCLA School of Medicine
Los Angeles, California

Harvey Max Chochinov, MD
University of Manitoba
Winnipeg, Manitoba

Charles L. Loprinzi, MD
Mayo Clinic
Rochester, Minnesota

Charles F. von Gunten, MD, PhD
San Diego Hospice and Palliative Care
San Diego, California

Nessa Coyle, PhD, NP, FAAN
Memorial Sloan-Kettering
Cancer Center
New York, New York

Matthew Loscalzo, MSW
City of Hope National Medical Center
Duarte, California

Jamie H. Von Roenn, MD
Editor Emeritus
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University
Chicago, Illinois

Robert Dreicer, MD, FACP
Cleveland Clinic Foundation
Cleveland, Ohio

Neil MacDonald, CM, MD, FRCP(C)
McGill University
Montreal, Quebec



On the cover It is apparent there is an increasing need for well-established patterns of communication between care providers. Dr. Peairs and colleagues have created a multidisciplinary approach for management of breast cancer survivors to improve communication and education between providers and patients. Photo: Copyright © Fotosearch.com

Correspondence

Inquires should be addressed to *The Journal of Supportive Oncology*, 60B Columbia Road, Morristown, NJ 07960; tel: (973) 290-8200; fax: (631) 424-8905.

Editorial correspondence should be addressed to the Editor-in-Chief, Michael J. Fisch, M.D., e-mail: jonology@elsevier.com. Author guidelines are available and manuscripts may be submitted for consideration at <http://ees.elsevier.com/jso>. For additional information, contact Susan Hite, Managing Editor, tel: (240) 221-2471; e-mail: susan.hite@elsevier.com.

Advertising

For information on advertising rates, reprints, or supplements, contact Devin Gregorie, tel: (516) 381-8613, e-mail: d.gregorie@elsevier.com, Adam Sansolo, tel: (973) 452-8140, e-mail: a.sansolo@elsevier.com.

Subscriptions

Annual subscription rates (6 issues): *Individual*: US \$318; Canada: US \$347; *International*: US \$347. *Institutional*: US \$318; Canada: US \$347; *International*: US \$347. *Single copy*: US \$42. For further information regarding subscriptions, contact subscriptions@supportiveoncology.net.

Change of Address

Postmaster: Send address changes to *The Journal of Supportive Oncology*, Circulation, Elsevier, Inc., 60B Columbia Road, Morristown, NJ 07960.

Copyright

Copyright © 2011 by Elsevier Inc. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without written permission from the publisher.

The Journal of Supportive Oncology (ISSN 1544-6794) is published 6 times per year by International Medical News Group, LLC, an Elsevier company, 60B Columbia Road, Morristown, NJ 07960. Periodicals postage paid at Morristown, NJ, and additional mailing offices.

The Journal of
**Supportive
ONCOLOGY**
Quality of Life • Symptoms/Side Effects • Palliative Care

The Journal of Supportive Oncology is indexed by Index Medicus/MEDLINE/PubMed, EMBASE/Excerpta Medica, Chemical Abstracts, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL)

REVIEW

197 Radiopharmaceuticals: When and How to Use Them to Treat Metastatic Bone Pain

Fabio M. Paes, MD, Vinicius Ernani, MD, Peter Hosein, MD, and Aldo N. Serafini, MD, *Department of Radiology, University of Miami/Jackson Memorial Medical Center, Sylvester Comprehensive Cancer Center; Division of Hematology Oncology, University of Miami/Jackson Memorial Medical Center, Sylvester Comprehensive Cancer Center, Miami, Florida.*

Peer Viewpoints

206 Radiopharmaceuticals: Present and Future

Bradley J. Atkinson, PharmD, and Shi-Ming Tu, MD, *Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas.*

208 Radiopharmaceuticals for Painful Bone Metastases: Perspective from Radiation Oncology

Elizabeth A. Barnes, MD, FRCP(C), *Department of Radiation Oncology, Odette Cancer Centre, Toronto, Canada.*

HOW WE DO IT

210 Coordination of Care in Breast Cancer Survivors: An Overview

Kimberly S. Peairs, MD, Antonio C. Wolff, MD, FACP, Sharon J. Olsen, PhD, Elissa T. Bantug, MHS, Lillie Shockney, RN, BS, MAS, Melinda E. Kantsiper, MD, Elisabeth Carrino-Tamasi, MSW, LGSW, and Claire F. Snyder, PhD, *The Johns Hopkins School of Medicine; The Johns Hopkins School of Medicine, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland.*

ORIGINAL RESEARCH

216 Documenting the Symptom Experience of Cancer Patients

Teresa L. Deshields, PhD, Patricia Potter, RN, PhD, FAAN, Sarah Olsen, RN, Jingxia Liu, PhD, and Linh Dye, DMGT, *The Siteman Cancer Center; Division of Biostatistics, Washington University School of Medicine; and Nursing Administration, Barnes-Jewish Hospital, St. Louis, Missouri.*

Mission

The *Journal of Supportive Oncology* publishes online and six times per year in print peer-reviewed original research and review articles on supportive care and quality-of-life studies in patients with cancer, including original clinical studies, state-of-the-art papers, peer viewpoints, "How We Do It" commentaries on incorporating best practices, and letters to the editor. In general, case reports will be considered as case letters to the editor.

Disclaimer

The ideas and opinions expressed in *The Journal of Supportive Oncology* are those of the authors and do not necessarily reflect the opinions of the Publisher, Editors, or Editorial Board. Publication of an advertisement or other product mention in *The Journal of Supportive Oncology* should not be construed as an endorsement of the product or the manufacturer's claims. Readers are encouraged to contact the manufacturer with any question about the features or limitations of the products mentioned. The Publisher does not assume any responsibility for any injury or damage to persons or property arising out of or related to any use of the material contained in this periodical. The reader is advised to check the appropriate medical literature and the product information currently provided by the manufacturer of each drug to be administered to verify the dosage, the method and duration of administration, or contraindications. It is the responsibility of the treating physician or other health care professional, relying on independent experience or knowledge of the patient, to determine drug dosages and the best treatment for the patient.

The Publisher reserves the right to reject any advertising that is not in keeping with the publication's standards.

This journal is printed on paper meeting the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper) effective with Volume 1, Issue 1, 2003.

ORIGINAL RESEARCH

224 **Efficacy and Safety of Fentanyl Pectin Nasal Spray Compared with Immediate-Release Morphine Sulfate Tablets in the Treatment of Breakthrough Cancer Pain: A Multicenter, Randomized, Controlled, Double-Blind, Double-Dummy Multiple-Crossover Study**

Marie Fallon, MB, ChB, MD, FRCP, Carlo Reale, MD, Andrew Davies, MBBS, MSc, MD, FRCP, A. Eberhard Lux, MD, Kirushna Kumar, MBBS, MD, Andrzej Stachowiak, MD, and Rafael Galvez, MD, on behalf of the Fentanyl Nasal Spray Study 044 Investigators Group, *The Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh; St. Luke's Cancer Centre, Royal Surrey County Hospital, Guildford, United Kingdom; Università degli Studi la Sapienza di Roma, Rome, Italy; St. Marien-Hospital, Lünen, Germany; Meenakshi Mission Hospital, Madurai, India; Regionalny Zespół Opieki Paliatywnej—Dom Sue Ryder, Bydgoszcz, Poland; and Unidad del Dolor/Hospital Virgen de las Nieves, Granada, Spain.*

OBSERVATIONS

232 **Highlights from the 2011 Annual Meeting of the American Society of Clinical Oncology**

Radiopharmaceuticals: When and How to Use Them to Treat Metastatic Bone Pain

Fabio M. Paes, MD; Vinicius Ernani, MD; Peter Hosein, MD; and Aldo N. Serafini, MD

Bone pain due to osseous metastasis constitutes the most frequent type of pain in cancer patients. It is significantly related to poor quality of life in the final stages of the disease. Although it is most commonly seen in the advanced stages, patients can often present with bone pain as the first symptom of cancer, particularly in prostate and breast cancers. The prevalence of painful osseous metastases varies among the different types of cancers. Approximately 65% of patients with prostate or breast cancer and 35% of those with advanced cancers of the lung, thyroid, and kidney will have symptomatic skeletal metastases. Breast and prostate cancers are responsible for more than 80% of cases of symptomatic bone metastases in any oncologic practice.^{1,2} This type of pain is distinct from neuropathic, visceral, or other types of somatic pain, such as inflammatory and arthritic pain, and presents with certain features during its course: initially, it is dull and of low intensity and progresses to a chronic state with intermittent severe breakthrough episodes of acute pain. Generally, the bone pain exacerbates at the end of dose of the analgesic, and it is often difficult to treat without being accompanied by significant, unwanted side effects. The pathophysiology is not well understood, and multiple mechanisms are postulated.³ Tumor-induced cytokines, stimulating factors released by tumor cells, and direct nerve injury have all been proposed as mechanisms that mediate skeletal pain. Infiltration of bone trabeculae and matrix by tumor-causing

Abstract Bone pain due to skeletal metastases constitutes the most common type of cancer-related pain. The management of bone pain remains challenging and is not standardized. In patients with multifocal osteoblastic metastases, systemic radiopharmaceuticals should be the preferred adjunctive therapy for pain palliation. The lack of general knowledge about radiopharmaceuticals, their clinical utility and safety profiles, constitutes the major cause for their underutilization. Our goal is to review the indications, selection criteria, efficacy, and toxicities of two approved radiopharmaceuticals for bone pain palliation: strontium-89 and samarium-153. Finally, a brief review of the data on combination therapy with bisphosphonates or chemotherapy is included.

osteolysis also generates skeletal pain, which is supported by the inhibitory osteoclastic effect of bisphosphonates in the treatment of bone pain.⁴ Peripheral nerve endings are also triggered by various substances produced by cells in response to the tumor (eg, prostaglandin E, interleukins, substance P, transforming growth factor) and by the tumor cell itself (tumor necrosis factor); these molecular signals lead to sensitization of the peripheral nervous system, causing allodynia and hyperalgesia.⁵

The appearance of bone involvement may be the first and only sign of solid tumor spread, detected in many instances before the primary site. Due to a high prevalence of osseous metastasis, screening whole-body bone scintigraphy has been part of the initial staging algorithm of prostate and breast cancers. Also, when osseous metastasis is suspected clinically or detected by other imaging modalities, bone scintigraphy helps to delineate the extension and severity of skeletal involvement and classify lesions as predominantly osteoblastic, lytic, or mixed type, which will be crucial in the correct treatment plan, as discussed later in this article.¹

Dr. Paes and Serafini are from the Department of Radiology, University of Miami/Jackson Memorial Medical Center, Sylvester Comprehensive Cancer Center, Miami, FL.

Dr. Ernani and Hosein are from the Division of Hematology Oncology, University of Miami/Jackson Memorial Medical Center, Sylvester Comprehensive Cancer Center, Miami, FL.

Manuscript submitted March 8, 2011; accepted June 16, 2011.

Correspondence to: Fabio M. Paes, MD, Department of Radiology, University of Miami/Jackson Memorial Medical Center, 1611 N.W. 12th Avenue, West Wing #279, Miami, FL 33136; telephone: (305) 585-7878; fax: (305) 585-5743; e-mail: fpaes@med.miami.edu

J Support Oncol 2011;9:197-205 © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.suponc.2011.06.004

The Challenge of Managing Bone Pain

The appropriate management of painful skeletal metastasis is complicated and expensive and should be carried out by a multidisciplinary approach.⁶ The current treatment strategy for cancer pain palliation involves a variety of modalities.

Most of the therapies targeted to destroy the tumor itself are effective methods of pain control, like chemotherapeutic agents, external beam radiation (XRT), radiofrequency ablation (RF), and surgery. However, they sometimes can be invasive (ie, surgery and RF) or arduous to administer (ie, chemotherapeutic regimens), can provide incomplete pain control, or can be accompanied by unwanted side effects, particularly in patients with extensive metastatic disease. Medications without tumoricidal effect targeted to diminish the pain associated with metastasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and opiates, are equally useful but also have dose-limiting side effects.

Despite a large armamentarium of available analgesics, it has been reported that at least 45% of cancer patients have insufficient and undermanaged pain control, due to a poor estimation of the patient's pain by the physician, inadequate pain assessment, treatment-associated side effects, and lack of knowledge of all treatment options.⁷ Symptomatic pain assessment must be performed with standardized measurement tools administered at appropriate intervals. Consistent pain measurement and systematic recording of analgesic use across clinical trials would enhance comparability of findings and facilitate the development of evidence-based guidelines for the management of metastatic bone pain. For instance, a consensus on palliative end-point measurements in bone metastases has been in use for XRT trials and can be used as a reference in future trials of other palliative modalities.⁸

Furthermore, the physician caring for these cancer patients should understand that no single method is capable of offering adequate pain control for most individual cases and frequently a combination of systemic and local treatment is necessary, particularly to avoid debilitating side effects. At this time, curative options do not exist for multiple skeletal metastases, and all described treatments are palliative.

Among available therapies, systemic radiopharmaceuticals are the least understood and used by clinical oncologists and pain specialists. Our major goal is to increase awareness of available radiopharmaceuticals for bone pain palliation. We will review the current indications, patient selection criteria, efficacy, and toxicity profile of two radiopharmaceuticals which are currently approved for bone pain palliation: strontium-89 chloride (Sr-89) and samarium-153 lexidronam (Sm-153). Finally, the available data on combination therapy of radiopharmaceuticals with bisphosphonates or chemotherapy will be discussed. The use of other available palliative treatment options, including pharmacological, surgical, and hormonal modalities, is beyond the scope of this article. However, since XRT is the main alternate modality to radiopharmaceuticals for the treatment of painful osseous metastasis, a short discussion of this method will be provided below.

External Beam Radiation for Pain Control

The therapeutic purposes of XRT for bone metastases are pain relief as measured by reduced pain intensity scores, elimination or reduction of analgesic usage, functional improvement such as increased ambulation, and reduction in the risk of fracture in weight-bearing bones. Extensive data from large multicenter, randomized trials conducted by the Radiation Therapy Oncology Group (RTOG) have demonstrated that 80%–90% of patients receiving radiation therapy for osseous metastases will experience complete or partial pain relief, typically within 10–14 days of the initiation of therapy with minimal side effects.⁹ Patients with metastases from slowly-proliferating tumors such as prostate cancer may respond less rapidly. The overall proportion of patients receiving pain relief rises to approximately 90% in 3 months; and 70% of the patients experiencing pain relief do not develop recurrent pain in the treated region. Sustained local pain relief for one year is noted in almost two-thirds of patients. Therefore, it is indisputable that patients with localized painful osseous metastasis accessible to XRT should initially receive such therapy for palliation.

However, XRT has limited use in extensive multifocal osseous metastasis or in metastatic sites included in previously treated radiation fields. Also, it does not preclude the development of other metastatic foci away from or nearby sites that were treated for disease. Although hemibody or total-body radiation can sometimes be utilized, the total delivered dose is limited due to its high risk of inducing severe bone marrow suppression. In addition, patients must be hospitalized and given extensive supportive care. Studies have shown that approximately 80% of patients may be successfully treated with sequential whole-skeleton radiation, in which 6–7 Gy is administered as a single fraction to either the upper and lower parts of the body, followed by a second dose of 6–8 Gy, given 4–6 weeks later, to the remainder of the body.¹⁰ Although the expected response is within 24–48 hours, depending on the location of the radiation treatment field, 60% of patients experience adverse side effects such as diarrhea, nausea, lymphedema, fatigue, radiation pneumonitis, and hair loss, all of which can be quite challenging.^{7,11} Also, the total cost of this treatment is significantly higher than conventional single or fractionated localized XRT.

Therefore, patients with widespread metastatic bone disease or osseous lesions within previously treated radiation fields may be ideal candidates for treatment with systemic radiopharmaceuticals. The possibility of combining radiopharmaceuticals and localized XRT is exciting, although limited data are available.¹²

Targeted Systemic Radionuclide Therapy with Bone-Seeking Radiopharmaceuticals

Systemic radionuclide therapy has shown its value in the management of painful bone metastasis in current clinical practice.^{1,7,13,14} However, radionuclide therapy remains a relatively unknown treatment modality for many physicians,

Table 1**Comparison Between Clinically Used Bone Seeking Radiopharmaceuticals**

RADIOPHARMACEUTICAL	HALF-LIFE (DAYS)	STANDARD DOSE (SI)	GAMMA-ENERGY (keV) (%)	BETA-ENERGY (MeV) (MAXIMUM)	MAXIMUM PENETRATION IN TISSUE (AVERAGE)	REMARKS
Sr-89 chloride	50.5	4 mCi (148 MBq)	910 (0.01%)	1.46	6 mm (2.4 mm)	Longest half-life
Sm-153 lexidronam	1.9	1 mCi/kg (37 MBq/kg)	103 (28%)	0.81	2.5 mm (0.6 mm)	Most common agent used in United States
Re-186 HEDP	3.8	35 mCi (1,295 MBq)	137 (9%)	1.07	4.5 mm (1.1 mm)	Approved only in Europe

Adapted from Paes et al.¹

even those working in the fields of oncology and pain palliation.

Radioactive isotopes of phosphorus-32 (P-32) and Sr-89 were the first bone-seeking radiopharmaceuticals approved for the treatment of painful bone metastases. These elements preferentially incorporate into the sites of osteoblastic bone metastases at rates 2–25 times greater than in normal metabolic active bone. The clinical use of P-32 has decreased since the 1980s in favor of Sr-89 and newer radionuclides. These newer beta-emitting isotopes were developed for palliation of cancer-induced bone pain and are currently administered using multidentate chelate complexes with more efficient pharmacokinetics, better decay properties, and a shorter beta range (Table 1).

Sm-153, rhenium-186 (Re-186), and rhenium-188 (Re-188) are categorized as newer bone-seeking radioisotopes^{15,16} and have been extensively studied in the treatment of painful bone metastasis. Sm-153 has been approved for use in the United States and Europe for more than one decade, whereas Re-186 has been approved only in Europe. Re-188 is still an investigational agent which shows a promising availability profile since it can be obtained from a generator.^{15,17}

Although all the beta-emitting radioisotopes differ significantly in their physical properties, they seem to have the same clinical efficacy in most trials for bone pain palliation conducted with these agents. The bone-seeking agent of choice has not yet been determined. Since all the commonly used radiopharmaceuticals have similar efficacy profiles, the agent should be selected in a case-based fashion, taking into consideration the availability, toxicity, and goal of therapy.

Different indications for clinical use of these agents, besides pain palliation, have also been studied in recent clinical trials, which include radioisotope treatment of hemophilic arthropathy,^{18,19} conditioning therapy prior to bone marrow transplantation in acute leukemias,^{20–22} and radioimmunotherapy using radiolabeled antibodies against different tumors.^{23–26}

Indications for Radionuclide Therapy in Bone Pain Management

Intravenous injection of Sr-89 chloride, Sm-153 lexidronam, and Re-186 etidronate is approved for the treatment of bone pain due to osteoblastic or mixed osseous metastasis from prostate and breast carcinomas (most common indications) and any other tumor presenting with painful osteoblas-

tic lesions documented by whole-body bone scintigraphy performed within eight weeks prior to therapy.^{1,14,27,28} The pain described by the patient should correlate to the areas of abnormal radiotracer accumulation in the bone scan. Most patients treated with radionuclide therapy have failed chemotherapy and other pharmacological therapy or have developed limiting side effects from these agents and are not candidates for XRT for reasons previously mentioned. Although these bone-seeking radioisotopes have been typically reserved for the treatment of diffuse osseous metastasis late in the course of the disease, an effort should be made to administer them early in the metastatic phase, to increase the rate of therapeutic response.²⁹ The paradigm of using systemic radionuclide therapy as a last resort should be avoided because its earlier use has been proven safe and effective for bone pain therapy in most clinical scenarios.³⁰ A common misconception is that the use of radiopharmaceuticals will preclude or limit the use of systemic chemotherapy or XRT in the patient with metastatic disease.³¹ If treated early, such patients can still be treated with systemic or localized therapies without significant side effects. Another theoretic advantage of early bone-targeted radionuclide treatment is that radiation can be delivered selectively to subclinical tumors and to metastases that are too small to be imaged and treated by surgical excision or local XRT.³²

The appropriate choice of radiopharmaceutical is based on physical characteristics of the radioisotope in relation to the extent of the disease, bone marrow reserve, and its availability in different countries. The clinically used radioisotopes have comparable efficacy with diverse biophysical properties and pharmacokinetic profiles, as will be discussed later (Tables 1 and 2).^{1,13,33}

Patient Selection, Expected Effect, and Contraindications

Theoretically, any patient with documented osteoblastic bone metastasis by bone scintigraphy with associated uncontrolled pain is a candidate for radiopharmaceutical therapy for pain palliation. However, in practice, it has been used in patients with more extensive metastatic bone disease that could not be controlled by localized XRT. Two important absolute contraindications for therapy with bone-seeking agents are pregnancy and breastfeeding. A pregnancy test should be obtained for all female patients of reproductive age. They should also be advised against conceiving for at least six

Table 2**Summary of Efficacy Studies on Sr-89 and Sm-153**

REFERENCES	YEAR	PATIENTS (N)	DOSE (SI)	CANCER	PAIN RELIEF
Sr-89 CHLORIDE					
Fuster et al. ⁵²	2000	40	4 mCi (148 MBq)	Breast	92%
Kraeber-Bodere et al. ²⁹	2000	94	4 mCi (150 MBq)	Prostate	78%
Turner et al. ⁵³	2001	93	4 mCi (150 MBq)	Prostate	63%
Dafermou et al. ³⁹	2001	527	4 mCi (148 MBq)	Prostate	59.80%
Ashayeri et al. ⁵⁴	2002	27	4 mCi (150 MBq)	Prostate and breast	81%
Zorga et al. ⁵⁵	2003	33	4 mCi (148 MBq)	Prostate, breast, bladder, and renal cell	82%
Baczyk et al. ⁵⁶	2003	70	4 mCi (148 MBq)	Prostate	88%
Gunawardana et al. ⁵⁷	2004	13	4 mCi (148 MBq)	Prostate	57%
Liepe et al. ⁵⁸	2007	15	4 mCi (148 MBq)	Prostate and breast	72%
Ma et al. ⁵⁹	2008	116	40–60 μ Ci/kg (1.48–2.22 MBq/kg)	Prostate	83.60%
Sm-153 lexidronam					
Serafini et al. ⁶⁰	1998	118	0.5–1 mCi/kg (18.5–37 MBq/kg)	Prostate, breast, others	62%–82%
Tian et al. ⁶¹	1999	105	1 mCi/kg (37 MBq/kg)	Prostate, breast, others	84%
Dolezal et al. ⁶²	2000	33	1 mCi/kg (37 MBq/kg)	Prostate, breast, others	70%
Wang et al. ⁶³	2003	9	1 mCi/kg (37 MBq/kg)	Prostate, breast, others	78%
Sapienza et al. ⁶⁴	2004	73	1 mCi/kg (37 MBq/kg)	Prostate, breast	76%
Etchebehere et al. ⁶⁵	2004	58	1.0–1.6 mCi/kg (37–59.2 MBq/kg)	Prostate, breast, others	78%
Sartor et al. ⁶⁶	2004	152	1 mCi/kg (37 MBq/kg)	Prostate	65%
Tripathi et al. ^{67,a}	2006	86	1 mCi/kg (37 MBq/kg)	Prostate, breast, others	73%
Ripamonti et al. ⁶⁹	2007	13	1 mCi/kg (40 MBq/kg)	Prostate	61.50%
Liepe et al. ⁵⁸	2007	15	1 mCi/kg (37 MBq/kg)	Prostate and breast	73%
Dolezal et al. ⁶⁸	2007	32	1 mCi/kg (37 MBq/kg)	Prostate	75%

Adapted from Paes et al.¹

^aResponse rates were 80.3% and 80.5% in breast and prostate cancers, respectively. One case each of Wilms tumor, ovarian cancer, germ cell tumor testis, multiple myeloma, primitive neuroectodermal tumor, and esophageal cancer did not respond to therapy.

months after a single therapeutic dose, even though there are no scientific data about related congenital abnormalities. It is also required to entirely discontinue breastfeeding before the radiopharmaceutical is administered.²⁷

The presence of cytopenia constitutes a relative contraindication since bone-seeking radiopharmaceuticals can cause further myelotoxicity, aggravating previous low blood cell counts. Blood transfusion and granulocyte colony-stimulating growth factors (G-CSFs) may be used either prior to or following radionuclide therapy in some situations. In those cases, the purpose is to salvage and stabilize patients until such time as bone marrow recovery occurs spontaneously.^{13,34–36} Most centers use the following blood cell count values as dose-limiting: hemoglobin (Hb) less than 9 mg/dL; absolute white blood cell (WBC) count less than 3,500 and platelet (PLT) count less than 100,000. These values must be stable for at least two to three weeks prior to therapy. Even patients with stable lower absolute WBC count (>2,400) and PLT count (>60,000) may be given consideration to receive systemic radionuclide therapy. However, the total injected activity may be reduced or fractionated in these cases.^{1,13,34}

Bone marrow involvement is not considered a contraindication by itself, unless the blood counts are significantly low. The appearance of the bone scintigraphy provides informa-

tion which helps to describe the extent of bone marrow involvement. The presence of a “superscan” appearance suggests limited bone marrow reserve, but it does not constitute an absolute contraindication for therapy. As long as the blood counts are stable above the described ranges, these patients can be treated with radiopharmaceuticals. As previously described, patients with mildly compromised bone marrow reserves also have two possible therapeutic options: be treated at lower dose levels or be treated with fractionated smaller doses.

The plasma clearance of these agents is dependent on renal function. Patients with impaired renal function (glomerular filtration rate [GFR] <30 mL/min) should not receive the radiopharmaceuticals due to a higher risk of myelotoxicity. Although there are no clinical data on patients undergoing dialysis, the risk of contamination and radiation exposure in the dialysis unit make it an absolute contraindication for the therapy, mostly due to logistic issues. By consensus, patients with moderate renal failure (GFR >30 and <50 mL/min) should have their dose lowered by 50%. In patients with impaired renal function, Sm-153 lexidronam and Re-186 etidronate are the preferred radiopharmaceuticals due to their lower physical half-lives, even though there are currently no significant data regarding their safety and toxicity. The pa-

Table 3**Checklist before Therapy with Radiopharmaceuticals and Contraindications**

Clinical information and imaging findings	
Recent positive bone scintigraphy within 8 weeks	
Positive correlation between osteoblastic lesions and painful sites	
Severe pain despite analgesics or analgesic side effects	
Not a candidate for local control with external beam radiation (XRT)	
No chemotherapy or large field XRT in the past 4–12 weeks	
Incontinence: place urinary catheter	
Life expectancy more than 4 weeks	
Signed informed consent	
Cervical spine involvement—consider steroid use prior to injection	
Laboratory data	
Hemoglobin >9.0 mg/dL	
Absolute WBC >3,500/dL (may consider in >2,400/dL)	
Absolute neutrophil >1,500/dL	
PLT >100,000/dL (may consider in >60,000/dL)	
Glomerular filtration rate (GFR) >50 mL/min—full dose	
GFR >30 and <50 mL/min—half dose	
Contraindication	
Pregnancy: obtain pregnancy test the day of injection	
Breastfeeding: stop permanently	
GFR <30 mL/min or dialysis	
Spinal cord compression and base of skull syndrome: needs XRT	
Extensive bone marrow involvement: low blood counts (“superscan”—relative contraindication)	

Adapted from Paes et al.¹

tient selection criteria and contraindications are summarized in Table 3.

It is vital to inform the patient and the referring physician what they should expect after the radiopharmaceutical is given. Onset of pain relief may occur within days or weeks, and its duration may also vary according to the extent of metastatic bone disease. In general, radionuclide therapy is not recommended in patients with a life expectancy of less than four weeks, given that the onset of pain relief may be delayed in some patients. Flare painful response (FPR) has been observed in 10%–15% of patients and is described as an initial aggravation of pain within the first few weeks. The pathophysiology of FPR is thought to be related to the release of cytokines and inflammatory-related substances. This may be helped by temporary use of analgesics and steroids. FPR is a marker of good targeting and related to satisfactory clinical response to the therapy.¹

Efficacy and Physical and Biological Characteristics of the Radiopharmaceuticals

The most common radiopharmaceuticals used for bone pain palliation in the United States are Sr-89 and Sm-153. Although they have a similar efficacy profile, they differ in their biological and physical characteristics and dose regimen.

STRONTIUM-89 CHLORIDE

Strontium is a divalent cation, similar to calcium, and is incorporated into hydroxyapatite in the bone after intravenous injection. Sr-89 chloride (Metastron[®]) was the first US Food and Drug Administration–approved radiopharmaceutical for bone pain palliation. The beta particles are responsible for its therapeutic effect and have an energetic penetration range within 6–7 mm in soft tissues and 3–4 mm in bone. It has a half-life of 50.5 days, decays to stable yttrium-89, emitting high-energy beta particles ($E_{\max} = 1.46$ MeV) and 0.01% of gamma-rays (910 keV).³⁷ There is no radiation risk to others after Sr-89 administration; therefore, patients should be treated on an outpatient basis. Studies of Sr-89 pharmacokinetics have demonstrated a variable plasma clearance (1.6–11.6 L/day) with overall total-body retention of 20% in a healthy population 90 days after injection, particularly in the normal skeleton. Osteoblastic lesions show up to five times greater radiopharmaceutical uptake and prolonged retention time compared to areas of normal bone in the same patient (lesion/normal bone ratio 5:1).^{2,38}

The standard recommended dose of Sr-89 chloride is 4 mCi (148–150 Mbq). No dose–response relationship for overall pain relief has been documented in the literature. There are extensive data on the efficacy of Sr-89 for bone pain palliation (Table 2) in different sets of patients with osseous metastasis, even though the majority of subjects in the clinical trials had breast or prostate cancer.

Some predictive factors for better response to Sr-89 have been described and included patients with limited skeletal involvement, those with higher performance status, and those with predominant osteoblastic lesions on bone scintigraphy. These subjects usually demonstrate greater pain relief with a longer duration of pain control.^{39,40}

SAMARIUM-153 LEXIDRONAM

Sm-153 lexidronam (Quadramet[®]) is a commonly used radiopharmaceutical for bone pain palliation in cancer centers in the United States. Sm-153 is produced by neutron irradiation of Sm-152 oxide, which can then be complexed with the calcium salt of ethylenediaminetetramethylene phosphonic acid (EDTMP) to produce Sm-153-EDTMP. Sm-153 is a radionuclide that emits beta particles ($E_{\max} = 640, 710, \text{ and } 810$ keV) with maximum energy of 0.81 MeV; it has a physical half-life of 46.3 hours and an average penetration range of 0.83 mm in water.³⁴ Its purity is practically 100%. The beta decay is accompanied by 28% emission of 103.2 keV gamma-rays, which can be used for imaging. Sm-153-EDTMP forms a complex that selectively accumulates in skeletal tissue in association with hydroxyapatite, particularly in areas where the rate of bone turnover is high. The total skeletal dose of Sm-153 is unpredictable and ranges from 15% to 95% depending of the osteoblastic activity. Bone metastases accumulate 5 times more Sm-153 than healthy bone tissue, so adjacent malignant cells are selectively exposed to higher doses of radiation. Sm-153 is cleared rapidly from the blood with a half-life of 5.5 minutes and <1% of the dose remaining in the

circulation one hour after administration. Urinary excretion is the main route of elimination and is complete within six hours.

Dose-escalation trials were performed in the early 1990s and demonstrated similar distribution of activity in doses ranging from 1 to 3 mCi/kg.^{36,41} Nonskeletal sites received negligible doses. Total absorbed estimated marrow doses ranged from 1,277 to 2,250 rad in the 3 mCi/kg dose, with only mild hematological toxicity.⁴¹ The current standard dose of Sm-153 lexitronam is 1 mCi/kg administered intravenously, which has been proven safe and effective, causing only mild reversible bone marrow suppression in patients with normal hematological parameters.

Prospective controlled trials were conducted in a large number of patients around the world, evaluating the efficacy of Sm-153 for the treatment of painful bone metastasis and are summarized in Table 2.

Administration, Precautions, Toxicity, and Follow-Up

The use of radiopharmaceuticals for metastatic bone pain is becoming more frequent. Thus, it is important to understand the appropriate management of these patients regarding administration, precautions, and toxicities. The administration of these agents is not dangerous for patients, administering personnel, and caretakers as long as standard radiation precautions are taken. The radiation safety measures vary according to the characteristics of the radioisotope used in the treatment. The radiation hazard is significantly minimized when the treating physician informs the patient of the basic precautions. The recommendations for patients undergoing treatment include the following: avoid pregnancy for at least 6–12 months, avoid contaminating shared toilets with radioactive urine and excrements, double toilet flushing for at least one week, bladder catheterization before injection if incontinent (Sr-89 for 4 days and Sm-153 for 24 hours), and avoid sexual contact for at least one week after injection. The administering physician must obtain an informed consent and use universal safety apparel during injection and handling of patients. The calculated dose of the radiopharmaceutical is administered on an outpatient basis with an injection over one to two minutes through a peripheral intravenous line, which is subsequently flushed with 10–20 mL of saline. After the drug is administered, patients should be observed for 4–6 hours to monitor possible site injection reaction and early side effects. The acquisition of a posttherapy total-body scan for Sm-153 to document adequate targeting is facultative (Figure 1).

The toxicity profiles of the radiopharmaceuticals are similar and can be used to implement a follow-up schedule. Regardless of the agent, approximately 10% of the patients will experience FPR. This reaction is typically transient, mild, and self-limiting, occurring within 72 hours of drug injection. When the osseous metastasis involves the cervical spine, a small chance of spinal cord compression posttherapy exists and prophylactic corticosteroids should be considered. Tran-

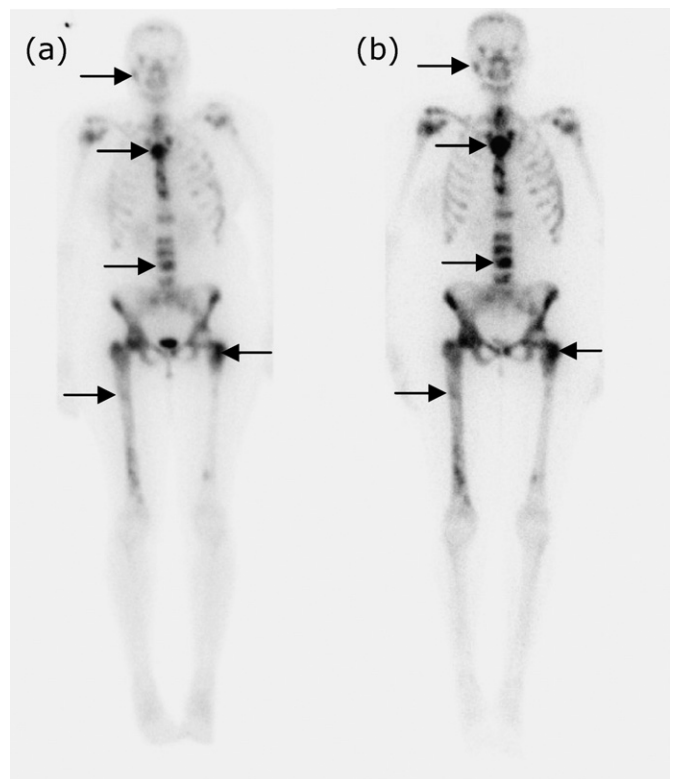


Figure 1 Targeting of Osteoblastic Metastases with Sm-153-EDTMP Posttherapy Scintigraphy

Anterior whole-body bone scan images of a patient with metastatic prostate cancer demonstrating several osteoblastic lesions in the axial and appendicular skeleton (arrows). Image a was acquired 4 hours after injection of Tc-99m-MDP, whereas image b was acquired 2 hours after a therapeutic dose (70 mCi) of Sm-153-EDTMP. There is adequate match of the metastatic foci between the two images. Adapted with permission from Paes et al.¹

sient myelosuppression, affecting mainly PLTs and WBCs, is expected and frequently observed. The nadir of myelosuppression is usually 4–8 weeks for Sr-89 and 3–5 weeks for Sm-153, which is delayed when compared to chemotherapeutic agents.⁴² The severity of the bone marrow damage is dependent upon the patient's bone marrow reserve and previous chemoradiation therapies. In the majority of patients, blood cell counts will return to baseline levels within three months of therapy. This time frame may be shorter if patients were not previously treated with chemotherapy. After the radiopharmaceutical infusion is complete, patients should follow up with their medical oncologist, nuclear physician, or primary care doctor for management of flare phenomena, pain medications, and other symptoms as needed. It is also recommended to closely monitor myelosuppression with a weekly complete blood count between the third and eighth weeks after treatment or until return to baseline levels.

Radiopharmaceuticals and Chemotherapy

Patients and clinicians are greatly interested in the use of combined modalities in the treatment of metastatic bone pain. Among them, chemosensitization is a well-recognized

method of improving the efficacy of any radiation-based therapy. The cytotoxic effect of chemotherapy causes tumor cells to be more susceptible to radiation effects, enhancing the overall efficacy of the bone-seeking agents. Unfortunately, few studies have evaluated the effect of the concomitant use of radiopharmaceuticals and chemotherapy. The majority of the clinical trials used Sr-89 as the radioisotope of choice in combination with different chemotherapeutic agents as the radiosensitizer.

An Italian group in the late 1990s used low-dose carboplatin (100 mg/m² at 7 and 21 days) as a radiosensitizer in patients with osseous metastasis treated with Sr-89. The pain response was assessed 8 weeks postinjection, with continued follow-up for one year. They were able to demonstrate pain improvement in 74% of the patients, with a superior statistical significant response in the patients treated with Sr-89 and carboplatin compared to the control group ($P = .025$). However, survival was only slightly better in the combined treatment group (8.1 vs. 5.7 months, $P = .19$). Importantly, no clinically significant adverse effects or myelosuppression by carboplatin were observed. It was the first trial to report the feasibility of concomitant use of radiopharmaceuticals and chemotherapeutic agents.⁴³

Another important randomized phase II clinical trial⁴⁴ evaluated patients after 2-3 cycles of induction chemotherapy (combination of ketoconazole and doxorubicin, alternating with estramustine and vinblastine) for hormone refractory prostate cancer. The patients who were stable or responsive after induction chemotherapy were randomly assigned to receive doxorubicin with or without Sr-89 every week for 6 weeks. Overall, 60% of patients had a 50% or greater reduction in serum prostate-specific antigen (PSA) that was maintained for at least 8 weeks, and 42% had an 80% or greater reduction. Almost 52% of the patients with bone pain at registration had complete resolution of pain. For the patients randomly assigned to receive Sr-89 and doxorubicin, the median survival time was 27.7 months (confidence interval [CI] 4.9–37.7), and for the 36 who received doxorubicin by itself the survival rate was 16.8 months (CI 4.4–34.2) ($P = .0014$). These results were the first to show possible improvement in overall survival with Sr-89 given as a consolidative therapy with doxorubicin after induction chemotherapy in patients with stable or responding metastatic prostate cancer.

Another group⁴⁵ published a small phase II study investigating the addition of Sr-89 to an alternating weekly regimen of doxorubicin, ketoconazole, paclitaxel, and estramustine in patients with metastatic prostate cancer. Interestingly, a $\geq 50\%$ reduction in PSA level was maintained for at least 8 weeks in 77.7% of the patients at 16 weeks and in 66.6% at 32 weeks. The median progression-free survival was 11.27 months (CI 1.83–29.53), and the median overall survival was 22.67 months (CI 1.83–57.73). Overall, this study suggested that chemotherapy combined with Sr-89 also demonstrated a prolonged progression-free and overall survival with acceptable toxicity when compared to historical data.

However, in current clinical practice it is not yet recommended to combine these therapies. The acceptable situation where chemotherapy and radiopharmaceuticals can be administered simultaneously is within experimental clinical trials focusing on the antitumoral effects of combining modalities. Although promising, the existing recommendation is to discontinue any myelosuppressive chemotherapy at least 4 weeks before the administration of Sr-89 or Sm-153 and withheld for 6–12 weeks posttherapy to avoid concomitant bone marrow suppression.^{13,46}

Radiopharmaceuticals and Bisphosphonates

Bone-seeking radiopharmaceuticals and bisphosphonates may be indicated in patients with cancer with painful osseous metastases to palliate pain symptoms or to prevent skeletally related events. Theoretically, both pharmaceuticals may have an additive or even synergistic palliative effect. The combined use is, however, currently controversial due to a hypothesis of possible competitive interaction between bisphosphonates and radiopharmaceuticals at the hydroxyapatite crystal surface in the skeleton, which could decrease the uptake and biological effect of both. Nevertheless, with the limited available data, there is no evidence of biological competition between these two modalities of treatment; therefore, they may be used concomitantly.

A pivotal trial divided patients with painful osseous metastasis from prostate and breast cancers in three therapeutic cohorts: group A included patients chronically treated with zoledronic acid, who received bone pain palliation with 4 mCi (150 MBq) of Sr-89 chloride, given at least 6 months after the bisphosphonate therapy began; group B included patients who received Sr-89 chloride alone; and group C patients were treated over a period of time and continued to receive only zoledronic acid therapy. Baseline characteristics were similar in all three groups, although the reduction of total discomfort and bone pain in group A was significantly greater compared to group B ($P < .01$) and group C ($P < .01$). During the monitored period, a significant improvement of clinical conditions was observed in group A compared to groups B and C.⁴⁷ These findings suggested that combined sequential therapy of Sr-89 chloride and zoledronic acid in patients with painful bone metastases is more effective at treating pain and improving clinical conditions than therapeutic modalities used separately.

Another group⁴⁸ recently evaluated the biodistribution and skeletal uptake of Sm-153 in patients with hormone-refractory prostate cancer treated with a combination regimen using zoledronic acid. After analyzing the urinary excretion, toxicity, and scintigraphic data, they concluded that zoledronic acid treatment did not influence Sm-153 skeletal uptake and suggested that combined treatment is both feasible and safe.

In a small study utilizing another bisphosphonate,⁴⁹ skeletal uptake of Sm-153-EDTMP before and 1-4 days after pamidronate infusion was compared in patients with breast cancer metastatic to bone. Two of these patients continued to com-

pare Sm-153-EDTMP uptake at approximately 1, 2, 3 and 4 weeks after pamidronate infusion. There was no difference in skeletal uptake of Sm-153-EDTMP before or after pamidronate infusion.

These findings support the theory of no significant biological competition of these agents. The clinical experience using combined bisphosphonates and bone-seeking radiopharmaceutical therapy is increasing rapidly in academic referral centers.⁵⁰

Conclusion

Bone pain palliation using the available radiopharmaceuticals is an effective systemic treatment for patients suffering with metastatic bone lesions and should always be considered in the earlier stages of osseous metastasis dissemination rather than as a last resort. This therapy decreases morbidity and improves patients' quality of life. The proper application of this modality will require continuous education of oncologists and pain specialists. At first, the task to propagate the proven efficacy of this therapy and advocate for the more widespread use of these agents lies with the nuclear medicine physician.

It is important to recognize that the radiopharmaceutical agent of choice has not yet been established, so therapy must be individualized. The agent should be selected taking into consideration the availability, toxicity, and goal of therapy. There are comprehensive review articles about the use of radiopharmaceuticals in the treatment of bone metastasis which support the above statements and are worthwhile reading.^{1,51}

Many questions regarding bone-seeking agents still require definite answers: Is there a true beneficial effect of combining them with chemotherapy or bisphosphonates? What factors are predictive of good response? Is it safe to use radiopharmaceuticals in patients with extensive bone marrow substitution? Further clinical trials are necessary not only to clarify these questions but also to evaluate a potential role of bone-seeking radiopharmaceuticals beyond palliation, toward improvement in survival.

Conflicts of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

References

PubMed ID in brackets

- Paes FM, Serafini AN. Systemic metabolic radiopharmaceutical therapy in the treatment of metastatic bone pain. *Semin Nucl Med* 2010; 40(2):89–104.
- Lam MG, de Klerk JM, van Rijk PP, et al. Bone seeking radiopharmaceuticals for palliation of pain in cancer patients with osseous metastases. *Anticancer Agents Med Chem* 2007; 7(4):381–397.
- Clines GA, Guise TA. Molecular mechanisms and treatment of bone metastasis. *Expert Rev Mol Med* 2008;10:e7.
- Clezardin P, Teti A. Bone metastasis: pathogenesis and therapeutic implications. *Clin Exp Metastasis* 2007;24(8):599–608.
- Saarto T, Janes R, Tenhunen M, et al. Palliative radiotherapy in the treatment of skeletal metastases. *Eur J Pain* 2002;6(5):323–330.
- Hillegonds DJ, Franklin S, Shelton DK, et al. The management of painful bone metastases with an emphasis on radionuclide therapy. *J Natl Med Assoc* 2007;99(7):785–794.
- Serafini AN. Therapy of metastatic bone pain. *J Nucl Med* 2001;42(6):895–906.
- Chow E, Wu JS, Hoskin P, et al. International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Radiother Oncol* 2002;64(3):275–280.
- Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases: final results of the Study by the Radiation Therapy Oncology Group. *Cancer* 1982;50(5):893–899.
- Poulter CA, Cosmatos D, Rubin P, et al. A report of RTOG 8206: a phase III study of whether the addition of single dose hemibody irradiation to standard fractionated local field irradiation is more effective than local field irradiation alone in the treatment of symptomatic osseous metastases. *Int J Radiat Oncol Biol Phys* 1992;23(1):207–214.
- Dy SM, Asch SM, Naeim A, et al. Evidence-based standards for cancer pain management. *J Clin Oncol* 2008;26(23):3879–3885.
- Hobbs RF, McNutt T, Baechler S, et al. A treatment planning method for sequentially combining radiopharmaceutical therapy and external radiation therapy. *Int J Radiat Oncol Biol Phys* 2011;80(4):1256–1262.
- Finlay IG, Mason MD, Shelley M. Radioisotopes for the palliation of metastatic bone cancer: a systematic review. *Lancet Oncol* 2005;6(6):392–400.
- Pandit-Taskar N, Batraki M, Divgi CR. Radiopharmaceutical therapy for palliation of bone pain from osseous metastases. *J Nucl Med* 2004; 45(8):1358–1365.
- Lambert B, de Klerk JM. Clinical applications of 188Re-labelled radiopharmaceuticals for radionuclide therapy. *Nucl Med Commun* 2006; 27(3):223–229.
- Lewington VJ. Cancer therapy using bone-seeking isotopes. *Phys Med Biol* 1996; 41(10):2027–2042.
- Ferro-Flores G, Arteaga de Murphy C. Pharmacokinetics and dosimetry of (188)Re-pharmaceuticals. *Adv Drug Deliv Rev* 2008; 60(12):1389–1401.
- Kavakli K, Aydogdu S, Taner M, et al. Radioisotope synovectomy with rhenium-186 in haemophilic synovitis for elbows, ankles and shoulders. *Haemophilia* 2008;14(3):518–523.
- Bucerius J, Wallny T, Brackmann HH, et al. Rhenium-186 hydroxyethylidenediphosphonate (186Re HEDP) for the treatment of hemophilic arthropathy: first results. *Clin J Pain* 2007;23(7): 612–618.
- Döbert N, Martin H, Kranert WT, et al. Re-186 HEDP conditioning therapy in patients with advanced acute lymphoblastic leukemia before allogeneic bone marrow transplantation. *Clin Nucl Med* 2003;28(9):738–742.
- Rodriguez V, Anderson PM, Litzow MR, et al. Marrow irradiation with high-dose 153Samarium-EDTMP followed by chemotherapy and hematopoietic stem cell infusion for acute myelogenous leukemia. *Leuk Lymphoma* 2006;47(8): 1583–1592.
- Rodriguez V, Erlandson L, Arndt CA, et al. Low toxicity and efficacy of (153)samarium-EDTMP and melphalan as a conditioning regimen for secondary acute myelogenous leukemia. *Pediatr Transplant* 2005;9(1):122–126.
- Luo TY, Tang IC, Wu YL, et al. Evaluating the potential of 188Re-SOCTA-trastuzumab as a new radioimmunoagent for breast cancer treatment. *Nucl Med Biol* 2009;36(1):81–88.
- Casacó A, López G, García I, et al. Phase I single-dose study of intracavitary-administered nimotuzumab labeled with 188 Re in adult recurrent high-grade glioma. *Cancer Biol Ther* 2008;7(3):333–339.
- Torres-Garcia E, Ferro-Flores G, Arteaga de Murphy C, et al. Biokinetics and dosimetry of 188Re-anti-CD20 in patients with non-Hodgkin's lymphoma: preliminary experience. *Arch Med Res* 2008;39(1):100–109.
- Fani M, Xanthopoulos S, Archimandritis SC, et al. Biodistribution and scintigraphic studies of 153Sm-labeled anti-CEA monoclonal antibody for radioimmunoscintigraphy and radioimmunotherapy. *Anticancer Res* 2003;23(3A):2195–2199.
- Bodei L, Lam M, Chiesa C, et al. EANM procedure guideline for treatment of refractory metastatic bone pain. *Eur J Nucl Med Mol Imaging* 2008;35(10):1934–1940.
- Silberstein EB, Taylor AT Jr. EANM procedure guidelines for treatment of refractory metastatic bone pain. *Eur J Nucl Med Mol Imaging* 2003;30(3):BP7–BP11.
- Kraeber-Bodere F, Campion L, Rousseau C, et al. Treatment of bone metastases of prostate cancer with strontium-89 chloride: efficacy

in relation to the degree of bone involvement. *Eur J Nucl Med* 2000;27(10):1487-1493.

30. Gkialas I, Iordanidou L, Galanakis I, et al. The use of radioisotopes for palliation of metastatic bone pain. *J BUON* 2008;13(2):177-183.

31. Tu SM, Kim J, Pagliaro LC, et al. Therapy tolerance in selected patients with androgen-independent prostate cancer following strontium-89 combined with chemotherapy. *J Clin Oncol* 2005;23(31):7904-7910.

32. Zafeirakis A. Can response to palliative treatment with radiopharmaceuticals be further enhanced? *Hell J Nucl Med* 2009;12(2):151-157.

33. Lin A, Ray ME. Targeted and systemic radiotherapy in the treatment of bone metastasis. *Cancer Metastasis Rev* 2006;25(4):669-675.

34. Farhanghi M, Holmes RA, Volkert WA, et al. Samarium-153-EDTMP: pharmacokinetic, toxicity and pain response using an escalating dose schedule in treatment of metastatic bone cancer. *J Nucl Med* 1992;33(8):1451-1458.

35. De Klerk JM, Zonnenberg BA, Blijham GH, et al. Treatment of metastatic bone pain using the bone seeking radiopharmaceutical Re-186-HEDP. *Anticancer Res* 1997;17(3B):1773-1777.

36. Collins C, Eary JF, Donaldson G, et al. Samarium-153-EDTMP in bone metastases of hormone refractory prostate carcinoma: a phase I/II trial. *J Nucl Med* 1993;34(11):1839-1844.

37. Taylor AJ Jr. Strontium-89 for the palliation of bone pain due to metastatic disease. *J Nucl Med* 1994;35(12):2054.

38. Blake GM, Zivanovic MA, Blaquiére RM, et al. Strontium-89 therapy: measurement of absorbed dose to skeletal metastases. *J Nucl Med* 1988;29(4):549-557.

39. Dafermou A, Colamussi P, Giganti M, et al. A multicentre observational study of radionuclide therapy in patients with painful bone metastases of prostate cancer. *Eur J Nucl Med* 2001;28(7):788-798.

40. Windsor PM. Predictors of response to strontium-89 (Metastron) in skeletal metastases from prostate cancer: report of a single centre's 10-year experience. *Clin Oncol (R Coll Radiol)* 2001;13(3):219-227.

41. Eary JF, Collins C, Stabin M, et al. Samarium-153-EDTMP biodistribution and dosimetry estimation. *J Nucl Med* 1993;34(7):1031-1036.

42. Robinson RG, Preston DF, Schiefelbein M, et al. Strontium 89 therapy for the palliation of pain due to osseous metastases. *JAMA* 1995;274(5):420-424.

43. Sciuto R, Tofani A, Festa A, et al. Platinum compounds as radiosensitizers in strontium-89 metabolic radiotherapy. *Clin Ther* 1998;149(921):43-47.

44. Tu SM, Millikan RE, Mengistu B, et al. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial. *Lancet* 2001;357(9253):336-341.

45. Amato RJ, Hernandez-McClain J, Henary H. Bone-targeted therapy: phase II study of strontium-89 in combination with alternating weekly chemohormonal therapies for patients with advanced androgen-independent prostate cancer. *Am J Clin Oncol* 2008;31(6):532-538.

46. Lewington VJ. Bone-seeking radionuclides for therapy. *J Nucl Med* 2005;46(suppl 1):385-475.

47. Storto G, Klain M, Paone G, et al. Combined therapy of Sr-89 and zoledronic acid in patients with painful bone metastases. *Bone* 2006;39(1):35-41.

48. Lam MG, Dahmane A, Stevens WH, et al. Combined use of zoledronic acid and 153Sm-EDTMP in hormone-refractory prostate cancer patients with bone metastases. *Eur J Nucl Med Mol Imaging* 2008;35(4):756-765.

49. Marcus CS, Saeed S, Mlikotic A, et al. Lack of effect of a bisphosphonate (pamidronate disodium) infusion on subsequent skeletal uptake of Sm-153 EDTMP. *Clin Nucl Med* 2002;27(6):427-430.

50. Lam MG, de Klerk JM, Zonnenberg BA. Treatment of painful bone metastases in hormone-refractory prostate cancer with zoledronic acid and samarium-153-ethylenediaminetetraethylphosphonic acid combined. *J Palliat Med* 2009;12(7):649-651.

51. Tu SM, Lin SH, Podoloff DA, et al. Multimodality therapy: bone-targeted radioisotope therapy of prostate cancer. *Clin Adv Hematol Oncol* 2010;8(5):341-351.

52. Fuster D, Herranz D, Vidal-Sicart S, et al. Usefulness of strontium-89 for bone pain palliation in metastatic breast cancer patients. *Nucl Med Commun* 2000;21(7):623-626.

53. Turner SL, Gruenewald S, Spry N, et al. Less pain does equal better quality of life following strontium-89 therapy for metastatic prostate cancer. *Br J Cancer* 2001;84(3):297-302.

54. Ashayeri E, Omogbehin A, Sridhar R, et al. Strontium 89 in the treatment of pain due to diffuse osseous metastases: a university hospital experience. *J Natl Med Assoc* 2002;94(8):706-711.

55. Zorga P, Birkenfeld B. Strontium-89 in palliative treatment of painful bone metastases. *Ortop Traumatol Rehabil* 2003;5(3):369-373.

56. Baczyk M, Milecki P, Baczyk E, et al. The effectiveness of strontium 89 in palliative therapy of painful prostate cancer bone metastases. *Ortop Traumatol Rehabil* 2003;5(3):364-368.

57. Gunawardana DH, Lichtenstein M, Better N, et al. Results of strontium-89 therapy in patients with prostate cancer resistant to chemotherapy. *Clin Nucl Med* 2004;29(2):81-85.

58. Liepe K, Kotzerke J. A comparative study of 188Re-HEDP, 186Re-HEDP, 153Sm-EDTMP and 89Sr in the treatment of painful skeletal metastases. *Nucl Med Commun* 2007;28(8):623-630.

59. Ma YB, Yan WL, Dai JC, et al. Strontium-89: a desirable therapeutic for bone metastases of prostate cancer [in Chinese]. *Zhonghua Nan Ke Xue* 2008;14(9):819-822.

60. Serafini AN, Houston SJ, Resche I, et al. Palliation of pain associated with metastatic bone cancer using samarium-153 leixidronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol* 1998;16(4):1574-1581.

61. Tian JH, Zhang JM, Hou QT, et al. Multicentre trial on the efficacy and toxicity of single-dose samarium-153-ethylene diamine tetramethylene phosphonate as a palliative treatment for painful skeletal metastases in China. *Eur J Nucl Med* 1999;26(1):2-7.

62. Dolezal J. Systemic radionuclide therapy with samarium-153-EDTMP for painful bone metastases. *Nucl Med Rev Cent East Eur* 2000;3(2):161-163.

63. Wang RF, Zhang CL, Zhu SL, et al. A comparative study of samarium-153-ethylenediaminetetraethylphosphonic acid with pamidronate disodium in the treatment of patients with painful metastatic bone cancer. *Med Princ Pract* 2003;12(2):97-101.

64. Sapienza MT, Ono CR, Guimaraes MI, et al. Retrospective evaluation of bone pain palliation after samarium-153-EDTMP therapy. *Rev Hosp Clin Fac Med Sao Paulo* 2004;59(6):321-328.

65. Etchebehere EC, Pereira Neto CA, Lima MC, et al. Treatment of bone pain secondary to metastases using samarium-153-EDTMP. *Sao Paulo Med J* 2004;122(5):208-212.

66. Sartor O, Reid RH, Hoskin PJ, et al. Samarium-153-leixidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology* 2004;63(5):940-945.

67. Tripathi M, Singhal T, Chandrasekhar N, et al. Samarium-153 ethylenediamine tetramethylene phosphonate therapy for bone pain palliation in skeletal metastases. *Indian J Cancer* 2006;43(2):86-92.

68. Dolezal J, Vizda J, Odrázka K. Prospective evaluation of samarium-153-EDTMP radionuclide treatment for bone metastases in patients with hormone-refractory prostate cancer. *Urol Int* 2007;78(1):50-57.

69. Ripamonti C, Fagnoni E, Campa T, et al. Incident pain and analgesic consumption decrease after samarium infusion: a pilot study. *Support Care Cancer* 2007;15(3):339-342.

Radiopharmaceuticals: Present and Future

Bradley J. Atkinson, PharmD; and Shi-Ming Tu, MD

Commentary on “Radiopharmaceuticals: When and How to Use Them to Treat Metastatic Bone Pain” by Paes et al. (page 197)

In cancer patients, bone metastasis is a common complication, with the highest prevalence among breast and prostate cancer patients.¹ Pain is one of the most feared and debilitating cancer-related symptoms, with an incidence of 62%–86%.² Pain related to bone metastases constitutes the most frequent type of pain. The objectives of treating bone metastases are to palliate pain, improve quality of life, prolong pain-free survival, and eradicate tumor cells in the bone. Traditional treatment approaches include external beam radiation, orthopedic intervention, chemotherapy, hormone therapy, bisphosphonates, steroids, and radiopharmaceuticals.³

Radiopharmaceutical treatment of metastatic bone pain has been in practice for more than three decades. Currently, three radiopharmaceuticals are approved by the US Food and Drug Administration for the treatment of painful bone metastasis: samarium-153 lexidronam (Sm-153), strontium-89 chloride (Sr-89), and phosphorus-32 (P-32).⁴ Rhenium-186 (Re-186) is widely used in Europe, and Re-188 is a promising investigational agent. P-32 has not been commonly used since the 1980s because of bone marrow toxicity. Radiopharmaceuticals have unique properties such as half-life, radiation energy, and tissue penetration that are associated with the onset of response, duration, and toxicity. Myelosuppression is the most common toxicity, which is often limited and reversible; this makes repetitive dosing practical, especially with short half-life radioisotopes. Several studies have

demonstrated the palliative efficacy of radiopharmaceuticals, with similar overall reported pain response rates of 60%–90%.⁵

Radiopharmaceuticals have had relatively limited use in the oncology setting despite the overwhelming prevalence of metastatic bone pain, decades of clinical experience, and demonstrated efficacy with limited toxicity. Typically, physicians do not consider radiopharmaceuticals until several other treatment regimens have failed. Patients at this point may have developed low bone marrow reserve, consequently limiting the use of radiopharmaceuticals. In addition, physicians may be hesitant to give a marrow-toxic agent for pain relief because it might prohibit later cytotoxic therapies. The review “Radiopharmaceuticals: When and How to Use Them to Treat Metastatic Bone Pain” by Paes and colleagues addresses several of these misconceptions that hinder the use of radiopharmaceuticals. In addition, it addresses patient selection, monitoring, and areas of uncertainty including concomitant therapy with chemotherapy or bisphosphonates.

Accumulating evidence suggests that radiopharmaceuticals may not only provide palliative benefit but also improve clinical outcomes such as overall (OS) and progression-free survival (PFS), possibly by modulating the onco-niche.⁶ Tu and colleagues⁷ conducted the first study that demonstrated both improved clinical outcomes and palliative benefits in patients with metastatic castrate-resistant prostate cancer. The patients were treated with doxorubicin and Sr-89, and achieved a significant improvement in OS compared to doxorubicin alone. Recent studies by Amato et al⁸ and Fizazi et al⁹ with alternative chemotherapy regimens and radiopharmaceuticals have demonstrated similar improved PFS and OS. Randomized phase III trials to confirm these results are ongoing.

The foundation of radiopharmaceuticals in the treatment of metastatic bone pain for palliative benefits is well established. Physicians should not relegate radiopharmaceuticals to a

Drs. Atkinson and Tu are from the Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas.

Correspondence to: Shi-Ming Tu, MD, Department of Genitourinary Medical Oncology, Unit 1374, The University of Texas MD Anderson Cancer Center, P.O. Box 301439, 1155 Pressler Street, Houston, TX 77230-1439; telephone: (713) 563-7268; fax: (713) 745-1625; e-mail: stu@mdanderson.org

J Support Oncol 2011;9:206–207
doi:10.1016/j.suonc.2011.06.005

© 2011 Elsevier Inc. All rights reserved.

treatment of last resort but should incorporate them into their multimodality treatment armamentarium. Further studies are needed to establish the palliative and potential clinical benefits of radiopharmaceuticals with concomitant chemotherapy and bisphosphonates, in addition to new therapies such as RANK ligand inhibitors and antiangiogenic agents.

Conflicts of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

References

PubMed ID in brackets

1. Lam MG, de Klerk JM, van Rijk PP, et al. Bone seeking radiopharmaceuticals for palliation of pain in cancer patients with osseous metastases. *Anticancer Agents Med Chem* 2007;7(4):381–397.
2. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, et al. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007;18(9):1437–1449.
3. Theriault RL, Biermann JS, Brown E, et al. NCCN Task Force Report. Bone health and cancer care. *J Natl Compr Canc Netw* 2006;4(suppl 2):S1–S20; quiz S21–S2.
4. Pandit-Taskar N, Batraki M, Divgi CR. Radiopharmaceutical therapy for palliation of bone pain from osseous metastases. *J Nucl Med* 2004;45(8):1358–1365.
5. Paes FM, Serafini AN. Systemic metabolic radiopharmaceutical therapy in the treatment of metastatic bone pain. *Semin Nucl Med* 2010;40(2):89–104.
6. Tu SM, Lin SH, Podoloff DA, et al. Multimodality therapy: bone-targeted radioisotope therapy of prostate cancer. *Clin Adv Hematol Oncol* 2010;8(5):341–351.
7. Tu SM, Millikan RE, Mengistu B, et al. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial. *Lancet* 2001;357(9253):336–341.
8. Amato RJ, Hernandez-McClain J, Henary H. Bone-targeted therapy: phase II study of strontium-89 in combination with alternating weekly chemohormonal therapies for patients with advanced androgen-independent prostate cancer. *Am J Clin Oncol* 2008;31(6):532–538.
9. Fizazi K, Beuzeboc P, Lumbroso J, et al. Phase II trial of consolidation docetaxel and samarium-153 in patients with bone metastases from castration-resistant prostate cancer. *J Clin Oncol* 2009;27(15):2429–2435.

Radiopharmaceuticals for Painful Bone Metastases: Perspective from Radiation Oncology

Elizabeth A. Barnes, MD, FRCP(C)

Commentary on “Radiopharmaceuticals: When and How to Use Them to Treat Metastatic Bone Pain” by Paes et al. (Page 197).

Cancer-related bone pain is a significant cause of morbidity and reduces quality of life for patients with bone metastases. Management should be conducted in a multidisciplinary setting with a multimodality approach. Radionuclides are an effective treatment option for patients with multifocal osteoblastic metastases, which are typically seen in patients with prostate cancer. Radionuclides can be given on an outpatient basis with simple radioactive precautions and do not require a visit to a radiotherapy center. However, the use of radiopharmaceuticals has been consistently reported as underutilized in the literature. Reasons for underutilization include lack of knowledge and awareness by community practitioners, misconceptions on the toxicity of treatment, and lack of health policy support.¹ There is worry about delayed myelosuppression preventing administration of chemotherapy. In addition, radionuclides are usually administered by nuclear medicine physicians, who are not involved in the direct clinical care of cancer patients.

Paes and colleagues provide a useful and informative review on the indications, selection criteria, efficacy, and toxicity of radionuclides, with details on strontium and samarium, the two most common radionuclides in clinical use in the United States. Radionuclides are often used as an alternative to external beam radiotherapy (EBRT), when several sites of painful osteoblastic metastases are present in a distribution greater than that which can be conveniently or safely treated with localized EBRT. The use of hemibody radiotherapy, which can also

target widespread bone disease, has largely fallen out of favor in the developed world due to worries about acute and late toxicity. The ASTRO evidence-based guidelines on palliative radiotherapy for bone metastases have recently been published.² They recognize that radionuclides are an important and often underused treatment option, as well as mention that their use does not obviate the need for EBRT. The guidelines state that additional prospective studies should address the prophylactic use of systemic radionuclides in patients with limited bone metastases as well as the possible combination of radionuclides with other systemic agents such as bisphosphonates or chemotherapy.

Paes and colleagues explore the possible role of chemotherapy as a radiosensitizer and present evidence that there is no biological competition between bisphosphonates and radionuclides so that both can be used in clinical practice. Moving beyond pain palliation, the authors advocate for the use of radionuclides early in the disease while marrow reserves are still high and where there may be a theoretical benefit of targeting subclinical disease and improving patient outcomes. A phase II trial suggested that in patients with advanced prostate cancer, the addition of radionuclides to systemic chemotherapy would improve survival.³

Using radionuclides for retreatment when normal tissue tolerance prevents repeat EBRT is also an area that has not been explored in prospective trials. The currently open NCIC SC20/RTOG 0433 trial randomizes between single and multiple fractions of local EBRT in the retreatment of painful bone metastases;⁴ however, a third course of EBRT is not usually possible due to concerns of normal tissue late toxicity. It would be very interesting to know the efficacy of radionuclides in this clinical situation.

In summary, there are many exciting questions that need to be answered to optimize the timing of radionuclide administration and its integration into management of metastatic bone disease. This article provides a welcome review on this topic with

Dr. Barnes is from the Department of Radiation Oncology, Odette Cancer Centre, Toronto, Canada.

Correspondence to: Elizabeth A. Barnes, MD, FRCP(C), Department of Radiation Oncology, Odette Cancer Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N3M5; telephone: (416) 480-4951; fax: (416) 480-6002; e-mail: toni.barnes@sunnybrook.ca

J Support Oncol 2011;9:208–209
doi:10.1016/j.suponc.2011.06.006

© 2011 Elsevier Inc. All rights reserved.

the goal of optimizing outcomes and quality care for patients with bone metastases.

Conflicts of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

References

PubMed ID in brackets

1. Damerla V, Packianathan S, Boerner PS, et al. Recent developments in nuclear medicine in the management of bone metastases: a review and perspective. *Am J Clin Oncol* 2005;28(5):513–520.
2. Lutz S, Berk L, Chang E, et al. American Society for Radiation Oncology (ASTRO). Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011;79(4):965–976.
3. Tu SM, Millikan RE, Mengistu B, et al. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial. *Lancet* 2001;357(9253):336–341.
4. ClinicalTrials.gov, Single-fraction compared with multiple-fraction therapy in treating patients with previously irradiated painful bone metastases, <http://clinicaltrials.gov/ct2/show/NCT00080912>.

Coordination of Care in Breast Cancer Survivors: An Overview

Kimberly S. Peairs, MD; Antonio C. Wolff, MD, FACP; Sharon J. Olsen, PhD; Elissa T. Bantug, MHS; Lillie Shockney, RN, BS, MAS; Melinda E. Kantsiper, MD; Elisabeth Carrino-Tamasi, MSW, LGSW; and Claire F. Snyder, PhD

Abstract

The number of breast cancer survivors in the United States is increasing. With longer survival, there has been an increase in the complexity and duration of posttreatment care. Multidisciplinary care teams are needed to participate across the broad spectrum of issues that breast cancer survivors face. In this setting, the need for well-established patterns of communication between care providers is increasingly apparent. We have created a multidisciplinary approach to the management of breast cancer survivors to improve communication and education between providers and patients. This approach could be extended to the care and management of survivors of other types of cancer.

Case

A 65-year-old woman with stage II breast cancer, mild hypertension, and obesity recently completed treatment for her estrogen/progesterone receptor-positive, HER 2-negative breast cancer. She was treated with lumpectomy, radiation therapy, and adjuvant chemotherapy with doxorubicin and cyclophosphamide followed by paclitaxel. She remains on an aromatase inhibitor and is experiencing arthralgias, numbness in her extremities, fatigue, and apprehension about cancer recurrence. She has not seen her primary care physician since the start of her cancer treatment but is concerned that her "heart" and bones may be affected by her therapy.

Scope of the Challenge

As of January 2007, the National Cancer Institute estimated that there are 11.7 million cancer survivors in the United States, which represents approximately 4% of the population. Breast cancer survivors comprise the largest proportion

at 22% of all survivors; and with the aging of the general population, the majority of breast cancer survivors are currently 65 years of age or older.¹ As these numbers expected to grow in the next decade, attention has turned toward the care of this group of patients. These patients, many having completed local and adjuvant cancer treatment with no evidence of recurrent cancer, present a unique set of health-care issues.² Often, they are faced with long-term and/or late-onset physical and psychosocial effects from their cancer and its treatment. They may also suffer from chronic comorbid conditions, such as hypertension or diabetes, that are not actively addressed during their acute cancer treatment. The path which leads the patient to the next step of their medical journey, transitioning from active cancer treatment to posttreatment care, is not always clear to the patient or the practitioners involved.

In 2006, the Institute of Medicine's (IOM) report *From Patient to Cancer Survivor: Lost in Transition* acknowledged and outlined the gaps in comprehensive and coordinated care for these patients as well as the complexity of their care.³ In addition to increasing the awareness of the consequences of cancer and its treatment, the report identified several areas that were considered "essential components" of survivorship care. These include prevention and surveillance for new or recurrent cancers, treatment of long-term

Dr. Peairs is from the Johns Hopkins School of Medicine, Baltimore, Maryland.

Dr. Wolff is from the Johns Hopkins School of Medicine, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland.

Dr. Olsen is from the Johns Hopkins School of Nursing, Baltimore, Maryland.

Dr. Bantug is from the Johns Hopkins School of Medicine, Baltimore, Maryland.

Dr. Shockney is from the Johns Hopkins School of Medicine, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland.

Dr. Kantsiper is from the Johns Hopkins School of Medicine, Baltimore, Maryland.

Dr. Carrino-Tamasi is from the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland.

Dr. Snyder is from the Johns Hopkins School of Medicine, Baltimore, Maryland.

Manuscript submitted March 3, 2011; accepted June 18, 2011.

Correspondence to: Kimberly S. Peairs, MD, Assistant Professor of Medicine, Division of General Internal Medicine, The Johns Hopkins School of Medicine, Suite 325, 10753 Falls Road, Lutherville, MD 21093; telephone: (410) 583-2774, ext. 8; fax: (410) 583-2883; e-mail: kpeairs@jhmi.edu

J Support Oncol 2011;9:210-215 © 2011 Elsevier Inc. All rights reserved. doi:10.1016/j.suponc.2011.06.008

Table 1**Components of Care for Cancer Survivors³**

1. Surveillance for recurrence of cancer
2. Surveillance and treatment of long-term and late effects of cancer treatment
3. Screening and prevention for second cancers
4. Assessment of psychosocial issues
5. Care of comorbid conditions
6. Preventative health including immunizations, diet, and exercise
7. Coordination between care providers

and late effects of cancer treatment, and coordination of care between oncology care providers and primary care providers (Table 1). The importance of patient and provider education and communication was highlighted as a means to enhance the transition phase from acute cancer treatment to long-term health. However, many hurdles exist in the present health-care structure, often making the delivery of optimal care for these patients difficult.

For a variety of reasons, the care of the breast cancer survivor no longer singularly can fall into the hands of the oncologist. With the aging population and increase in cancer survivors, the demand for oncologists will continue to increase at a much higher pace than the number of oncologists available.⁴ In order to continue to evaluate newly diagnosed cancer patients, oncologists must partner with other health-care providers to manage the cancer survivor. Surveillance, Epidemiology, and End Results (SEER)–Medicare analyses on patterns of preventive care among breast cancer survivors have shown that breast cancer survivors observed by both a primary care practitioner and oncology specialist are more likely to receive appropriate care,^{5,6} supporting the integration of practitioners for improving outcomes. The patient-centered medical home model has been proposed as an approach to improve the quality and cost of health care by enhancing communication. In this primary care physician (PCP)–led initiative, there is to be coordinated, evidence-based care between health-care professionals, with patient involvement.^{7,8} Breast cancer survivorship care could be enhanced if this type of model is effective; however, improved coordination will require clarification of each practitioner's role in care provision.

Patients and practitioners have concerns about the present communication between providers. In a survivor/physician survey, there were differences in expectations of care delivery between patients and their physicians as well as between PCPs and oncologists,⁹ with PCPs expecting more involvement in survivorship care than patients had perceived. Both PCPs and oncologists felt they should be prominently involved in cancer surveillance and screening as well as preventive health care, making it less clear who was to complete the task. In a cross-sectional survey of breast cancer patients, while survivors' perceived confidence in PCPs' survivorship care increased with the frequency of office visits, most patients felt the communication between PCPs and oncologists was poor.¹⁰ Similarly, many PCPs consider the transfer of care

and information provided from the treating oncologist as fair or poor.^{11–13}

Primary care providers may also have reservations about survivorship care and about their ability to successfully integrate care for an already complex medical patient. In a survey of community- and academically based internal medicine physicians, 47% of respondents lacked formal training in cancer survivorship and felt inadequately prepared. Eighty-two percent felt that primary care guidelines for adult cancer survivors were not well defined.¹³ Despite this uncertainty, there is evidence suggesting that noncancer physicians are able to deliver appropriate long-term care to breast cancer survivors. Studies by Grunfeld et al.¹⁴ comparing PCP follow-up with oncologist follow-up of survivors of early-stage breast cancer in Canada demonstrated no difference in recurrence-related serious clinical events or health-related quality of life. Patient satisfaction was better and health service costs were lower with PCP delivery of long-term follow-up.^{15,16}

A specific recommendation of the IOM report to improve the transition period for the cancer survivor is the completion of a comprehensive care summary and follow-up plan termed a "Survivorship Care Plan."³ The goals of a treatment summary should be to improve communication between care providers as well as to serve as educational material for future care of the breast cancer survivor by all providers. It should involve a written consolidation of the cancer treatment history with specifics on cancer type, surgeries, radiation treatment, chemotherapy, as well as any additional therapy planned. The physicians involved in the patient's care and their contact information should be included to streamline communication. The survivorship care plan would be an individualized assessment of the posttreatment and long-term effects of the cancer treatment.^{17–19} A care-plan template proposed by the American Society of Clinical Oncology includes follow-up care testing recommendations for care provider visit frequency, mammography, breast exam, pelvic examination, and genetic counseling. It also addresses the importance of coordination of care between providers to clarify appropriate follow-up. Available evidence-based clinical practice guidelines should be reviewed and shared with other health-care providers involved in the patient's care. The care plan should delineate responsibilities of all care providers in an effort to facilitate seamless coordination and communication. The timing of the completion of a care summary may be patient-dependent but often occurs at a point when surgery, chemotherapy, and/or radiation are completed. Some have suggested that these discussions occur during a dedicated clinic visit or some other protected time.

In addition to reviewing and documenting the patient's cancer treatment and coordinating health-care providers, this visit or protected time is an opportunity to refocus the patient on other health-care issues. Often, comorbidities are an afterthought to patients and practitioners during cancer treatment, but the implications can be just as serious. Recent studies of postmenopausal breast cancer survivors show higher risks of death from cardiovascular disease than from breast

cancer,^{20,21} especially for those diagnosed with early-stage breast cancer. Obesity and diabetes have also been linked to worse outcomes in breast cancer patients.^{22,23} Other known or newly-identified comorbidities should be discussed to ensure a follow-up care plan is in place and routine preventative health measures such as exercise, diet, immunizations, and cancer screening are reviewed.

Optimizing Care Delivery

In addition to instituting a care plan and treatment summary, the relationship between treating providers should be examined. The most common model that exists in practice is that in which a newly diagnosed cancer patient's care is assumed by an oncologist during the active treatment phase and years thereafter for monitoring of recurrence or long-term side effects of therapy. The role of the PCP is unclear during this time, and the dissemination of treatment information is limited. While oncologists are trained in internal medicine, the noncancer medical issues of the patient may be given lower priority. After acute cancer treatment is completed, the role of the PCP may still be unclear. Patients may feel an intense relationship with their oncologists and express anxiety about leaving their care. PCPs may not receive enough information regarding the cancer patient's treatment course and long-term cancer-related side effects.¹²

A shared-care model of health-care delivery involves a more coordinated effort between practitioners with regard to communication and delineation of responsibilities and has been proposed as a model that may enhance survivorship care for breast cancer patients.²⁴ In this model, the roles of the oncologist and the PCP would be clarified and complement one another. At the time of cancer diagnosis, the primary responsibilities for treatment would be with the oncologist but the management of comorbid illnesses and health maintenance would be handled by the PCP. Primary responsibility for patient care would then shift back to the PCP at a transition point in the patient's cancer care. The oncologist's role would entail short- and mid-term surveillance of cancer, treatment of acute- and short-term complications, and screening for second cancers. The primary care domain would involve preventive services, screening for second cancers, long-term surveillance, and treatment of long-term complications. Implicit in the shared-care model is ongoing exchange of information between care providers with the oncologist available and accessible for consults and dissemination of new surveillance recommendations or information on long-term side effects from treatments.

Completion and utilization of a cancer treatment summary and survivorship care plan could be a pivotal accessory for the physical and psychological transfer of care responsibilities between practitioners. However, the timing and completion of the document may be more complex. A risk-stratified approach for the timing of transition has been implemented for the care of pediatric cancer survivors and involves an individualized assessment for risk of recurrence or late effects as well as patient preferences.²⁵ A similar model for breast

cancer survivors could be employed with those having the lowest risk of cancer-related health problems transitioning at the completion of active treatment and patients with a higher risk of side effects or recurrence remaining closely linked with their cancer care provider but having continued involvement of their PCP.²⁴

Models of Care

The mechanism to complete survivorship care plans and optimize the shared-care model for cancer survivors may depend on the resources available. At large academic centers there often exist many resources for cancer survivors, but coordinating their efforts may be difficult. The use of electronic health records can improve communication between providers within an institution and may help facilitate the transfer of information beyond a single care setting.

Models of survivorship care are evolving within programs designed to utilize the expertise of multidisciplinary teams to deliver or coordinate long-term care for the cancer survivor.²⁴ The first model of long-term cancer survivorship care originates from the pediatric cancer survivor population. These programs typically follow the pediatric cancer survivor longitudinally and are comprised of a team of practitioners, including an oncologist, and often coordinated by an oncology nurse practitioner. They may also utilize pediatric and adult medicine specialists, social workers, and psychologists.²⁶ Annual visits include surveillance for recurrence, evaluation of long-term side effects, counseling for symptom management, and patient education.

From this paradigm, some cancer centers are developing programs that involve the survivorship care of multiple cancer groups and are more diverse than the pediatric survivorship population. The unifying goal is to bring physicians, nurses, social workers, mental health-care providers, and other relevant experts in cancer survivorship together to maximize the available services for the cancer survivor. Within these programs, various care-delivery patterns exist, such as that of a one-time consultative visit with a practitioner with survivorship expertise in which the cancer treatment summary and care plan are completed.

Another type of care is a survivorship clinic led by a nurse practitioner. Here, cancer patients who have completed acute treatment are followed for a period of time by the nurse practitioner with cancer expertise and then transitioned back to their PCP, with the nurse practitioner acting as the liaison in the shared-care model to maximize support of long-term care.

A third type of care delivery for comprehensive survivorship programs is similar to the pediatric long-term follow-up clinic and entails a multidisciplinary team of care providers involved in the assessment of the patient's needs, including oncology nurse experts, mental health-care providers, social workers, physical therapists, oncologists, and consultants. Physicians, sometimes nononcologists, who are not involved in active treatment assume the role of survivorship care and long-term follow-up.

Other centers have chosen to focus efforts on disease-specific survivorship programs, coordinating efforts of disciplines relevant to treatment issues and side effects of an individual cancer such as breast cancer. These often serve as the springboard to coordinate larger survivorship initiatives within an institution.

How We Do It

At our institution, the evolution of the care delivery for breast cancer survivors has involved a multidisciplinary team identifying distinct areas of need for improvement in implementing survivorship care. We established a collaborative relationship across the schools of nursing, medicine, and public health and received funding from Susan G. Komen of Maryland to develop a multifaceted program. Our working group consists of a breast oncologist, general internists, advanced-practice oncology nurses, social worker, breast cancer survivors, and researchers with expertise in nursing and health-care outcomes. Goals for improving the transition of care for breast cancer survivors included implementing a multidisciplinary approach to survivorship care planning and education of survivors and care providers.

The development of risk-adjusted individualized care strategies was paramount to coordination of care between oncology providers including medical oncologists, surgeons, and radiation oncologists, as well as identifying the appropriate time to initiate a transition of care. This approach was developed to avoid overlap of care services between oncology providers and to offer a guide for practitioners and patients on care expectations. Development of these strategies was complicated by varying expectations from the oncology practitioners and their desire for continued follow-up for even low-risk patients. Provider expectations and concerns regarding survivorship care delivery were clarified through focus groups conducted with patients, oncologists, and PCPs.¹² The limitations of the use of established survivorship care plan templates were identified and led to modifications that would be piloted.

Educational endeavors for stakeholders involved in optimizing breast cancer survivorship care were developed. A Web site was created for patients as well as practitioners, addressing issues such as symptom management, follow-up care, survivorship care planning, side effects of therapy, reducing risk of recurrence, fertility issues, and genetic counseling. Videos of breast cancer survivors discussing their experiences are accessible on the site, and further patient specific-materials were developed to complement the summary care plan.²⁷ Within the school of nursing, an oncology student interest group was established with a focus on lectures promoting cancer survivorship issues. Several nursing initiatives to increase the exposure of students to breast cancer survivor issues were implemented, including clinical placements in oncology settings. To increase the awareness of PCPs and oncology providers to the unique needs of breast cancer survivors, a wide range of educational seminars were given at the local and national levels. These included multidisciplinary panel presentations involving advanced nurse

specialists, internists, oncologists, gynecologists, and a health services researcher.

The timing, content, and method of a transition experience from acute oncology treatment to long-term follow-up care and coordination with primary care was determined by several factors at our institution. Practitioner availability, location, and reimbursement parameters factored into the development of our care model. Many of our clinical resources are not physically or operationally centralized, and simplifying this for patients was a consideration. The model in existence had breast cancer survivors maintaining a long-term relationship with either their oncologist or an oncology nurse practitioner with little coordination of care between nononcology providers for long-term survivorship issues or general medical health care. There existed no formalized mechanism to institute a transition visit or complete a survivorship care plan.

Initially, and during the piloting phase of the cancer survivorship care plan template, we envisioned the transition visit would be best handled between the oncology physician and patient. The presumed benefits would be the familiarity of the relationship and the physician's knowledge of cancer treatment. The appropriate timing would be determined based on the individual's risk of recurrence and comfort with transition. Practitioners, while supportive of the concept of the visit and coordination of care, found it difficult to utilize the oncology appointment solely for this purpose and found the completion of the care summary time-consuming.

We tested a model for referral of patients who were completing the active treatment phase to an internal medicine provider with experience in breast cancer survivorship care for a consultative one-time evaluation. The physician was linked with oncology providers by an electronic medical record facilitating the review of prior cancer treatment but was in a separate clinical care area. Benefits of this approach were the psychological and physical shift of focus from acute cancer treatment to survivorship care issues. Attention to comorbid illnesses and health prevention was emphasized in addition to identification of side effects from treatment. This approach had several limitations, including practitioner availability, as many patients then wished to continue their long-term primary care with this care provider after the completion of the visit. Most important, we wanted to maintain the established relationships many patients may have had with their PCPs prior to their cancer treatment and had concerns this model might undermine those relationships. Additionally, the treatment care summaries were not being completed by a cancer care provider and the perspective of an oncology care provider was being lost. The financial feasibility of the model was also of concern as insurance reimbursements for a consultative survivorship visit delivered by a PCP were variable.

To maintain the relationship of the patient with the oncology center yet coordinate transition of long-term care to the PCP, we then considered utilizing the expertise of the oncology advanced-practice nurses (nurse practitioners and a clinical nurse specialist) embedded in the cancer center. These providers had already established relationships with

many of the breast cancer patients during their active treatment phase and were intimate with the nuances of the oncology care and symptom management. Their nursing backgrounds also included a focus on health promotion and supportive care. Our multidisciplinary group met to outline and clarify the expectations, goals, and best practices of a survivorship care transition visit for these clinicians. Integral to the mission was patient and staff education, patient self-care guidance, resource identification to address the unique physical and psychosocial referral needs of the survivors, and the development and communication of treatment summaries and survivorship care plans for PCP follow-up.

Patients are identified for the transition visit by either their breast cancer physician or oncology nurse practitioner based on an individualized risk-adjusted stratification, as well as by patient interest. A distinct appointment is made for this coordination of care visit, establishing it as a unique counseling appointment. After completion of the visit, a treatment summary and care plan are provided for the patient and her care providers. Patient-directed educational resources are also made available.

Discussion

With the growing population of breast cancer survivors, the importance of coordinated care to foster improved long-term follow-up for these patients is paramount. The IOM's report on cancer survivorship has identified gaps in care delivery and provider awareness of the issues unique to these patients. As models of care are developed, mechanisms for assessment must follow to continue to refine efforts aimed at improving care delivery and patient outcomes. In the context of our program, short-term feedback from patients completing cancer treatment summaries and survivorship care plans during the transition visit with an advanced nurse practitioner will be obtained with regard to patient expectation, achievement of stated goals, and satisfaction with the process. Educational materials will be developed as areas of further need are clarified. Similar feedback from other clinicians involved in the care of the patient will be incorporated into the process and dissemination of care plans. Our experience in developing a survivorship care model for breast cancer is paving the way for other cancer types, such as prostate and colon, that also continue to have a growing survivor population.

At our institution, the coordination of care for breast cancer survivors has demonstrated the complexities of the multidisciplinary approach to patient care. Identifying, engaging, and organizing the various stakeholders involved in care delivery can be both challenging and rewarding. Physicians' and patients' attitudes toward a shared-care model have been varied, but all agree communication between providers is essential. Patient-specific recommendations from oncologist to PCP can alleviate some of the uncertainties of care,²⁸ and summary information should be adapted to the needs of the care provider so as not to make care plans so complex that they are not practical. Clarifying the timing of a transition visit in the trajectory of breast cancer care must be individ-

ualized, and this is best accomplished by the oncology care providers. The transition of care goals should be patient-centered, with the patient's symptoms and concerns clearly identified and triaged appropriately. The utilization of advanced-practice oncology nurses to meet the multifaceted needs of the breast cancer survivor and coordinate communication between the oncology and primary care settings has been an effective model. Adequate training for these professionals in the area of cancer survivorship should be expanded and refined as more evidence-based guidelines are developed. Identification of referral bases for physical therapy, psychological support, social work, or gynecological care is necessary to expand survivorship resources.

We present our experience from a large tertiary care facility, but there are components that are adaptable to clinical care settings in the community. First, the education of oncology and noncancer practitioners on the importance and specifics of care relevant to the breast cancer survivor can be achieved through continuing medical education, Web-based educational modules, and treatment summaries with evidence-based guidelines. Limited practitioner time and availability may dictate the flexibility for survivorship visits but with the implementation of a cancer treatment summary and survivorship care plan, clinicians may engage their nononcology counterparts in a shared-care model and refocus their efforts on acute care management. Through patient education and information sharing, the cancer survivor may also better navigate the health-care system. Access to Web-based educational material for patients and providers that is developed and curated by reputable organizations, such as cancer.net by the American Society of Clinical Oncology, offers the opportunity to reach out to patients and PCPs whenever convenient.

While some of the medical or psychological implications of cancer treatment are related to the particular cancer type, many of the survivorship issues patients face are similar regardless of their specific cancer. Patients with early-stage cancers that are amenable to treatment with a curative intent and have a favorable prognosis may have few long-term oncologic needs, but appropriate screening and surveillance planning as well as assessment of long-term side effects is warranted. Similarly, patients undergoing cancer treatments that have more debilitating side effects may benefit from the multidisciplinary services identified in a survivorship program, including nutrition, physical therapy, pain management, and psychological support. While the timing or need for a transition visit may be different for other cancers, the concepts of patient education and consolidation of a treatment summary still apply as ways to enhance communication with the patients' primary care provider.

Conclusion

The patient case presented is emblematic of a course for an early-stage breast cancer survivor. She is experiencing side effects from her therapy that are common with treatments that may be managed by her oncologist or her PCP. She has

been disengaged from her PCP during her acute cancer treatment and may be unsure of who should address her physical and psychological concerns including the long-term and latent side effects that may remain. In a model of survivorship care, she could be evaluated by an oncology nurse specialist or care provider with survivorship expertise, who would identify her ongoing symptoms and put them in the context of her cancer treatment. A care plan would be devised to include appropriate follow-up with the clinicians best suited for her needs, including listing contact information of oncology providers and her PCP. Educational information in the form of printed materials and Web-site resources detailing the evaluation and treatment options for her symptoms such as neuropathy and fatigue would be provided, and consideration of referrals for other services such as physical therapy or a mental

health-care provider may be discussed. A printed copy of coordination of clinician visits, screening guidelines, and surveillance of long-term side effects from therapy that is individualized would be provided for the patient and physicians. By engaging the patient as a health advocate and improving lines of communication and education between providers, the care of breast cancer survivors will continue to improve.

Acknowledgments: This work was made possible in part by a grant from Susan G. Komen for the Cure Maryland.

Conflicts of interest: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Shockney reported receiving payment for lectures including service on speakers bureaus from ONS and for royalties from Jones & Bartlett Publishing. All other authors had no potential conflicts of interest to report.

References

PubMed ID in brackets

- National Cancer Institute. Cancer Survivorship Research. <http://cancercontrol.cancer.gov/ocs/prevalence/index.html>. Accessed February 20, 2011.
- Grunfeld E, Earle C. The interface between primary and oncology specialty care: treatment through survivorship. *J Natl Cancer Inst Monogr* 2010;40:25–30.
- Hewitt M, Greenfield S, Stovall E. *From Patient to Cancer Survivor: Lost in Transition*. Washington DC: National Academies Press; 2006.
- Erikson C, Salsberg E, Forte G, et al. Future supply and demand for oncologists: challenges to assuring access to oncology services. *J Oncol Pract* 2007;3:79–86.
- Snyder C, Frick K, Kantsiper M, et al. Prevention, screening and surveillance care for breast cancer survivors compared with controls: changes from 1998 to 2002. *J Clin Oncol* 2009;27:1054–1061.
- Snyder C, Frick K, Peairs K, et al. Comparing care for breast cancer survivors to non-cancer controls: a five-year longitudinal study. *J Gen Intern Med* 2009;24:469–474.
- Sinsky C. The patient-centered medical home neighbor: a primary care physician's view. *Ann Intern Med* 2011;154:61–62.
- Yee H. The patient-centered medical home neighbor: a subspecialty physician's view. *Ann Intern Med* 2011;154:63–64.
- Cheung W, Neville B, Cameron D, et al. Comparisons of patient and physician expectations for cancer survivorship care. *J Clin Oncol* 2009;27:2489–2495.
- Mao J, Bowman M, Stricker C, et al. Delivery of survivorship care by primary care physicians: the perspective of breast cancer patients. *J Clin Oncol* 2009;27:933–938.
- Nissen M, Beran M, Lee M, et al. View of primary care providers on follow-up care of cancer patients. *Fam Med* 2007;39:477–482.
- Kantsiper M, McDonald E, Geller G, et al. Transitioning to breast cancer survivorship: perspective of patients, cancer specialists and primary care providers. *J Gen Intern Med* 2009;24: S459–S466.
- Bober S, Recklitis C, Campbell E, et al. Caring for cancer survivors: a survey of primary care physicians. *Cancer* 2009;115:4409–4418.
- Grunfeld E, Levine M, Julian J, et al. Randomized trial for long-term follow-up for early-stage breast cancer: a comparison of family physician versus specialist care. *J Clin Oncol* 2006;24: 848–855.
- Grunfeld E, Fitzpatrick R, Mant D, et al. Comparison of breast cancer patient satisfaction with follow-up in primary care versus specialist care: results for a randomized controlled trial. *Br J Gen Pract* 1999;49:705–710.
- Grunfeld E, Gray A, Mant D, et al. Follow-up of breast cancer in primary care versus specialist care: results of an economic evaluation. *Br J Cancer* 1999;79:1227–1233.
- Ganz P, Hahn E. Implementing a survivorship care plan for patients with breast cancer. *J Clin Oncol* 2008;26:759–767.
- Grunfeld E. Optimizing follow-up after breast cancer treatment. *Curr Opin Obstet Gynecol* 2009;21:92–96.
- Khatcheressian J, Wolff A, Smith T, et al. American Society of Clinical Oncology 2006 update of breast cancer follow-up and management guidelines in the adjuvant setting. *J Clin Oncol* 2006;24:5091–5097.
- Giordano S, Hortobagyi G. Time to remove the subspecialty blinders: breast cancer does not exist in isolation. *J Natl Cancer Inst* 2008;20:230–231.
- Chapman J, Meng D, Shepherd L, et al. Competing causes of death from a randomized trial of extended adjuvant endocrine therapy for breast cancer. *J Natl Cancer Inst* 2008;20:252–260.
- Peairs K, Barone B, Snyder CF, et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. *J Clin Oncol* 2011;29:40–46.
- Ewertz M, Jensen M, Gunnarsdottir K, et al. Effect of obesity on prognosis after early-stage breast cancer. *J Clin Oncol* 2011;29:25–31.
- Oeffinger KC, McCabe MS. Models for delivering survivorship care. *J Clin Oncol* 2006;24: 5117–5124.
- Oeffinger KC, Eshelman DA, Tomlinson GE, et al. Programs for adult survivors of childhood cancer. *J Clin Oncol* 1998;16:2864–2867.
- Wallace WH, Blacklay A, Eiser C, et al. Developing strategies for long term follow-up of survivors of childhood cancer. *BMJ* 2001;323: 271–274.
- Johns Hopkins Medicine. Breast Cancer Survivor Care. http://www.hopkinsmedicine.org/avon_foundation_breast_center/treatments_services/survivor_care. Accessed February 28, 2011.
- Del Giudice E, Grunfeld E, Harvey B, et al. Primary care physicians' view of routine follow-up care of cancer survivors. *J Clin Oncol* 2009;27:3338–3345.

Documenting the Symptom Experience of Cancer Patients

Teresa L. Deshields, PhD; Patricia Potter, RN, PhD, FAAN; Sarah Olsen, RN; Jingxia Liu, PhD; and Linh Dye, DMGT

In 2010, the Centers for Disease Control and Prevention estimated that 12 million cancer survivors were living in the United States. With improvements in screening, detection, and treatment, more individuals diagnosed with cancer are surviving their disease,¹ thus affording the opportunity for researchers to examine patients' symptom experiences during and after treatment.²⁻⁴ The Institute of Medicine's report "From Cancer Patient to Cancer Survivor: Lost in Transition" focused on adult cancer survivors and noted the substantial consequences of cancer and its treatment.⁵ Patients with cancer experience multiple concurrent symptoms that affect their physical and psychosocial outcomes.^{2,6} A National Institutes of Health State-of-the-Science Conference explored symptom management in cancer and recommended larger studies to provide more accurate estimates of the incidence of particular symptoms and to investigate the relationship between various symptoms and patient characteristics.⁷

The symptom experience of cancer patients has been studied widely, often with a focus on single symptoms or on single disease types.⁸⁻¹⁰ In fact, patients rarely present with a single symptom. Researchers have found that most cancer patients experience multiple symptoms,^{6,10,11} with the range of symptoms varying by type of treatment, sex, age, and cancer type. Previous studies have established the average number of symptoms reported by cancer survivors as ranging

Abstract

BACKGROUND: Cancer patients experience symptoms associated with their disease, treatment, and comorbidities. Symptom experience is complicated, reflecting symptom prevalence, frequency, and severity. Symptom burden is associated with treatment tolerance as well as patients' quality of life (QOL).

OBJECTIVES: The purpose of this study was to document the symptom experience and QOL of patients with commonly diagnosed cancers. The relationship between symptoms and QOL was also explored.

METHODS: A convenience sample of patients with the five most common cancers at a comprehensive cancer center completed surveys assessing symptom experience (Memorial Symptom Assessment Survey) and QOL (Functional Assessment of Cancer Therapy). Patients completed surveys at baseline and at 3, 6, 9, and 12 months thereafter. This article describes the study's baseline findings.

RESULTS: Surveys were completed by 558 cancer patients with breast, colorectal, gynecologic, lung, or prostate cancer. Patients reported an average of 9.1 symptoms, with symptom experience varying by cancer type. The mean overall QOL for the total sample was 85.1, with results differing by cancer type. Prostate cancer patients reported the lowest symptom burden and the highest QOL.

LIMITATIONS: The sample was limited in terms of racial diversity. Because of the method of recruitment, baseline data were collected 6-8 months after diagnosis, meaning that participants were at various stages of treatment.

CONCLUSIONS: The symptom experience of cancer patients varies widely depending on cancer type. Nevertheless, most patients report symptoms, regardless of whether or not they are currently receiving treatment. Patients' QOL is inversely related to their symptom burden.

from 8 to 12.^{6,11} The concept of symptom burden includes the prevalence, frequency, and severity of symptoms and the level of physical and emotional distress caused by symptoms that go untreated or unrelieved.¹²⁻¹⁵ Tishelman and colleagues found that concordance among these aspects of symptoms varied by severity of illness, with greater concordance in patients closer to death.¹³ The complexity of symptom experience poses challenges for successful treatment of patients over the long term. A recent study dem-

From the Siteman Cancer Center; Division of Biostatistics, Washington University School of Medicine; and Nursing Administration, Barnes-Jewish Hospital, St. Louis, Missouri. Manuscript submitted January 11, 2011; accepted June 9, 2011.

Correspondence to: Teresa L. Deshields, PhD, Siteman Cancer Center, 4921 Parkview Place, MS: 90-35-703, St. Louis, MO 63110; telephone: (314) 454-7474; fax: (314) 362-1904; e-mail: tld2593@bjc.org

J Support Oncol 2011;9:216-223 © 2011 Elsevier Inc. All rights reserved. doi:10.1016/j.suponc.2011.06.003

onstrated that providing early symptom management through palliative care to metastatic lung cancer patients resulted in better quality of life (QOL), better mood, and longer survival.¹⁶

QOL is a multifactorial concept that has also been widely examined in a variety of disease types.^{17–19} In the cancer arena, focus has centered on patients' perceptions of well-being in several domains: physical, psychological, social, and functional.²⁰ In cancer care, QOL has been recognized as important to the outcome of cancer treatment³ and as a component of the symptom experience.^{8,21} The number and type of symptoms cancer patients experience have been significantly related to impairment in performance status, psychological distress, and overall QOL.^{6,8} Recently, several studies have demonstrated that pretreatment QOL is predictive of survival in patients with cancer of various types—advanced colorectal,²² various stage esophageal,²³ advanced non-small cell lung,²⁴ and metastatic prostate.²⁵

It is important for oncology clinicians to better understand the symptom experience of cancer survivors. Further research is needed to identify ways to minimize symptom persistence and relieve symptom burden and, thus, to improve patients' QOL. The primary aim of this study was to document the symptoms and QOL experienced by cancer survivors with commonly diagnosed cancers. This article describes the baseline findings of a longitudinal study.

Materials and Methods

This was a longitudinal (12-month) study using a repeated measures design involving a convenience sample of outpatients diagnosed with cancer at a large National Cancer Institute–designated comprehensive cancer center. The Protocol Review and Monitoring Committee of the cancer center and the Human Research Protection Office of the affiliated university approved the study.

PARTICIPANTS

Patients diagnosed with one of the top five cancers (breast, colorectal, gynecological, lung, and prostate) by volume at the cancer center and with stage I, II, or III disease were eligible for participation in this study. Patients with stage 0 disease were excluded because this stage is unusual outside of breast cancer. Patients with stage IV disease were excluded, to minimize attrition over the course of the longitudinal portion of the study (not described here) and because of the chronicity of treatment. Potential participants were identified through the cancer center's cancer registry.

PROCEDURES

New cases for the cancer center's tumor registry are entered into a database typically 6–8 months following initial diagnosis. Each month following study implementation, all eligible patients newly entered into the database received a letter informing them of the research study and inviting them to participate. The letter was accompanied by a consent document, which included the elements of informed consent and the assessment measures. The consent form included

Table 1

Patient Characteristics

VARIABLE	RESPONDERS (N = 558), N (%)	NONRESPONDERS (N = 1,036), N (%)
Currently receiving cancer treatment	189 (35%)	
Sex		
Female	298 (53%)	591 (57%)
Male	262 (47%)	443 (43%)
Age	X = 60.3, SD = 10.8	X = 60.6, SD = 12.4
Race ^a		
Minority	60 (11%)	253 (25%)
White	499 (89%)	780 (75%)
Cancer type		
Breast	164 (29%)	252 (24%)
Colorectal	34 (6%)	97 (9%)
Gynecological	96 (17%)	224 (22%)
Lung	44 (8%)	171 (17%)
Prostate	221 (40%)	290 (28%)
Cancer stage		
I	167 (30%)	382 (37%)
II	279 (50%)	435 (42%)
III	113 (20%)	217 (21%)
Comorbidity score ^b		
0	180 (32%)	288 (28%)
1	253 (45%)	424 (41%)
2	85 (15%)	181 (17%)
3	40 (7%)	141 (14%)
Number of symptoms		
Breast	X = 11.0, SD = 8.2	
Colorectal	X = 12.3, SD = 7.9	
Gynecologic	X = 11.6, SD = 8.3	
Lung	X = 11.1, SD = 6.8	
Prostate	X = 5.5, SD = 5.6	

^a*P* < .01.

^b*P* < .001.

permission for the researchers to obtain the patient's clinical information from the tumor registry. Patients who returned completed assessment measures were considered to have consented to participate. Those who did not want to participate could return an opt-out card or could decline to return completed surveys from 2 consecutive mailings. If patients did not return the surveys from the first mailing, a follow-up phone call was made to determine whether they received the study packet and whether they had any questions about the study. Patients could decline to participate during the phone call or could request that the study packet be resent. If patients failed to return surveys from 1 mailing, they received one further mailing. If they failed to respond to 2 mailings, they were dropped from the study. All study measures were completed by patients at home and returned to the researchers by mail.

Patients who agreed to participate were asked to complete a set of surveys on their own at baseline and at 3, 6, 9, and 12 months.

Table 2**Top Symptoms from the MSAS for Those Reporting Symptoms**

RANK AND SYMPTOM	OVERALL	BREAST	COLORECTAL	GYNECOLOGIC	LUNG	PROSTATE
Lack of energy						
Prevalence ^a	332 (60%)	115 (71%)	27 (79%)	68 (72%)	32 (74%)	90 (41%)
Frequency	2.6 (0.9)	2.5 (0.8)	2.7 (0.9)	2.8 (0.8)	2.9 (0.9)	2.4 (1.0)
Severity	2.0 (0.7)	1.9 (0.6)	2.4 (0.8)	2.0 (0.7)	2.2 (0.8)	1.9 (0.8)
Distress	2.3 (0.9)	2.3 (0.8)	2.7 (1.0)	2.5 (0.8)	2.5 (0.7)	2.1 (0.9)
Symptom score	2.3 (0.7)	2.3 (0.7)	2.6 (0.8)	2.4 (0.7)	2.6 (0.7)	2.1 (0.8)
Difficulty sleeping						
Prevalence	290 (52%)	96 (59%)	24 (71%)	60 (64%)	23 (55%)	87 (39%)
Frequency	2.5 (0.9)	2.4 (0.8)	2.5 (0.9)	2.6 (0.9)	2.4 (0.8)	2.5 (0.9)
Severity	2.1 (0.8)	1.9 (0.7)	2.3 (0.9)	2.2 (0.8)	2.3 (0.9)	2.1 (0.8)
Distress	2.4 (0.9)	2.2 (0.8)	2.7 (1.0)	2.5 (0.9)	2.5 (0.9)	2.3 (0.9)
Symptom score	2.3 (0.7)	2.2 (0.6)	2.5 (0.9)	2.4 (0.8)	2.4 (0.8)	2.3 (0.8)
Problems with sexual interest/activity						
Prevalence	282 (52%)	70 (43%)	10 (30%)	40 (44%)	12 (29%)	150 (69%)
Frequency	3.1 (1.0)	2.8 (1.0)	3.3 (0.8)	2.8 (1.0)	2.7 (1.1)	3.3 (0.9)
Severity	2.8 (1.0)	2.5 (1.0)	3.0 (1.1)	2.5 (1.1)	2.8 (1.3)	2.9 (1.0)
Distress	2.7 (1.0)	2.2 (1.0)	2.5 (1.4)	2.5 (1.1)	2.0 (0.7)	2.9 (0.9)
Symptom score	2.8 (0.9)	2.5 (0.8)	2.9 (1.1)	2.7 (1.0)	2.5 (0.7)	3.0 (0.8)
Pain						
Prevalence	250 (45%)	104 (64%)	18 (53%)	44 (48%)	26 (59%)	58 (26%)
Frequency	2.2 (0.9)	2.2 (0.9)	2.1 (0.8)	2.4 (0.9)	2.4 (0.9)	2.0 (0.9)
Severity	1.8 (0.7)	1.7 (0.8)	1.7 (0.8)	2.1 (0.8)	1.8 (0.7)	1.7 (0.6)
Distress	2.1 (0.8)	2.1 (0.9)	2.2 (0.6)	2.5 (0.9)	2.1 (1.0)	1.8 (0.7)
Symptom score	2.0 (0.7)	2.0 (0.8)	2.0 (0.6)	2.3 (0.8)	2.1 (0.8)	1.8 (0.6)
Feeling drowsy						
Prevalence	232 (42%)	84 (51%)	22 (65%)	52 (56%)	24 (56%)	50 (23%)
Frequency	2.2 (0.8)	2.2 (0.8)	2.5 (0.7)	2.3 (0.8)	2.3 (0.7)	2.0 (0.8)
Severity	1.8 (0.7)	1.7 (0.6)	2.1 (0.7)	1.8 (0.8)	1.8 (0.5)	1.7 (0.7)
Distress	1.9 (0.8)	1.9 (0.7)	2.1 (1.0)	1.9 (0.9)	1.7 (0.7)	1.7 (0.7)
Symptom score	2.0 (0.7)	2.0 (0.6)	2.2 (0.7)	2.0 (0.8)	1.9 (0.5)	1.8 (0.6)
Worrying						
Prevalence	229 (42%)	86 (53%)	13 (38%)	55 (59%)	16 (36%)	59 (27%)
Frequency	2.2 (0.9)	2.1 (0.8)	2.0 (0.7)	2.6 (1.0)	2.3 (1.0)	1.9 (0.7)
Severity	1.9 (0.9)	1.7 (0.7)	1.8 (0.8)	2.2 (1.0)	2.2 (1.0)	1.7 (0.8)
Distress	2.3 (0.9)	2.2 (0.7)	2.3 (0.7)	2.6 (1.0)	2.4 (1.0)	2.1 (0.8)
Symptom score	2.1 (0.8)	2.0 (0.7)	2.0 (0.7)	2.5 (0.9)	2.3 (0.9)	1.9 (0.7)
Feeling sad						
Prevalence	224 (40%)	81 (50%)	16 (47%)	57 (61%)	17 (39%)	53 (24%)
Frequency	2.1 (0.9)	2.1 (0.8)	2.0 (0.9)	2.2 (0.9)	2.3 (1.1)	1.9 (0.8)
Severity	1.8 (0.8)	1.8 (0.8)	1.9 (0.9)	1.7 (0.9)	1.9 (1.0)	1.9 (0.8)
Distress	2.2 (0.8)	2.2 (0.8)	2.2 (0.8)	2.2 (0.8)	2.2 (0.8)	2.1 (0.8)
Symptom score	2.0 (0.8)	2.0 (0.7)	2.1 (0.8)	2.0 (0.9)	2.1 (1.0)	2.0 (0.7)
Difficulty concentrating						
Prevalence	219 (40%)	85 (53%)	15 (44%)	46 (50%)	22 (50%)	51 (23%)
Frequency	2.0 (0.8)	2.1 (0.7)	1.9 (0.5)	2.0 (0.8)	1.9 (0.7)	1.7 (0.8)
Severity	1.6 (0.7)	1.6 (0.7)	1.5 (0.5)	1.6 (0.8)	1.5 (0.6)	1.6 (0.8)
Distress	2.2 (0.9)	2.2 (1.0)	2.5 (0.9)	2.5 (0.9)	2.0 (0.8)	1.9 (0.8)
Symptom score	1.8 (0.7)	1.9 (0.7)	1.7 (0.5)	1.8 (0.7)	1.7 (0.6)	1.7 (0.7)

Table continued on the following page

Table 2**Top Symptoms From the MSAS For Those Reporting Symptoms (continued)**

RANK AND SYMPTOM	OVERALL	BREAST	COLORECTAL	GYNECOLOGIC	LUNG	PROSTATE
Numbness/tingling in hands/feet						
Prevalence	220 (40%)	77 (47%)	23 (68%)	51 (54%)	19 (43%)	50 (23%)
Frequency	2.6 (1.0)	2.6 (1.0)	3.0 (0.8)	2.9 (1.0)	2.3 (1.2)	2.2 (1.0)
Severity	1.9 (0.9)	1.9 (0.9)	2.2 (0.8)	2.1 (1.0)	1.6 (0.7)	1.8 (0.8)
Distress	2.2 (0.9)	2.2 (1.0)	2.5 (0.9)	2.5 (0.9)	2.0 (0.8)	1.9 (0.8)
Symptom score	2.3 (0.8)	2.3 (0.8)	2.6 (0.7)	2.5 (0.8)	2.0 (0.8)	2.0 (0.7)
Feeling irritable						
Prevalence	206 (37%)	82 (50%)	12 (36%)	44 (47%)	19 (43%)	49 (22%)
Frequency	2.0 (0.8)	1.8 (0.8)	2.3 (0.8)	2.2 (0.8)	2.0 (0.8)	1.9 (0.8)
Severity	1.7 (0.8)	1.6 (0.7)	1.7 (0.6)	1.9 (0.9)	1.7 (0.9)	1.9 (0.8)
Distress	2.1 (0.8)	2.0 (0.7)	2.2 (0.8)	2.1 (1.0)	2.0 (0.8)	2.2 (0.8)
Symptom score	1.9 (0.7)	1.8 (0.6)	2.1 (0.6)	2.1 (0.8)	1.9 (0.8)	2.0 (0.7)

^a Prevalence scores reported as n (%) of those responding "yes" to the presence of this symptom. All other scores are reported as mean (SD). Frequency, severity, and distress scores calculated using only those participants reporting the given symptom.

The survey packet contained 2 measurement tools, the Memorial Symptom Assessment Scale and the Functional Assessment of Cancer Therapy–General Scale, and a demographic information form (including current treatment status). Clinical data, including comorbidity, disease type and stage, and treatment type (chemotherapy, surgery, radiation, hormonal therapy, or mixed), were captured from the tumor registry database. At baseline, survey packets were mailed to 1,594 patients, and 558 patients returned the completed surveys, yielding a participation rate of 35%. This article describes the baseline assessment results.

MEASURES

The Memorial Symptom Assessment Survey (MSAS)²⁶ is a 32-item measure and well-validated in oncology populations. The tool captures the multidimensional nature of symptoms (symptom presence, frequency, intensity, and symptom-related distress).^{3,26,27} The MSAS has three subscales: the Physical Symptom Subscale (PHYS), the Psychological Symptom Subscale (PSYCH), and the Global Distress Index (GDI). The GDI was developed by Portenoy et al²⁶ as a clinically useful measure of global distress based on 10 selected psychological and physical items most likely to reflect a patient's clinical status. The Total MSAS is a summary measure of overall symptom burden, determined by both the number of symptoms experienced by a patient and the various ratings associated with each symptom. We computed a composite symptom score, which combined the patient's ratings (frequency, intensity, related distress) for each symptom, as a measure of burden associated with a particular symptom.^{3,26,27} The alpha reliability score for the MSAS has been reported as ranging from 0.83 to 0.88^{2,23} and in this study was 0.90. The MSAS takes approximately 10 minutes to complete.

The Functional Assessment of Cancer Therapy–General Scale (FACT-G)²⁰ is a 27-item measure of QOL. It is well validated and widely used with oncology patients. The instru-

ment assesses 4 domains of well-being—Physical, Emotional, Social, and Functional—producing 4 subscale scores as well as a total summary QOL score. The alpha reliability score for the FACT-G has been reported as 0.89¹⁷ and in this study was 0.92. The FACT-G takes approximately 5 minutes to complete.

Patient comorbidities were measured using the Adult Comorbidity Evaluation–27 (ACE-27), a comorbidity index developed for patients with cancer.²⁸ The ACE-27 was developed through modification of the Kaplan-Feinstein Comorbidity Index (KFI). After adjusting for TNM stage, the ACE-27 comorbidity score has been found to be an independent, statistically significant prognostic factor.²⁹ Comorbidities on the scale are measured from grade 1 through grade 3 (mild to severe) by body systems; therefore, higher scores represent greater comorbidity.

DATA ANALYSIS

Descriptive statistics were used to analyze the frequencies and means of demographic and clinical characteristics and scale measures for the study sample. Due to the data not having a normal distribution, the majority of continuous variables were compared with nonparametric methods (eg, Kruskal-Wallis test). Categorical variables were examined with χ^2 tests. Analysis of variance (ANOVA) was used to compare differences between cancer types on single dependent measures. Multivariate ANOVA (MANOVA) was used to examine differences between cancer types on multiple dependent variables. All tests were 2-sided, and the significance level was set at 0.05. The statistical package SAS 9.1 was used for all statistical calculations (SAS Institute, Cary, NC).

Results

We received baseline surveys from 558 patients. The distribution of cancer diagnoses was as follows: prostate = 220,

breast = 164, gynecologic = 96, lung = 45, and colorectal = 33. There were slightly more females ($n = 298$) than males ($n = 262$) in our sample. Most patients reported having stage II ($n = 278$) disease. Patient characteristics are presented in Table 1.

We compared responders with nonresponders on demographic and clinical variables. Race was the only demographic variable that distinguished the groups ($\chi^2 = 43.4$, $P < .001$), with a higher response rate among whites than minorities. Among clinical variables, the groups differed by comorbidity ($\chi^2 = 15.52$, $P = .001$), with nonresponders having higher comorbidity scores. The groups also differed by cancer stage ($\chi^2 = 10.03$, $P = .01$), with nonresponders being more likely to have stage I disease and responders being more likely to have stage II disease. The groups also differed by cancer type ($\chi^2 = 45.72$, $P < .001$), with more responders having breast and prostate cancers and more nonresponders having colorectal, gynecological, and lung cancers.

While 37 patients reported no symptoms at all, there was an average of 9.1 symptoms (range = 0–32) per patient on the MSAS. The number of symptoms varied by type of cancer, with prostate patients reporting an average of 5.6 symptoms and colorectal patients reporting an average of 12.3 symptoms. More than one symptom was reported by 85% of participants. Of the 36% of participants receiving active treatment at baseline, 94% reported more than 1 symptom, with the number of symptoms averaging 11.2 (SD = 7.7). Among those patients no longer receiving treatment at baseline, 81% reported more than 1 symptom, with the average number of symptoms being 7.8 (SD = 7.3).

Overall, the prevalence of symptoms varied by cancer type (see Table 2). The five most prevalent symptoms for all patients included lack of energy, difficulty sleeping, problems with sexual interest or activity, pain, and feeling drowsy. Lack of energy was among the top three symptoms for all cancer types—experienced by 79% of colorectal patients, 74% of lung patients, 72% of gynecologic patients, 71% of breast patients, and 41% of prostate patients. Among the 5 most prevalent symptoms for all patients, problems with sexual interest or activity had the highest mean individual symptom score ($X = 2.9$) in comparison with all other symptoms, followed by difficulty sleeping and lack of energy (X for both = 2.3).

The MSAS total scores were significantly different by cancer group ($P < .001$), with prostate cancer patients indicating less symptom burden ($X = 0.3$) than all other patient groups (see Table 3). Prostate cancer patients also reported fewer symptoms ($X = 5.6$) and lower GDI scores ($X = 0.4$) than all other cancer groups. The mean MSAS PHYS scores ranged between 0.23 (prostate) and 0.82 (colorectal). Prostate cancer patients had lower scores than all other groups. The mean MSAS PSYCH scores ranged between 0.45 (prostate) and 1.11 (gynecologic). MANOVA for the various subscale scores, total score, and number of symptoms demonstrated an overall effect by cancer type ($F = 6.44$, $P < .001$). Significant between-group differences indicated

Table 3

Mean MSAS Scores

CANCER TYPE	MSAS TOTAL*	TOTAL SYMPTOMS	GDI	PHYS	PSYCH
Breast	0.7	11.0	1.2	0.6	1.0
Colorectal	0.8	12.2	1.2	0.9	0.9
Gynecological	0.8	11.6	1.4	0.8	1.2
Lung	0.7	11.6	1.2	0.7	0.9
Prostate	0.4	5.5	0.6	0.3	0.5
Overall	0.59	9.1	1.0	0.5	0.8

* $P < .01$.

Table 4

FACT Scores

CANCER TYPE	EMOTIONAL	FUNCTIONAL	PHYSICAL	SOCIAL	TOTAL*
Breast	19.9	21.6	23.9	22.7	84.9
Colorectal	19.5	17.9	20.8	22.9	81.1
Gynecological	19.2	19.9	21.8	20.4	77.0
Lung	18.6	19.8	24.2	23.7	80.5
Prostate	22.2	23.7	25.9	21.7	90.0
Overall	20.6	21.8	24.2	22.0	85.1

* $P < .01$.

that prostate cancer patients differed from all other cancer types. In addition, breast cancer patients differed significantly from colorectal and lung cancer patients, and colorectal cancer patients differed significantly from gynecologic cancer patients.

The QOL data are presented in Table 4. There was a significant difference among the diagnostic groups on the overall QOL score ($P < .001$). The mean overall QOL score (range = 0–108) for the entire sample was 85.1, with prostate patients reporting higher overall QOL ($X = 90.24$) than all other cancer groups. MANOVA for the various subscales demonstrated an overall effect by type of cancer ($F = 8.86$, $P < .001$). Significant between-group differences indicated that prostate cancer patients differed from all other cancer types. In addition, breast cancer patients differed significantly from colorectal, gynecologic, and lung cancer patients. Also, gynecologic patients differed significantly from colorectal and lung cancer patients.

There were significant negative correlations between overall QOL and the number of symptoms ($r = -0.61$, $P < .001$), the severity of symptoms ($r = -0.64$, $P < .001$), the GDI ($r = -0.69$, $P < .001$), and the MSAS total score ($r = -0.68$, $P < .001$). All symptom composite scores for the MSAS were significantly negatively correlated with overall QOL at $P < .01$ or better. There were also significant correlations between comorbidity scores and both the MSAS total score ($r = 0.12$, $P = .006$) and overall QOL ($r = -0.11$, $P = .01$).

We compared the data from patients receiving treatment at the time of the assessment with data from patients not actively receiving treatment, using the Kruskal-Wallis test;

Table 5
Comparison of Patients by Treatment Status

ASSESSMENT MEASURE	CURRENTLY RECEIVING TREATMENT, MEAN (SD)	NOT RECEIVING TREATMENT, MEAN (SD)
FACT Emotional	19.6 (3.9)	19.6 (3.9)
FACT Functional**	19.9 (6.5)	21.4 (6.2)
FACT Physical***	21.8 (6.0)	24.4 (4.4)
FACT Social*	21.8 (6.0)	20.8 (6.2)
FACT Total	83.0 (17.7)	86.2 (15.9)
MSAS Total***	0.67 (0.55)	0.45 (0.45)
MSAS number of symptoms***	11.2 (7.7)	7.8 (7.3)
MSAS GDI***	0.88 (0.75)	0.62 (0.71)
MSAS Physical***	0.66 (0.62)	0.39 (0.50)
MSAS Psychological**	0.86 (0.77)	0.70 (0.81)

* $P < .05$, ** $P < .01$, *** $P < .001$.

these results are presented in Table 5. These groups differed on every MSAS subscale: PSYCH ($P < .01$), PHYS ($P < .001$), GDI ($P < .001$), and Total ($P < .001$). All of these results reflected higher symptom burden in those receiving treatment. Patients receiving treatment reported more symptoms than those not receiving treatment ($X = 11.2$ vs. $X = 7.8$, $P < .001$). We also examined differences in QOL between these groups. There was no significant difference between these groups on Overall QOL or Emotional QOL, but the groups were significantly different in terms of Physical QOL ($P < .001$), Social QOL ($P < .05$), and Functional QOL ($P < .01$). All of these results reflected poorer QOL in those patients receiving active treatment.

Discussion

This study highlights the varied symptom experience and QOL of a diverse sample of cancer survivors. The results revealed a high prevalence of symptoms among cancer survivors undergoing active treatment as well as those no longer receiving treatment. This is in concordance with previous research.^{30–32} A systematic review of studies examining the symptoms of cancer patients undergoing treatment indicated that 40% of patients experienced more than one symptom.³⁰ This is in contrast to our rate of 93%. Our result is similar to the findings of the LIVESTRONG survey of 2,307 cancer survivors, in which 91% of respondents reported experiencing 1 or more physical concerns after the completion of treatment.³³ This difference may be due to the choice of instruments selected for symptom measurement. In a review of 18 published studies, researchers found that symptom-specific scales used in many studies offer valuable information on the multiple dimensions of a single symptom, while inventories such as the MSAS capture the occurrence, severity, and distress of multiple concurrent symptoms.²⁶ There is also variability in the number of symptoms measured in multi-symptom inventories; for example, the MSAS assesses 32 symptoms, while the MD Anderson Symptom Inventory uses 13 items.

An important finding was the prevalence of symptoms among patients no longer receiving active treatment; specifically, in our sample, 80% of these patients reported multiple symptoms. This result raises concerns about the adequacy of current symptom assessment and management by oncology clinicians. This result also underscores the critical need for ongoing palliative care for cancer survivors, perhaps through the vehicle of survivorship clinics, as recommended by the Institute of Medicine report.⁵

We found differences by cancer type in the patient reports of their symptom experience and QOL. Prevalent symptoms by cancer type were clearly associated with the nature of the cancer. For example, shortness of breath was most prevalent among lung cancer patients, diarrhea among colorectal cancer patients, and difficulty urinating among prostate cancer patients. Prostate cancer patients had the lowest symptom scores altogether, with the lowest MSAS Total score, number of total symptoms, GDI, PHYS score, and PSYCH score. The only symptoms that were endorsed more highly by prostate cancer patients compared to patients with other cancer types were “problems with sexual interest/activity” (69%) and “problems urinating” (43%).

Prostate cancer patients endorsed the highest overall QOL scores and the highest QOL subscale scores except for Social Well-being. These results suggest that prostate cancer patients are faring better than the other 4 diagnostic groups after diagnosis of and treatment for their disease, perhaps indicating that treatment for prostate cancer is easier to tolerate or that this diagnosis is less distressing. Our data indicate that most prostate cancer patients do not receive chemotherapy, and this difference in treatment may impact the findings for symptom burden and QOL. The results also may reflect that this patient population is less likely to complain about symptoms, although the majority of this group endorsed problems with sexual interest and sexual functioning. Nevertheless, previous research has suggested that men are less likely to complain about symptoms they are experiencing compared to women.^{34,35}

In terms of which diagnostic group did most poorly, the results are less clear. Colorectal and gynecologic cancer patients had equally high MSAS Total scores, reflecting worse overall symptom burden. However, colorectal cancer patients endorsed more physical difficulties, with the highest number of symptoms overall and the highest scores on the MSAS PHYS. Yet, gynecologic cancer patients endorsed more psychosocial difficulties, with the highest GDI and PSYCH scores. This same dichotomy was found in terms of QOL, with colorectal cancer patients reporting poorer Functional and Physical Well-being, but gynecologic patients reporting poorer Social Well-being and Overall QOL.

Study results indicate that the cancer experience, particularly in terms of symptom burden and QOL, varies depending on the specific cancer diagnosis, necessitating an individualized approach to symptom management and palliative care. When patients experience multiple symptoms caused by treatment, the result can be disruption of treatment or premature treatment termination, while

residual treatment-related symptoms can complicate posttreatment rehabilitation.³⁶ In general, it is clear that symptom burden is significantly related to patients' QOL and that these aspects of the patient's experience are intertwined. These findings suggest that attention to patients' symptom experience is important as one avenue for facilitating optimal QOL.

There are several limitations of this study that have implications for the generalizability of the results. First, the sample is fairly homogeneous from a racial standpoint, being primarily Caucasian. Second, data were collected via mailed questionnaires. Although the return rate was comparable to many survey studies, it is unclear whether this method of data collection instilled some systematic bias. Third, the MSAS is a complicated measure to complete. Examination of the returned surveys suggests that some patients had difficulty understanding how to complete the measure (eg, provided inconsistent answers). Fourth, because potential participants were identified from the cancer center's cancer registry, patients were not identified until 6–8 months after diagnosis, meaning that these results do not include a true baseline, collected at the time of diagnosis. Finally, because different patients and different cancer groups had different treatment regimens, the timeline for treatment was inconsistent across patients. This meant that data collection on a calendar-based timeline may have missed important clinical

milestones (eg, changes in treatment regimen, end of treatment) for particular patients.

Conclusions

These results indicate that the symptom experience for patients varies widely depending on the type of cancer. Moreover, symptoms persist beyond treatment, suggesting that symptom burden is a long-term issue for cancer survivors. Our findings also underscore the strong connection between symptom experience and patients' QOL, suggesting that symptoms significantly negatively impact overall well-being of patients. These results lend weight to efforts to promote symptom reporting and symptom management throughout the continuum of oncology care.

Acknowledgments: The authors thank Lori Grove for her assistance in identifying and recruiting participants for this study. The authors acknowledge the support of the Biostatistics Core, Siteman Comprehensive Cancer Center, and NCI Cancer Center Support Grant P30 CA091842.

Conflicts of interest: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. DeShields received reimbursement for consultancy services, honoraria, development of education presentations including service on speakers' bureaus, and for travel/accommodations expenses from Lilly Oncology. All other authors have no potential conflicts of interest to disclose.

References

PubMed ID in brackets

- American Cancer Society. Cancer Facts & Figures 2010. Atlanta: American Cancer Society; 2010.
- Molassiotis A, Wengstrom Y, Kearney N. Symptom cluster patterns during the first year after diagnosis with cancer. *J Pain Symptom Manage* 2010;39:847–858.
- Akin S, Can G, Aydinler A, et al. Quality of life, symptom experience and distress of lung cancer patients undergoing chemotherapy. *Eur J Oncol Nurs* 2010;14:400–409.
- Dodd MJ, Miaskowski C, Paul SM. Symptom clusters and their effect on the functional status of patients with cancer. *Oncol Nurs Forum* 2001;28:465–470.
- Institute of Medicine, National Research Council. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, DC: National Academy Press, 2006.
- Portenoy RK, Thaler HT, Kornblith AB, et al. Symptom prevalence, characteristics and distress in a cancer population. *Qual Life Res* 1994; 3:183–189.
- National Institutes of Health. State-of-the-Science Panel, National Institutes of Health State-of-the-Science conference statement. Symptom management in cancer: pain, depression, and fatigue. July 15–17, 2002. *J Natl Cancer Inst* 2003;95: 1110–1117.
- Sun V, Ferrell B, Juarez G, et al. Symptom concerns and quality of life in hepatobiliary cancers. *Oncol Nurs Forum* 2008;35:E45–E52.
- Yamagishi A, Morita T, Miyashita M, et al. Symptom prevalence and longitudinal follow-up in cancer outpatients receiving chemotherapy. *J Pain Symptom Manage* 2009;37: 823–830.
- Baggott C, Dodd M, Kennedy C, et al. Multiple symptoms in pediatric oncology patients: a systematic review. *J Pediatr Oncol Nurs* 2009;26:325–339.
- Chang VT, Hwang SS, Feuerman M, et al. Symptom and quality of life survey of medical oncology patients at a veterans affairs medical center: a role for symptom assessment. *Cancer* 2000;88:1175–1183.
- Burkett VS, Cleeland CS. Symptom burden in cancer survivorship. *J Cancer Surviv* 2007; 1:167–175.
- Tishelman C, Petersson LM, Degner LF, et al. Symptom prevalence, intensity, and distress in patients with inoperable lung cancer in relation to time of death. *J Clin Oncol* 2007; 25:5381–5389.
- Lobchuk MM. The Memorial Symptom Assessment Scale: modified for use in understanding family caregivers' perceptions of cancer patients' symptom experiences. *J Pain Symptom Manage* 2003;26:644–654.
- Henry DH, Viswanathan HN, Elkin EP, et al. Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the US. *Support Care Cancer* 2008;16:791–801.
- Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; 363:733–742.
- Bosma I, Reijneveld JC, Douw L, et al. Health-related quality of life of long-term high-grade glioma survivors. *Neurooncology* 2009;11: 51–58.
- Lev EL, Eller LS, Gejerman G, et al. Quality of life of men treated for localized prostate cancer: outcomes at 6 and 12 months. *Support Care Cancer* 2009;17:509–517.
- Le T, Menard C, Samant R, et al. Longitudinal assessments of quality of life in endometrial cancer patients: effect of surgical approach and adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys* 2009;75:795–802.
- Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy Scale: development and validation of the general measure. *J Clin Oncol* 1993;11:570–579.
- Miaskowski C, Cooper BA, Paul SM, et al. Subgroups of patients with cancer with different symptom experiences and quality-of-life outcomes: a cluster analysis. *Oncol Nurs Forum* 2006;33:E79–E89.
- Maisey NR, Norman A, Watson M, et al. Baseline quality of life predicts survival in patients with advanced colorectal cancer. *Eur J Cancer* 2002;38:1351–1357.
- van Heijl M, Sprangers MA, de Boer AG, et al. Preoperative and early postoperative quality of life predict survival in potentially curable patients with esophageal cancer. *Ann Surg Oncol* 2010;17:23–30.
- Maione P, Perrone F, Gallo C, et al. Pre-treatment quality of life and functional status assessment significantly predict survival of el-

- derly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian Lung Cancer in the Elderly study. *J Clin Oncol* 2005;23:6865–6872.
25. Sullivan PW, Nelson JB, Mulani PM, et al. Quality of life as a potential predictor for morbidity and mortality in patients with metastatic hormone-refractory prostate cancer. *Qual Life Res* 2006;15:1297–1306.
26. Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. *Eur J Cancer* 1994;30A:1326–1336.
27. Sun CC, Bodurka DC, Weaver CB, et al. Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer. *Support Care Cancer* 2005;13:219–227.
28. Piccirillo J, Costas I, Claybour P, et al. The measurement of comorbidity by cancer registries. *J Registry Manage* 2003;30:8–14.
29. Piccirillo JF, Tierney RM, Costas I, et al. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA* 2004;291:2441–2447.
30. Esther Kim JE, Dodd MJ, Aouizerat BE, et al. A review of the prevalence and impact of multiple symptoms in oncology patients. *J Pain Symptom Manage* 2009;37:715–736.
31. Dirksen S, Belyea M, Epstein D. Fatigue-based subgroups of breast cancer survivors with insomnia. *Cancer Nurs* 2009;32:404.
32. Ferreira KA, Kimura M, Teixeira MJ, et al. Impact of cancer-related symptom synergisms on health-related quality of life and performance status. *J Pain Symptom Manage* 2008;35:604–616.
33. Rechis R, Boerner L. How cancer has affected post-treatment survivors: a LIVESTRONG report. Available at: <http://www.livestrong.org/pdfs/3-0/LSSurvivorSurveyReport>. Accessed November 30, 2010.
34. Barsky AJ, Peekna HM, Borus JF. Somatic symptom reporting in women and men. *J Gen Intern Med* 2001;16:266–275.
35. Kroenke K, Spitzer RL. Gender differences in the reporting of physical and somatoform symptoms. *Psychosom Med* 1998;60:150–155.
36. Cleeland CS. Symptom burden: multiple symptoms and their impact as patient-reported outcomes. *J Natl Cancer Inst Monogr* 2007;37:16–21.

Efficacy and Safety of Fentanyl Pectin Nasal Spray Compared with Immediate-Release Morphine Sulfate Tablets in the Treatment of Breakthrough Cancer Pain: A Multicenter, Randomized, Controlled, Double-Blind, Double-Dummy Multiple-Crossover Study

Marie Fallon, MB, ChB, MD, FRCP; Carlo Reale, MD; Andrew Davies, MBBS, MSc, MD, FRCP; A. Eberhard Lux, MD; Kirushna Kumar, MBBS, MD; Andrzej Stachowiak, MD; and Rafael Galvez, MD; on behalf of the Fentanyl Nasal Spray Study 044 Investigators Group

Breakthrough cancer pain (BTCP) is defined as “a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain.”¹ BTCP is a distinct entity, reported to affect up to 80% of all cancer patients with pain.² The typical BTCP episode is moderate to severe and sometimes even excruciating in intensity, rapid in onset (time from onset to peak pain intensity [PI] ~1–3 minutes),^{3,4} and relatively short in duration (median 45 minutes).⁴

Currently, oral immediate-release morphine sulfate (IRMS) is the most common treatment for BTCP.^{5,6} However, at least 30 minutes usually elapse before effectiveness is quantifiable,

From the Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh, and St. Luke's Cancer Centre, Royal Surrey County Hospital, Guildford, United Kingdom; Università degli Studi la Sapienza di Roma, Rome, Italy; St. Marien-Hospital, Lünen, Germany; Meenakshi Mission Hospital, Madurai, India; Regionalny Zespo Opieki Paliatywnej-Dom Sue Ryder, Bydgoszcz, Poland; and Unidad del Dolor/Hospital Virgen de las Nieves, Granada, Spain.

Manuscript submitted February 10, 2011; accepted July 18, 2011.

Correspondence to: Marie Fallon, MB, ChB, MD, FRCP, Edinburgh Cancer Research Centre, Western General Hospital, Crewe Road South, Edinburgh, EH4 2XR, UK; telephone: 0044 131 777 3518; fax: 0044 131 777 3520; e-mail: Marie.Fallon@ed.ac.uk

J Support Oncol 2011;9:224–231
doi:10.1016/j.suponc.2011.07.004

© 2011 Published by Elsevier Inc.

BACKGROUND: Immediate-release morphine sulfate (IRMS) remains the standard treatment for breakthrough cancer pain (BTCP), but its onset of effect does not match the rapid onset and short duration of most BTCP episodes.

OBJECTIVE: This study will evaluate the efficacy/tolerability of fentanyl pectin nasal spray (FPNS) compared with IRMS for BTCP.

METHODS: Patients (n = 110) experiencing one to four BTCP episodes/day while taking ≥ 60 mg/day oral morphine (or equivalent) for background cancer pain entered a double-blind, double-dummy (DB/DD), multiple-crossover study. Patients completing a titration phase (n = 84) continued to a DB/DD phase: 10 episodes of BTCP were randomly treated with FPNS and oral capsule placebo (five episodes) or IRMS and nasal spray placebo (5 episodes). The primary end point was pain intensity ($P < .05$ FPNS vs. IRMS) difference from baseline at 15 minutes (PID₁₅). Secondary end points were onset of pain intensity (PI) decrease (≥ 1 -point) and time to clinically meaningful pain relief (CMPR, ≥ 2 -point PI decrease). Safety and tolerability were evaluated by adverse events (AEs) and nasal assessments. By-patient and by-episode analyses were completed.

RESULTS: Compared with IRMS, FPNS significantly improved mean PID₁₅ scores. 57.5% of FPNS-treated episodes significantly demonstrated onset of PI improvement by 5 minutes and 95.7% by 30 minutes. CMPR (≥ 2 -point PI decrease) was seen in 52.4% of episodes by 10 minutes. Only 4.7% of patients withdrew from titration (2.4% in DB/DD phase) because of AEs; no significant nasal effects were reported.

CONCLUSION: FPNS was efficacious and well tolerated in the treatment of BTCP and provided faster onset of analgesia and attainment of CMPR than IRMS.

making IRMS too slow in onset for the management of BTCP.⁷⁻⁹ Development of alternative BTCP treatments has focused on the opioid fentanyl because it has a relatively short half-life and its lipophilic nature is ideal for rapid transmucosal absorption. Oral transmucosal fentanyl formulations have been developed but have not fully met the need for very rapid onset of action. Furthermore, their use can be significantly limited by oral problems such as xerostomia, which is common (up to 78%) in patients with advanced cancer.¹⁰⁻¹²

Intranasal drug delivery offers a simple, acceptable route for strong analgesic administration; rapid, efficient drug absorption occurs because nasal tissues are highly vascularized and easily permeable and first-pass hepatic metabolism is avoided.^{13,14} Conventional nasal fentanyl products are simple aqueous solutions delivered as sprays, but this may not be the most appropriate formulation because drug absorption can be variable and cannot be adequately controlled given the potential problems with nasal drip and with unpredictable drainage from the nose.¹⁵ Recently, a fentanyl pectin nasal spray (FPNS) has been developed to optimize the absorption profile of fentanyl across the nasal mucosa. FPNS combines fentanyl with a proprietary delivery platform (PecSys[®]; Archimedes Pharma, Reading, UK), allowing fentanyl to be delivered as an aqueous solution in a low-volume fine mist of similarly sized droplets. When sprayed into the nasal passage, the pectin in the solution forms a thin layer of flexible gel on contact with calcium ions found in the nasal mucosa. This ensures no unwanted runoff or swallowing of the solution and rapid but controlled delivery of fentanyl.¹⁵

It has been reported¹⁶ that FPNS provides significant pain relief when compared with placebo. A rapid clinical effect was observed in that study; superiority was demonstrated for onset of effect from 5 minutes after dosing and for clinically meaningful reduction in pain from 10 minutes after dosing. The main objective of this study was to evaluate the efficacy of FPNS compared with IRMS in the management of BTCP.

Methods

STUDY DESIGN

This multicenter, randomized, double-blind/double dummy (DB/DD), crossover study was conducted at 35 centers in Europe and India. The study was executed in accordance with all regulatory requirements and good clinical practice guidelines, approved by ethics committees and institutional review boards at the participating institutions, and conducted in accordance with the Declaration of Helsinki. Participating patients provided signed informed consent before enrollment.

The study consisted of four phases: screening (maximum 10 days), open-label dose-titration (maximum 14 days), DB/DD treatment (minimum 3 days, maximum 21 days), and end-of-treatment (1-14 days after last dose). The open-label dose-titration phase was used to identify an effective FPNS dose between 100 and 800 μg /episode of target BTCP. Patients had to complete the dose-titration phase (titration to an effective dose of FPNS that successfully treated 2 consec-

utive BTCP episodes without unacceptable adverse events [AEs]) to be eligible to continue to the DB/DD phase in which up to 10 BTCP episodes were treated (5 treated with FPNS and encapsulated oral placebo and 5 with IRMS and nasal spray placebo). The possible effective doses of FPNS were 100, 200, 400, and 800 μg administered using a multi-use nasal delivery device (Pfeiffer, Radolfzell, Germany). The 100- and 200- μg doses were administered using a 100- μg per 0.1-mL spray "low-dose" bottle and the 400- and 800- μg doses were administered using a 400- μg per 0.1-mL spray "high-dose" bottle. The multispray device featured a self-advancing countermechanism and emitted a loud click upon each actuation to confirm that a spray had been administered. Patients were instructed to take the oral treatment just before the nasal treatment for all episodes. The IRMS dose was determined according to the European Association for Palliative Care (EAPC) recommendations as one-sixth the total daily oral morphine dose equivalent of the patient's background opioid medication,¹⁷ unless the patient had a previously identified effective dose of IRMS for BTCP.

PATIENTS

Participants were eligible if they had histologically confirmed diagnoses of cancer, were receiving fixed-schedule opioid regimens at a total dose equivalent to ≥ 60 mg/day oral morphine for background cancer-related pain, and had 1-4 episodes per day of BTCP. BTCP was defined as a transitory flare of moderate to severe pain that occurred on a background of persistent pain controlled to moderate intensity or less by the fixed-schedule opioid regimen. If a patient had more than one type of BTCP, then one was identified as the target BTCP.

Patients with uncontrolled or rapidly escalating background pain or who were medically unstable were ineligible for the study. Other exclusion criteria included breakthrough pain not related to cancer, past inability to tolerate fentanyl or other opioids, history of alcohol or substance abuse, treatment with monoamine oxidase inhibitors, anticipated therapy during study with any treatment that might affect pain levels (eg, radiotherapy, chemotherapy), treatment with another investigational drug within the previous 30 days, and any disorder or medication use likely to adversely affect normal functioning of the nasal mucosa.

EFFICACY ASSESSMENTS AND OUTCOME MEASURES

Electronic diaries (e-diaries, stored overnight on charger units that automatically connected to a central server for the daily upload of data) in local languages were used to collect patient data in real time during the dose-titration and DB phases. Patients were trained in their use at the investigator site and received written instructions in their local languages. Baseline PI before treatment of a BTCP episode was recorded on a standard 11-point numeric scale (0 = no pain, 10 = worst possible pain). After this measurement, the study drug was taken. The e-diary then provided cues so that PI and pain relief (PR) scores were recorded at 5, 10, 15, 30, 45, and 60

minutes after dosing. PR was measured on a 5-point numeric scale (0 = none, 4 = complete). Use of other rescue medications was also recorded in the e-diaries throughout the study.

SAFETY AND TOLERABILITY ASSESSMENTS

AEs were recorded throughout the study. All AEs reported within a 24-hour period of a dose of FPNS were associated with FPNS even though they might have been treated with IRMS subsequently during the DB period. Objective clinical nasal assessments were performed by the study physician at screening and at treatment end. Subjective nasal assessments were measured on a 4-point scale (0 = absent, 3 = severe) by the patient completing a 10-item questionnaire before the first use of the study drug, 1 hour after each dose of the study medication, and at the final study visit. Items rated were stuffy/blocked nose, runny nose, itching/sneezing, crusting/dryness, burning/discomfort, nosebleed, cough, postnasal drip, sore throat, and taste disturbance.

STATISTICAL ANALYSIS

The sample size was based on data from a similarly designed study of oral transmucosal fentanyl citrate compared with IRMS.¹⁸ Based on the results of the previous study, it was estimated that the ratio of the effect size to SE for this study would be about 3.15 for a sample of 75 patients. Assuming 33% of patients would not complete the open-label dose-titration phase and an additional 33% would discontinue prior to taking 10 doses of the study drug, 180 patients were required to enter the open-label dose-titration phase to ensure that 80 patients completed the DB/DD treatment phase.

The primary end point was patient-averaged PI difference 15 minutes after dosing (PID_{15}). PID_{15} was defined as the difference between PI at baseline and at 15 minutes. Secondary end points included patient- and episode-averaged PID, summed PID (SPID), PI, PR, and summed PR (TOTPAR) scores at 5, 10, 15, 30, 45, and 60 minutes. Onset of analgesia with FPNS vs. IRMS was analyzed by assessing percentages of episodes with ≥ 1 -point reductions in PI and PR scores at each time point. Onset of clinically meaningful pain relief (CMPR) was analyzed by assessing percentages of episodes with ≥ 2 -point reductions or 33% reductions in PI and SPID.¹⁹ PR scores were further examined, and the incidence of BTCP episodes with maximum PR as defined by a PR score of 4 on a 5-point scale (0–4) was determined over time. The percentage of BTCP episodes that required additional rescue medication within 60 minutes was also recorded.

Statistical analysis used a modified intent-to-treat (mITT) approach that included all patients in the randomized population who treated at least one pain episode with FPNS and oral placebo and at least one pain episode with IRMS and nasal spray placebo and, for each of these episodes, had at least one baseline and one postbaseline PI measurement. The safety analysis set included all patients who received at least one dose of FPNS or IRMS. Analyses were performed at the patient level (patient averages, percentages of patients) and at

the episode level (percentages of episodes). The last observation carried forward was used to input missing data before average values were calculated for each patient. For the primary end point, analysis of covariance was used to compare treatments, with the PID_{15} score as the dependent variable and treatment group (FPNS and IRMS) and center as covariates. Secondary end points comparing treatment differences at each time point were analyzed using a model similar to the primary end point. Additionally, numbers and percentages of episodes in each treatment group achieving ≥ 1 -point, ≥ 2 -point, or $\geq 33\%$ reductions in PI scores were summarized. All hypothesis testing was conducted using two-sided tests, with the alpha set at the 0.05 level.

Results

PATIENT DISPOSITION AND BASELINE DEMOGRAPHICS

A total of 135 patients were screened for the study, and 110 were enrolled in the titration phase (Fig. 1). Of these 110 patients, 106 took study medication and were included in the safety population. Mean age at baseline was 55.9 ± 12.3 years; 65.1% of patients were 60 or younger (Table 1). Among the 106 patients who commenced titration, opioids in use for background medication were morphine (59.4% of patients), fentanyl (33.0%), oxycodone (8.5%), buprenorphine (1.9%), pentazocine (1.9%), and hydromorphone (1.9%) (Table 1). A total of 93.4% of patients were using a single opioid for background pain; the most common of these was morphine (49.1%). The mean daily background oral morphine equivalent was 201.9 mg.

Eighty-four patients (76%) identified an effective and tolerable FPNS dose during the titration phase (Fig. 1). The mean \pm SD dose of IRMS was 29.4 ± 38.9 mg. Of the 84 patients in the DB/DD treatment phase, 79 (94.0%) completed the study and were included in the mITT population. A total of 740 BTCP episodes—372 treated with FPNS, 368 treated with IRMS—were considered mITT-evaluable.

EFFICACY

Analysis of the primary end point, patient-averaged PID_{15} , revealed a significant difference between BTCP episodes treated with FPNS and those treated with IRMS; mean \pm SE was 3.02 ± 0.21 for FPNS doses and 2.69 ± 0.18 for IRMS ($P < .05$) (Fig. 2A). Statistical superiority of FPNS compared with IRMS on patient-averaged PID scores was maintained at each point from 15 minutes through 60 minutes ($P < .05$) (Fig. 2B).

Mean baseline PI scores were slightly higher for patient-averaged FPNS-treated episodes than for IRMS-treated episodes (7.76 vs. 7.65, respectively; $P < .05$). After treatment, mean PI scores were lower for FPNS-treated episodes than for IRMS-treated episodes from 10 minutes onward, with statistical significance between treatments shown at all points from 30 to 60 minutes ($P \leq .05$). Patient-averaged PR scores were greater after FPNS administration than after IRMS administration at all observed time points, with statistical significance

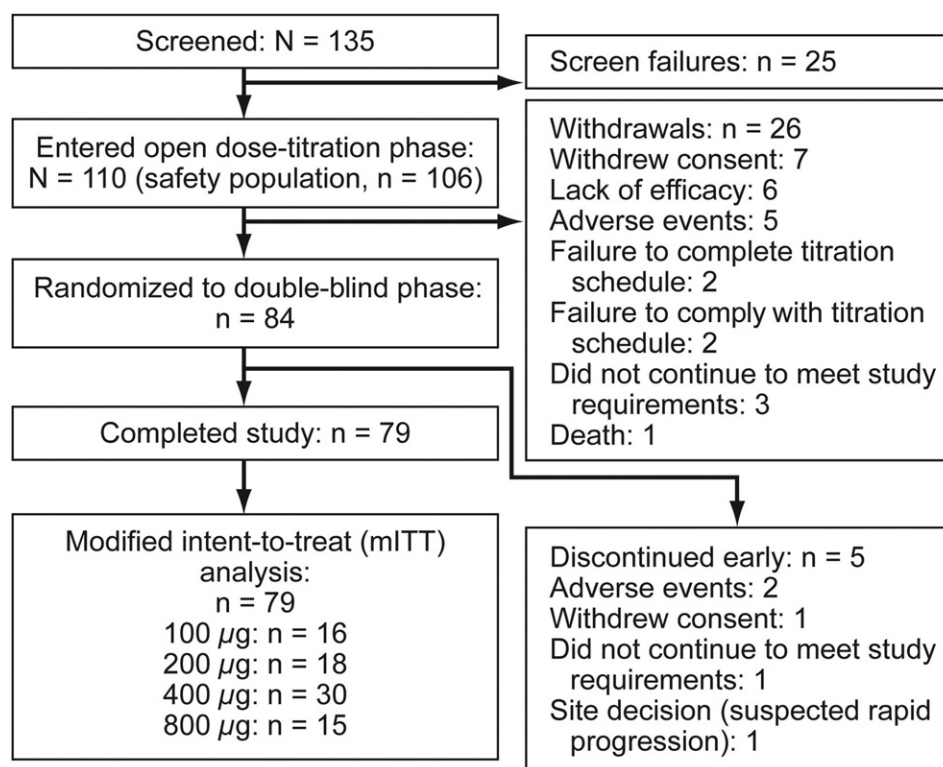


Figure 1 Study Disposition (CONSORT Diagram)

shown at all points from 30 to 60 minutes ($P \leq .005$). Similarly, patient-averaged mean differences in TOTPAR were significant from 15 minutes and at all points to 60 minutes ($P < .05$).

Episode-level analyses were performed as indicators of the consistency of effect, and percentages of episodes with PR scores ≥ 1 or ≥ 1 -point reductions in PI score were calculated to evaluate the onset of effect. The superiority of FPNS vs. IRMS was apparent as early as 5 minutes after dosing, with significant differences in the percentages of episodes showing a ≥ 1 -point change in PI and PR scores after FPNS treatment vs. IRMS treatment ($P < .05$ and $P < .001$, respectively). Statistical significance between treatments was maintained for episodes with PR scores ≥ 1 point at 5, 10, and 30 minutes ($P < .05$) but was not statistically significant at 15 minutes ($P = .0508$). Results for episodes showing ≥ 1 -point reductions in PI showed some temporal variation ($P < .05$ at 30 minutes, $P > .05$ at other time points). Similarly, significantly more episodes with CMPR (mean PI score reductions ≥ 2 or $\geq 33\%$) were observed after the administration of FPNS than that of IRMS at 10 and 15 minutes after dose (both $P < .05$) (Fig. 3). There was no significant difference between treatments from 30 minutes. In addition, significantly more episodes had a ≥ 2 -point mean reductions in SPID score at 10 minutes after FPNS than after IRMS administration ($P < .05$). The superiority of FPNS over IRMS in providing CMPR at 10 minutes was further supported by significantly higher percentages of episodes with mean reductions in SPID score of ≥ 2 , ≥ 3 , and ≥ 4 . Similarly, the

number of treated episodes with a $\geq 33\%$ reduction in PI score at 10 minutes was significantly larger after FPNS use than after IRMS use (33.9% vs. 28.3%, $P < .0357$) and at 15 minutes (55.4% vs. 47.3%, $P < .0056$).

The number of BTCP episodes achieving a maximum PR score of 4 with FPNS was higher compared with IRMS at 30 minutes (17.6% vs. 12.6%, $P = .05$) and significantly higher at 45 (31.1% vs. 21.5%, $P < .01$) and 60 (50.1% vs. 34.3%, $P < .0001$) minutes (Fig. 4). Approximately half the BTCP episodes at 60 minutes had achieved maximum pain relief with FPNS compared with just over one-third for IRMS. This represented a 46.1% improvement in maximal pain relief efficacy with FPNS.

Slightly lower proportions of FPNS-treated (3.0%) than IRMS-treated (3.8%) episodes necessitated the use of rescue medication from 0 to 60 minutes after treatment, but the difference did not reach statistical significance ($P = .57$).

SAFETY

Overall, more treatment-emergent AEs (TEAEs) were reported after FPNS than after IRMS treatment, and a higher percentage of TEAEs was observed after 400- and 800- μg doses of FPNS than after 100- and 200- μg doses. TEAEs with FPNS were mainly mild to moderate in severity. The most commonly reported TEAEs following last treatment with FPNS were vomiting, somnolence, dehydration, and nausea (Table 2). Only 4.7% of patients withdrew from titration because of AEs.

Table 1
Summary of Patient Demographic Characteristics (Safety Population)

PARAMETER	SUMMARY STATISTICS
n	106
Age (years)	
Mean ± SE	55.9 ± 1.19
Range	18–82
≤60	65.1
>60	34.9
Race, n (%)	
Caucasian	52 (49.1)
Black	1 (0.9)
Indian	53 (50.0)
Sex, n (%)	
Male	57 (53.8)
Female	49 (46.2)
Weight (kg)	
Mean ± SE	59.8 ± 1.81
Range	30.0–129.4
Eastern Cooperative Oncology Group score (%)	
0	4.7
1	59.4
2	35.8
Baseline opioid use,^a n (%)	
Morphine	63 (59.4)
Fentanyl	35 (33.0)
Oxycodone	9 (8.5)
Pentazocine	2 (1.9)
Buprenorphine	2 (1.9)
Hydromorphone	2 (1.9)

^aSome subjects used more than one opioid medication.

Fourteen serious AEs (12 events after FPNS treatment of the preceding episode, two events after IRMS treatment of the preceding episode) were reported by 8 patients (6 after FPNS, 2 after IRMS). A total of 6 deaths occurred during the study: 3 patients died during screening before taking any study drug, 2 died during the dose-titration phase, and 1 died during the DB/DD phase. Most serious AEs and deaths were considered not related to the study drug; however, 1 death was assessed as possibly related to the study drug (circulatory insufficiency, hypotension, anuria following last treatment with FPNS). No treatment-emergent changes in mean values of laboratory or clinical safety parameters occurred that were suggestive of safety issues associated with either treatment. No patients were suspected of abuse or diversion of the study drug at any center involved in the trial.

NASAL TOLERABILITY

There were no changes on objective clinical assessment of the nose. At the final study visit, ≤5.7% of patients reported itching/sneezing, crusting/drying of the nose, stuffy/blocked

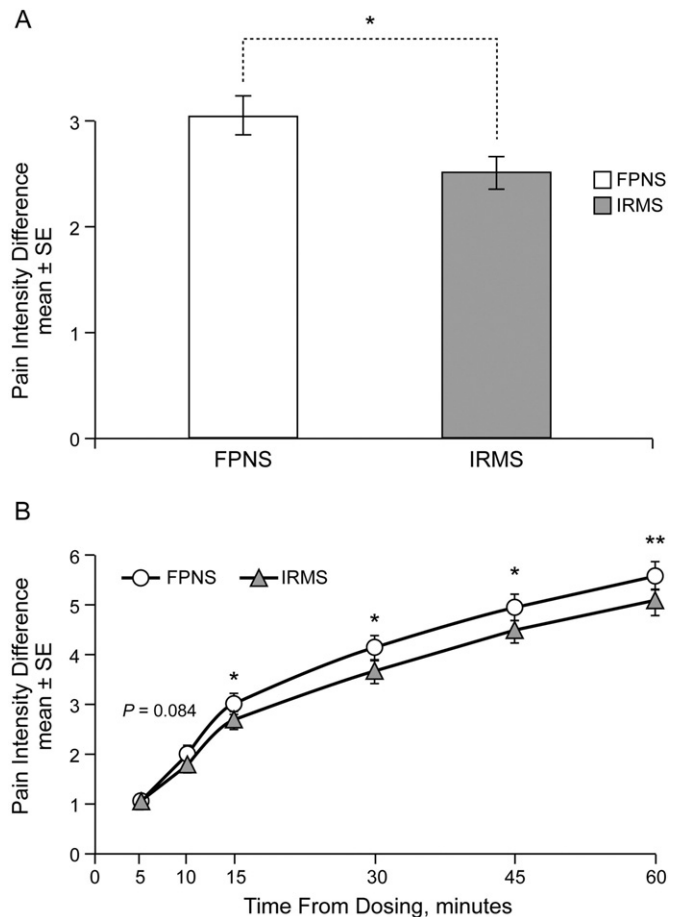


Figure 2 PID Scores at 15 Minutes (A) and At All Time Points (Patient-Averaged Values) (B)
(A) *P < .05 FPNS vs. IRMS. (B) *P < .05 FPNS vs. IRMS, **P < .01 FPNS vs. IRMS

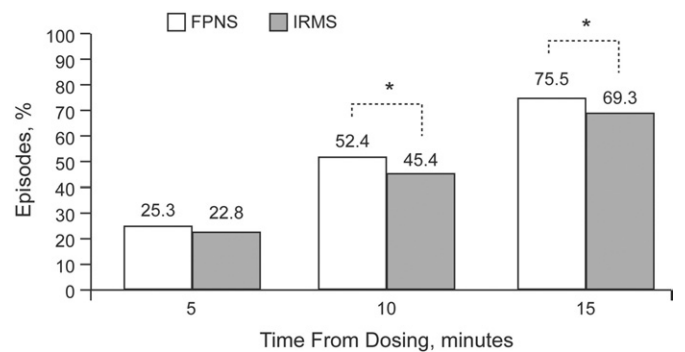


Figure 3 Percentages of Episodes with Clinically Meaningful Pain Relief (≥2-Point Reductions in Pain Intensity)

*P < .05 FPNS vs. IRMS

nose, cough, sore throat, burning/discomfort, nasal bleeding, or postnasal drip above a mild intensity (ie, intensity >1). One patient experienced severe taste disturbance at the final study visit. The overall percentage of patients reporting any of

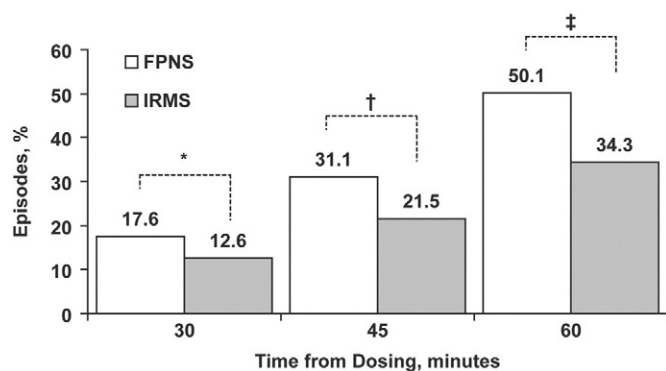


Figure 4 Percentages of Episodes with Maximal Pain Relief (PR = 4)

* $P = .05$, † $P < .01$, ‡ $P < .0001$ FPNS vs. IRMS

these events at mild or moderate intensity before the first use of the study drug ($\leq 10.7\%$) decreased at the final study visit ($\leq 7.3\%$). No statistically significant difference was noted between FPNS and IRMS (nasal placebo) treatments for any subjective nasal tolerability parameter.

Discussion

This is the first study to compare the efficacy and tolerability of intranasal fentanyl with IRMS in the management of BTCP. It demonstrated a statistically significant improvement in PID_{15} of FPNS compared with IRMS ($P < .05$). Significant benefits in episode PR scores and PID scores were reported with FPNS compared to IRMS within only 5 minutes of dosing, and clinically meaningful levels of pain relief were observed across several parameters from 10 minutes after dosing.

The efficacy of FPNS within 5 minutes of dosing was also reported in an earlier study in which the onset of CMPR was again observed within 10 minutes of administration.¹⁶ This rapid onset of effect is of major importance in the management of BTCP. Although IRMS remains a common therapy for BTCP, it is often criticized for its 30-minute onset of effect, which is usually not fast enough to meet patients' needs.⁷ The clinical relevance of this delayed onset of effect was clearly observed in our study. Using a commonly accepted metric of ≥ 2 -point reduction in PI as an indicator of clinically meaningful response,¹⁹ significantly more episodes met the criterion for meaningful pain relief with FPNS than with IRMS at 10 and 15 minutes ($P < .05$). The cumulative advantage of FPNS at 10 minutes was further supported by statistically significant differences in the percentages of episodes showing SPID values at the ≥ 2 -point, ≥ 3 -point, and ≥ 4 -point thresholds ($P = .0146$, $P = .0348$, $P = .0338$, respectively).

From 30 minutes, the differences between the two treatments remained the same or started to close, suggesting that IRMS started to match the analgesic effect of FPNS only from this time. It is, of course, likely that a proportion of BTCP episodes resolved spontaneously by 30 minutes. However, a

further examination of BTCP episodes achieving a maximum PR score of 4 showed that FPNS was more effective at providing maximal pain relief for the full duration of a typical BTCP episode, which surveys have shown lasts an average of 45–60 minutes (range 5–360 minutes).⁴ This correlates with the pharmacokinetics of FPNS, which studies have shown still provides therapeutic levels of plasma fentanyl at 60 minutes.²⁰ At 60 minutes, approximately half the episodes had achieved maximum pain relief compared with just over one-third for IRMS, representing a 46.1% improvement in maximal pain relief efficacy with FPNS.

Efficacy scores for IRMS at the early time points were not entirely consistent with the expected pharmacodynamic profile of oral morphine^{7,9} and were higher than those demonstrated by previous studies in BTCP (e.g., PID_{60} of IRMS was ~ 5 points in the present study vs. ~ 3.5 points in the study by Coluzzi et al.¹⁸). Although this may suggest that some BTCP episodes were short-lived, the multiple-crossover design means that this was likely equally true for both treatments. Another potential explanation is a significant effect of the trial design. A “training effect” of patient expectations (similar to a placebo response) possibly occurred during the open-label dose-titration phase with FPNS. Thus, having experienced an effective dose of FPNS, it is possible that patients were primed to expect rapid pain relief. In support of this notion, recent brain imaging studies have suggested that the main effect of placebo arises from the reduction of anticipation of pain during placebo conditioning (or, in the present study, the titration phase).^{21,22} Given that the perception of pain is highly subjective, this training effect might have impacted the results, especially at earlier time points. Studies of BTCP characteristics have focused primarily on duration from onset until peak pain.²³

More TEAEs were reported after FPNS than after IRMS treatment. However, it is difficult to relate the occurrence of AEs to a specific treatment in a study using a short-interval, multiple-crossover design. In studies of medications for BTCP, this problem is further compounded because all patients are given a background treatment of daily opioid therapy, which is expected to contribute to the overall AE rate. In this study, all AEs reported within a 24-hour period of an FPNS dose were conservatively associated with FPNS, even if the patient had also been treated that day with IRMS. This led to obvious skewing toward a higher AE rate with FPNS. Safety results include the open-label dose-titration phase; therefore, each patient treated had significantly more episodes with FPNS than with IRMS, again skewing the comparison. Two deaths occurred after FPNS administration in the open-label dose-titration phase and one occurred after IRMS administration in the DB/DD treatment phase. All were likely related to the underlying disease process. All TEAEs that led to study drug discontinuation were recognized side effects of fentanyl or other opioids or related to the underlying disease process.

The study design was comparable to that of previous studies of other fentanyl formulations for BTCP.¹⁸ This crossover

Table 2**Summary of Common Treatment-Emergent Adverse Events (Safety Population)**

PREFERRED TERM	FPNS				IRMS TOTAL (N = 80)
	100 µg (N = 105)	200 µg (N = 82)	400 µg (N = 60)	800 µg (N = 23)	
Overall	25 (23.8%)	15 (18.3%)	20 (33.3%)	8 (34.8%)	13 (16.3%)
Vomiting	4 (3.8%)	2 (2.4%)	3 (5.0%)	2 (8.7%)	3 (3.8%)
Somnolence	2 (1.9%)	4 (4.9%)	3 (5.0%)	0 (0.0%)	1 (1.3%)
Dehydration	1 (1.0%)	3 (3.7%)	1 (1.7%)	1 (4.3%)	1 (1.3%)
Nausea	1 (1.0%)	1 (1.2%)	2 (3.3%)	2 (8.7%)	1 (1.3%)
Constipation	2 (1.9%)	1 (1.2%)	3 (5.0%)	0 (0.0%)	1 (1.3%)
Dizziness	2 (1.9%)	2 (2.4%)	2 (3.3%)	0 (0.0%)	0 (0.0%)
Headache	1 (1.0%)	2 (2.4%)	1 (1.7%)	0 (0.0%)	0 (0.0%)
Asthenia	1 (1.0%)	1 (1.2%)	1 (1.7%)	0 (0.0%)	1 (1.3%)

FPNS = fentanyl pectin nasal spray; IRMS = immediate-release morphine sulfate.

design is considered most suitable for studies of BTCP because each patient acts as his or her own control, thereby eliminating the significant issues of between-patient variability in reporting pain and in BTCP characteristics. As discussed, however, this does complicate efforts to identify and interpret the relationship between medication and TEAEs. Another strength of the study is the use of a double-dummy as an additional measure against bias or placebo effect because all patients were given either placebo or active drug by both delivery routes for each episode during the double-blind assessment. Limitations of the study include its relatively short duration and the lack of titration to an effective dose of IRMS. However, longer-term studies with FPNS have been conducted,²⁴ and the dose of IRMS was calculated using the equivalent 4-hour dose of morphine, per EAPC guideline recommendations at the time the study was conducted.¹⁷ Although it could be argued that this approach is not ideal, even in routine practice, it was the intention of the study to reflect the clinical use of IRMS as much as possible. Moreover, the higher than expected efficacy scores for IRMS appear to rule out any underdosing. Although the use of an open-label dose-titration phase to identify a tolerable but effective dose (enrichment approach) can draw criticism^{25,26} and might have led to a training effect, the fact that rapid-onset opioids for the treatment of BTCP must always be titrated means

this approach mirrors clinical practice. Furthermore, only 5.5% of patients failed to identify an effective dose because of lack of efficacy, indicating that this approach and the dose range selected are appropriate to clinical practice.

Conclusions

The results of this study demonstrate that FPNS is efficacious, safe, and well tolerated for the treatment of breakthrough pain in a population of cancer patients receiving around-the-clock opioid treatment for chronic cancer-related pain. Treatment with FPNS was effective at delivering significant early, clinically meaningful reductions in pain that matched or exceeded the therapeutic effect of IRMS as well as providing more complete pain relief throughout the duration of the BTCP episodes treated.

Acknowledgments: The authors acknowledge i3Research, which conducted the study; the technical and editorial support provided by Anita Chadha-Patel at ApotheCom; and the Fentanyl Nasal Spray Study 044 Investigators. This study was sponsored by Archimedes Development, Ltd.

Conflicts of interest Disclosure: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Davies has served as a consultant for Archimedes and received support from Archimedes to travel to meetings to present trial data. No other conflicts of interest were reported.

References

PubMed ID in brackets

- Davies AN, Dickman A, Reid C, et al. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain* 2009;13:331–338.
- Mercadante S, Radbruch L, Caraceni A, et al. Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care. *Cancer* 2002;94:832–839.
- Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. *Pain* 1990;41:273–281.
- Portenoy R, Bruns D, Shoemaker B, et al. Breakthrough pain in community-dwelling patients with cancer pain and noncancer pain, 1: prevalence and characteristics. *J Opioid Manag* 2010;6:97–108.
- Wiffen PJ. Evidence-based pain management and palliative care in issue one for 2008 of the Cochrane Library. *J Pain Palliat Care Pharmacother* 2008;22:239–242.
- Ruiz-Garcia V, Lopez-Briz E. Morphine remains gold standard in breakthrough cancer pain. *BMJ* 2008;337:a3104.
- Zeppetella G. Dynamics of breakthrough pain vs. pharmacokinetics of oral morphine: implications for management. *Eur J Cancer Care (Engl)* 2009;18:331–337.
- Zeppetella G. Opioids for cancer breakthrough pain: a pilot study reporting patient assessment of time to meaningful pain relief. *J Pain Symptom Manage* 2008;35:563–567.
- Collins SL, Faura CC, Moore RA, et al. Peak plasma concentrations after oral morphine: a systematic review. *J Pain Symptom Manage* 1998;16:388–402.
- Davies AN, Broadley K, Beighton D. Xerostomia in patients with advanced cancer. *J Pain Symptom Manage* 2001;22:820–825.

11. Davies AN, Vriens J. Oral transmucosal fentanyl citrate and xerostomia. *J Pain Symptom Manage* 2005;30:496–497.
12. Jacobsen R, Moldrup C, Christrup L. Clinical rationale for administering fentanyl to cancer pain patients: two Delphi surveys of pain management experts in Denmark. *J Opioid Manag* 2008;4:383–391.
13. Dale O, Hjortkjaer R, Kharasch ED. Nasal administration of opioids for pain management in adults. *Acta Anaesthesiol Scand* 2002;46:759–770.
14. Illum L. Nasal drug delivery—possibilities, problems and solutions. *J Control Release* 2003;87:187–198.
15. Watts P, Smith A. PecSys: in situ gelling system for optimised nasal drug delivery. *Expert Opin Drug Deliv* 2009;6:543–552.
16. Portenoy R, Burton AW, Gabrail N, et al. A multicenter, placebo-controlled, double-blind, multiple-crossover study of fentanyl pectin nasal spray (FPNS) in the treatment of breakthrough cancer pain. *Pain* 2010;151:617–624.
17. Hanks GW, Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001;84:587–593.
18. Coluzzi PH, Schwartzberg L, Conroy JD, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Pain* 2001;91:123–130.
19. Farrar JT, Berlin JA, Strom BL. Clinically important changes in acute pain outcome measures: a validation study. *J Pain Symptom Manage* 2003;25:406–411.
20. Fisher A, Watling M, Smith A, et al. Pharmacokinetics and relative bioavailability of fentanyl pectin nasal spray 100–800 μg in healthy volunteers. *Int J Clin Pharmacol Ther* 2010;48:860–867.
21. Watson A, El-Derey W, Iannetti GD, et al. Placebo conditioning and placebo analgesia modulate a common brain network during pain anticipation and perception. *Pain* 2009;145:24–30.
22. Ploner M, Lee MC, Wiech K, et al. Pre-stimulus functional connectivity determines pain perception in humans. *Proc Natl Acad Sci USA* 2010;107:355–360.
23. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain* 1999;81:129–134.
24. Portenoy RK, Raffaelli W, Torres LM, et al. Long-term safety, tolerability, and consistency of effect of fentanyl pectin nasal spray for breakthrough cancer pain in opioid-tolerant patients. *J Opioid Manag* 2010;6:319–328.
25. Lemmens HJ, Wada DR, Munera C, et al. Enriched analgesic efficacy studies: an assessment by clinical trial simulation. *Contemp Clin Trials* 2006;27:165–173.
26. Straube S, Derry S, McQuay HJ, et al. Enriched enrollment: definition and effects of enrichment and dose in trials of pregabalin and gabapentin in neuropathic pain: a systematic review. *Br J Clin Pharmacol* 2008;66:266–275.

Highlights from the 2011 Annual Meeting of the American Society of Clinical Oncology

Survey Highlights Survivor Care Issues

MAJOR FINDING: Medical oncologists and primary care physicians perceive different barriers to care when dealing with survivors of breast and colon cancer. Barriers include inadequate physician training, the practice of defensive medicine (against malpractice), and confusion about responsibility and delivery of care. More education and survivorship care planning are needed.

DATA SOURCE: Survey study of 2,202 physicians (from an AMA cohort of 5,275).

DISCLOSURES: Cosponsored by the National Cancer Institute and the American Cancer Society. Dr. Virgo reported no relevant financial conflicts.

BY RICHARD HYER

Elsevier Global Medical News

Primary care physicians and oncologists expressed their concerns about continuity and coordination of care for cancer survivors in a survey of more than 2,000 physicians.

The degree of concern about different survivor care issues varied by specialty. For example, primary care physicians were more likely than were oncologists to be concerned about malpractice suits and about a lack of adequate training.

The Survey of Physician Attitudes Regarding the Care of Cancer Survivors (SPARCCS) is the first nationwide study to focus on physician beliefs, knowledge, attitudes and practices regarding breast and colorectal cancer survivorship care.

“Increased coordination of care is needed to ensure continuity of care,” said lead author Katherine S. Virgo, Ph.D., director of health services research at the American Cancer Society, which cosponsored the study with the National Cancer Institute. “Yet barriers to achieving care remain in our fragmented health care system.”

A total of 1,072 primary care physicians (internists, family physicians, and ob.gyns.) and 1,130 medical oncologists were asked about their perceptions of the barriers to care for survivors of breast and colorectal cancer.

The survey asked about problems encountered when caring for breast or colon cancer survivors who had completed active treatment at least 5 years earlier. Five problem areas were identified in the survey: increased testing as malpractice protection; uncertainty regarding general preventive health care responsibility; duplicated care; missed care; and lack of adequate knowledge or training.

“Bivariate results show that the physicians’ specialty was significantly associated with all five barriers,” Dr. Virgo said.

Almost 60% of oncologists said malpractice was never or rarely a barrier, versus almost 50% of primary care physicians. More primary care physicians said fear of malpractice

was sometimes (40% versus 31%) or often/always (16% vs. 10%) a barrier, (P less than .001 in all cases).

As for missed care, 43% of primary care physicians said it was never/rarely an issue, versus 40% of oncologists. More oncologists said it was sometimes an issue (48% vs. 42%), but more primary care physicians said it was often or always (15% vs. 12%) an issue, (P less than .0047 in all cases).

“PCPs were also significantly more likely to be concerned about lacking adequate training to manage patient problems,” said Dr. Virgo.

Indeed, almost 90% of oncologists said lack of training was never or rarely an issue, versus 54% of primary care physicians (P less than .0001 in all cases).

For primary care physicians and oncologists, duplicated care was never or rarely an issue (52% versus 44%, respectively), sometimes a problem (37% vs. 43%), and often/always a problem (11% vs. 13%), she said. (P = .0035 in all cases).

“Medical oncologists were also significantly more likely to report, often/always and sometimes, concerns about which physician is providing general preventive care services,” said Dr. Virgo.

Physicians included in the survey had to practice in a non-federal setting, be 76 years of age or younger, and dedicate at least 20% of their professional time to patient care. Additional criteria were specific to the specialty: medical oncologists must have cared for breast or colon cancer patients within the past year, and primary care physicians must have had office-based practices.

Conventional Cardiovascular Risk Factors Hit Cancer Survivors Hard

MAJOR FINDING: The 45-year cumulative incidence was higher among survivors than siblings for grades 3-5 coronary artery disease (4.5% vs. 0.8%), heart failure (4.7% vs. 0.5%), valve abnormality (1.3% vs. 0.1%), and arrhythmia (0.8% vs. 0%).

DATA SOURCE: Retrospective analysis of 13,268 adult survivors of childhood and adolescent cancer and a cohort of 4,023 siblings.

DISCLOSURES: The Childhood Cancer Survivor study is funded by the National Cancer Institute. Dr. Armstrong and his coauthors reported having no relevant conflicts.

BY PATRICE WENDLING

Elsevier Global Medical News

The presence of conventional cardiovascular risk factors further increases the risk for poor cardiovascular outcome among adult survivors who were exposed to cardio-

toxic cancer therapy as children, according to a report from the Childhood Cancer Survivor Study.

At age 50 years or older, 39% of adult survivors reported being treated for hypertension, compared with 28% of siblings. They also reported higher rates of treatment for dyslipidemia (29% vs. 18%) and diabetes (8% vs. 5%), but not for obesity, defined as a body mass index of at least 30 kg/m² (22% vs. 36%).

Almost 10% of the 13,268 survivors had at least three of these four risk factors compared with 8.5% of the 4,023 sibling cohort, said Dr. Gregory Armstrong of St. Jude's Children's Research Hospital in Memphis, Tenn.

"The take-home point is that these are all modifiable risk factors," he said.

Not surprisingly, the cumulative incidence at age 45 years was also higher among survivors than siblings for grade 3-5 coronary artery disease (4.5% vs. 0.8%), heart failure (4.7% vs. 0.5%), valve abnormality (1.3% vs. 0.1%), and arrhythmia (0.8% vs. 0%).

A previous report from the long-running study revealed that the risk among adult survivors was increased nearly sixfold for heart failure, fivefold for myocardial infarction, and sixfold for valvular disease, and that the risk continues to increase even 30 years after diagnosis (BMJ 2009 Dec. 8 [doi:10.1136/bmj.b4606]).

The current analysis assessed associations between cardiovascular outcomes and the presence of a cardiovascular risk factor (CVRF) cluster of three or more conventional risk factors.

Patients who had a CVRF cluster alone had nearly a sevenfold increased risk of developing coronary artery disease by age 50, compared with the referent group who received no chest-directed radiotherapy and did not have a CVRF cluster (odds ratio, 6.8).

Patients who had chest radiation and no CVRF cluster had a sixfold increased risk of coronary artery disease (OR, 6.3). This risk was 28-fold higher (OR, 28.2) if they had chest radiation and went on to develop a CVRF cluster (P value less than .001), he said.

The risk of heart failure was fourfold higher among patients treated with chest radiation alone (OR, 4.3) and 16-fold higher if chest radiation was compounded by a CVRF cluster (OR, 16.2), although the difference was not statistically significant.

The addition of a CVRF cluster to chest radiation significantly increased the risk of a valve abnormality, from an odds ratio of 15.9 to a staggering 55.7 (P = .03) and of an arrhythmia from an odds ratio of 1.9 to 15.8 (P = .01).

Patients who received chest radiation did not need to have a cluster of CV risk factors to be at increased risk for heart disease. A comparison between chest radiation alone and chest radiation plus hypertension revealed a significant increase in the risk of coronary artery disease (OR, 6.6 vs. 46.7), heart failure (OR, 4.0 vs. 66.3), valve abnormality (OR, 21.9 vs. 217.7) and arrhythmia (OR, 1.8 vs. 15.5), Dr. Armstrong said (P less than .001 for all).

The researchers also looked at the impact of anthracyclines, which are known to be cardiotoxic, and found that the addition of a CVRF cluster to anthracycline use significantly

increased the risk of heart failure from an odds ratio of 3.2 to 11.4 (P = .04).

In all, 190 cardiac deaths were identified among the cancer survivors. The cumulative incidence of cardiac mortality at 30 years was 1%. The standardized mortality ratio was 4.85, representing a nearly fivefold increased risk of cardiac death in the cancer survivors compared with the general population, he said.

In an analysis that adjusted for sex, ethnicity, education, and household income, the presence of hypertension (hazard ratio, 5.8; P less than .0001) and diabetes (HR, 2.2; P = .08) was associated with cardiac death. No significant association was observed between smoking and the outcomes.

Dr. Armstrong acknowledged that the study relied on self-reported outcomes.

"We can clearly state that these are risks. We also increase our opportunities to speak about them and educate our population," he said.

The retrospective cohort was younger than 21 years old at the time of cancer diagnosis, 2,297 received any chest-directed radiotherapy, 2,176 were exposed to a cumulative anthracycline dose of 1-299 mg/m², and 1,993 received at least 300 mg/m² of anthracycline exposure. The median age at last follow-up was 32 years (range 5.6-59 years).

Colorectal Cancer Survivors Lag in Care for Comorbid Conditions

MAJOR FINDING: Among colorectal cancer survivors, there were four indicators of worse chronic care (COPD visits, lipid monitoring after angina, diabetes eye exams, and diabetes monitoring) and three of worse acute care (acute MI and heart failure visits, and cholecystectomy), compared with controls.

DATA SOURCE: A retrospective, cross-sectional study of care given to 8,661 cancer survivors and 17,322 controls, all aged 66 years or older.

DISCLOSURES: The study was funded by the National Cancer Institute. Dr. Snyder and Dr. Wagner disclosed no relevant relationships.

BY RICHARD HYER

Elsevier Global Medical News

The quality of care that older cancer survivors receive for comorbid conditions such as diabetes and heart failure varies by tumor type, according to a retrospective, cross-sectional analysis of database records for more than 25,000 people.

Colorectal cancer survivors fared the worst of three tumor cohorts studied. Compared with a control group of cancer-free patients, they were more likely to receive acute and chronic care that was subpar on a variety of measures, Claire Snyder, Ph.D., reported at the meeting.

Breast cancer survivors fared best, receiving equivalent acute and better chronic care than did cancer-free controls. Prostate cancer survivors came out somewhere in the middle,

receiving worse acute care but better chronic care.

The study “does not explain why care was or was not provided,” Dr. Snyder said, listing its limitations. She hopes to explore why survivor care varies by tumor type as well as possible relationships with cost, she added.

“The issue of comorbid-condition care in cancer survivors has been understudied. As our treatments improve and survivors live longer with a history of a cancer diagnosis, quality care for comorbid conditions takes on greater importance,” said Dr. Snyder of Johns Hopkins University in Baltimore.

Cancer survivors’ health care needs include surveillance for recurrence and monitoring for the physical and psychosocial long-term and late effects of the disease and its treatment, she said. Their needs also include general primary and preventive care, and often care for comorbid conditions,

This study used data from the SEER (Surveillance, Epidemiology and End Results)-Medicare database, a cancer registry linked with Medicare claims data. The nation’s 17 SEER registries cover a representative sample of more than one-quarter of the U.S. population. Medicare claims data on noncancer controls who live in SEER regions were used for comparison.

The study population was diagnosed with locoregional breast, prostate, or colorectal cancer in 2004. They were at least 66 years old and were enrolled in fee-for-service Medicare during the study period. They had survived at least 3 years from diagnosis, and had no evidence of ongoing cancer treatment.

The 8,661 cancer survivors in the study were “frequency matched” with 17,322 cancer-free controls. Slightly more than half of the cancer group (4,559) had survived prostate cancer; 2,231 had survived colorectal cancer; and 1,871 survived breast cancer. The study period covered years 2 and 3 from day of diagnosis.

The final sample had a mean age of approximately 75 years; nearly two-thirds were men, and 85% were white. More than 88% in both case and control groups lived in an urban area.

There were 9 quality indicators for care of chronic conditions, and 19 for care of acute conditions. To calculate the percentage of survivors receiving appropriate care, investigators divided the number of cases and controls who received appropriate care by the number eligible for each indicator.

A summary analysis showed that among colorectal cancer survivors, there were four indicators of worse chronic care (chronic obstructive pulmonary disease visits, lipid monitoring after angina, diabetes eye exams, and diabetes monitoring), and three indicators of worse acute care (visits after acute MI and heart failure hospitalizations, and cholecystectomy), compared with controls.

Prostate cancer survivors had three indicators of worse acute care (ECG after heart failure, chest film after heart failure, and cholecystectomy), but two indicators of better chronic care (COPD and diabetes visits).

The breast cancer survivors did better on COPD and diabetes visits.

Among the study’s strengths, Dr. Snyder said that it examined the initial transition from acute cancer treatment to survivorship, an important time to ensure that survivors do not get lost in transition.

Discussant Lynne I. Wagner, Ph.D., of Northwestern University in Chicago said that this represented a novel contribution to the evidence base in survivorship care. “The comorbidity issues are extremely important. This is probably the tip of the iceberg in terms of what’s going on,” she said.

TNF-Alpha Activity Eyed for Role in ‘Chemo Brain’

MAJOR FINDING: sTNFR_{II}, a stable measure of TNF-alpha activity, was significantly increased in patients who received chemotherapy as part of their primary treatment for breast cancer (2,492.5 pg/mL), as compared to patients who did not (2,115.6 pg/mL); P = .007.

DATA SOURCE: Longitudinal data on 93 women enrolled after primary therapy for breast cancer; 49 had received chemotherapy, 44 had not.

DISCLOSURES: The study was funded by the National Cancer Institute and the Breast Cancer Research Foundation. Dr. Ganz and Dr. Mustian said they had no relevant financial relationships.

BY RICHARD HYER

Elsevier Global Medical News

Circulating tumor necrosis factor appears to play a role in the cognitive dysfunction called “chemo brain” that some women experience after receiving chemotherapy as part of their primary treatment for newly diagnosed breast cancer.

Preliminary data on 93 women in a prospective observational cohort study show that women who underwent chemotherapy had higher levels of circulating tumor necrosis factor (TNF) than did similar women who had not received chemotherapy as part of their primary treatment.

The chemotherapy group also started the study with worse quality of life and poorer cognitive function, compared with patients who did not have chemotherapy before enrolling in the study. None of the women had started endocrine therapy at that point.

“These effects are specific to TNF and were not associated with other biomarkers of inflammation studied,” Dr. Patricia A. Ganz reported.

TNF may, therefore, represent a biologic target for pharmacologic therapy, as well as a biomarker that could help identify patients at increased risk for so-called “chemo brain,” cognitive complaints during adjuvant chemotherapy that can persist for years afterward in up to 25% of breast cancer survivors, according to Dr. Ganz, director of prevention and control research at the Jonsson Comprehensive Cancer Center at the University of California, Los Angeles.

The study is thought to be among the first to comprehensively examine the relationship between inflammatory markers and cognitive changes in breast cancer patients, she said. It was suggested in part by a study of doxorubicin exposure in an animal model, which found systemic increases in the proinflammatory cytokine TNF-alpha. This cytokine is able to cross the blood-brain barrier and accumulate in the central

nervous system (Neurobiol. Dis. July 2006;23:127-39).

The current study enrolled 191 women within 3 months of completion of primary therapy (surgery, radiation, and/or chemotherapy), and prior to initiating endocrine therapy for recently diagnosed breast cancer. All women underwent comprehensive assessments at baseline, 6 months, and 12 months after enrollment. A subset of 16 women also participated in a PET scan substudy and had brain scans at baseline and 12 months later.

The longitudinal data reported by Dr. Ganz was based on the first 93 women with complete cytokine assessments: 49 women who received chemotherapy and 44 women who did not have chemotherapy as part of their primary treatment. Similar proportions of both groups had undergone mastectomy (28% overall) and radiotherapy (76% overall) during primary treatment; 72% of the total population went on to receive endocrine therapy. The women had a mean age of 51 years and were enrolled an average of 7 months after diagnosis of breast cancer.

At baseline, the postchemotherapy group reported significantly poorer quality of life and functioning on several standardized measures, including the SF36 physical and mental component summary scales, sleep, fatigue, and depression.

Self-reported measures of cognitive complaints, including the multidimensional Patients Assessment of Own Functioning Inventory (PAOFI), also suggested that they had greater memory impairments. A significant correlation was found between the PAOFI memory subscale score and cognitive complaints in the chemotherapy group (correlation with log $r = 0.33$, $P = .05$).

Fasting blood specimens were tested for four inflammatory markers: interleukin-1 receptor antagonist, interleukin-6, C-reactive protein, and soluble TNF receptor type II (sTNFR_{II}), which provides a stable assessment of TNF-alpha activity.

Only sTNFR_{II} was significantly increased in the chemotherapy-treated group (2,492.5 pg/mL vs. 2,115.6 pg/mL in the other patients, $P = .007$). Over the course of the year, it decreased to the point where the difference between groups was no longer significant.

In the 16 patients with complete PET scan data, soluble TNF receptor level at baseline was negatively correlated with metabolic activity in the inferior frontal gyrus in chemotherapy-treated patients ($P = .04$). Patients with higher levels of TNF receptor had lower levels of metabolic activity. This, however, also improved over 12 months.

Finally, genetic analysis suggests that the GG allele of the TNF-alpha 308 single nucleotide polymorphism was associated with more cognitive complaints. It may enhance the patient's vulnerability to cognitive complaints and cognitive dysfunction.

Discussant Karen Mustian, Ph.D., of the University of Rochester (N.Y.) said, "The strengths of this study include its prospective longitudinal design as well as the examination of potential biological mechanisms, including inflammation, genetic polymorphisms, and cerebral function."

She described examination of biomarkers and mechanisms as important in supportive care research, and expressed optimism that this type of research has only just begun.

Novel Anticoagulant Semuloparin Prevents VTEs During Chemotherapy

MAJOR FINDING: The rate of VTE events was 1.2% in patients given prophylactic semuloparin vs. 3.4% in a control group treated with placebo (HR, 0.36; P less than .0001).

DATA SOURCE: A phase III trial in 3,200 cancer patients who were scheduled to receive at least 3 months of chemotherapy.

DISCLOSURES: The study was sponsored by Sanofi-Aventis. Dr. George disclosed numerous relationships with pharmaceutical companies, including consultant or advisory role, honoraria, and speakers bureau with Sanofi-Aventis. Dr. Agnelli disclosed receiving honoraria from Sanofi-Aventis and relationships with other companies. Dr. Stearns disclosed honoraria and research funding from other companies.

BY RICHARD HYER

Elsevier Global Medical News

Prophylaxis with semuloparin, an experimental ultralow-molecular-weight heparin, achieved a significant 64% reduction in relative risk for venous thromboembolism events among cancer patients undergoing chemotherapy in a large, randomized, double-blind, phase III trial called SAVE-ONCO.

An intent-to-treat analysis found that the rate of venous thromboembolism (VTE) events - a composite of symptomatic deep vein thrombosis, any pulmonary embolism, and VTE-related death - was 1.2% in patients treated with semuloparin vs. 3.4% in a control group treated with placebo (hazard ratio, 0.36; P less than .0001).

Benefits trended in favor of semuloparin for all components of the composite end point, including any pulmonary embolism (odds ratio, 0.41) and VTE-related death (OR, 0.77), reported Dr. Daniel J. George, who presented the paper on behalf of Dr. Giancarlo Agnelli of Perugia (Italy) University at the meeting.

Although the incidence of clinically relevant bleeding was higher at 2.8% with semuloparin vs. 2% for placebo, Dr. George added that a safety analysis found that the incidence of major bleeding was similarly low, at 1.2% and 1.1%, respectively.

Based on the trial results, Dr. Elias Zerhouni, president of global research and development at trial sponsor Sanofi-Aventis, announced that the company plans "to submit semuloparin for regulatory filing" in the third quarter of 2011. Still investigational, the selectively engineered anticoagulant has high anti-coagulation factor Xa activity and minimal anti-coagulation factor IIa activity with a half-life of 16-20 hours.

Although it is advocated for cancer patients who are hospitalized or undergoing surgery and is not contraindicated for anticoagulation, the routine prophylaxis of ambulatory cancer patients receiving chemotherapy is not currently recommended.

"So this leaves us with the question, Which cancer patients should we now consider for thromboprophylaxis?" said Dr. George of Duke University Medical Center in Durham, N.C. "Already our guidelines suggest that those patients with cancer undergoing major surgery, or hospitalized, or acutely ill, ought to be anticoagulated with low-molecular-weight hepa-

rin during those periods of time.

“I would now submit that the SAVE ONCO data would support having patients initiating chemotherapy, in the setting of locally advanced or metastatic disease, as a third population that we could consider for thromboprophylaxis,” he said.

Although discussant Dr. Vered Stearns of Johns Hopkins University in Baltimore viewed the findings favorably, she cautioned that “SAVE-ONCO should not change current practice for the overall population.”

Dr. Stearns emphasized that predictive models are needed to determine which ambulatory patients are at the highest risk for VTE, “and who should be offered prophylaxis in the context of expected clinical outcomes.” Biomarkers such as circulating coagulating factors are also important, she added.

“Semuloparin is an efficacious and safe agent. That’s very exciting,” Dr. Stearns said. “The reduction in [VTE] events is consistent throughout the report, and my understanding is [that] the group is conducting subgroup analysis and evaluation of predictive markers that may help us select the population that would benefit from primary prophylaxis.”

A multinational study, the SAVE-ONCO trial enrolled 3,200 patients who were at high risk of VTE. Participants had metastatic or locally advanced solid tumors such as lung, pancreas, stomach, colon/rectal, bladder, or ovarian tumors for which they were starting a new course of chemotherapy with minimum treatment intent of 3 months.

Patients were randomized 1:1 to standard-care chemotherapy plus either placebo or semuloparin 20 mg subcutaneously once daily for the length of their chemotherapy.

Patient characteristics were well balanced across both arms: The median age was 60 years, and 60% of patients were men. More than two-thirds had metastatic disease. Lung cancer was the most common tumor type (36%) followed by colon/rectal cancer (28%). The remainder had cancer of the stomach, ovary, pancreas, or bladder. Treatment duration was approximately 3.5 months in both groups.

In response to audience questions, Dr. George said that the study did not show a survival benefit, but “there is likely a subset of patients” for whom this made a dramatic impact in their early morbidity and mortality.

The study did not address cost, but that will be a factor if prophylaxis is introduced for a large population of cancer patients, he acknowledged, “It really comes down to safety and cost,” he said.

Paclitaxel-Associated Pain Predicts Peripheral Neuropathy

MAJOR FINDING: Paclitaxel-associated acute pain syndrome appeared in 88% of adult patients, and severity was associated with peripheral neuropathy ($P = .0017$).

DATA SOURCE: Self-reports completed by 85 patients receiving 175 mg/m² of paclitaxel with concomitant carboplatin every 3 weeks for various cancers.

DISCLOSURES: This study was funded by a grant from the National Cancer Institute’s Community Clinical Oncology Program. Dr. Reeves said she had no conflicts of interest.

BY SUSAN HITE

Elsevier Global Medical News

Paclitaxel-associated acute pain syndrome is common, and its severity appears to track with the emergence of peripheral neuropathy, according to a prospective cohort study from the North Central Cancer Treatment Group.

“The more severe the pain, the more likely it was that a patient would experience peripheral neuropathy during 18 weeks of treatment,” Dr. Brandi N. Reeves reported in a poster presented at the annual meeting of the American Society of Clinical Oncology. The association was highly significant ($P = .0017$), noted Dr. Reeves of the Mayo Clinic, Rochester, Minn.

Lung and ovarian cancers were the most common in the study. Patients completed a daily questionnaire on days 2-7 following chemotherapy, rating the severity of their pain on a 10-point scale, with 10 being the worst. They also completed a questionnaire (the European Organisation for the Research and Treatment of Cancer’s Quality of Life Chemotherapy-Induced Peripheral Neuropathy-20 [EORTC-CIPN-20] instrument) at the beginning of each cycle and monthly after completion of chemotherapy.

The results showed that most patients receiving 175 mg/m² or more of paclitaxel every 3 weeks with concomitant carboplatin can expect to experience the arthralgias and myalgias that comprise paclitaxel-associated acute pain syndrome. Among 85 patients on this regimen, 88% experienced pain, most prominently in the hips and lower extremities.

Pain peaked each cycle at day 4 after paclitaxel treatment, according to the investigators. Of the 78 patients who reported worst pain severity after the first cycle, 59% had a pain score of five or greater. Sixty-three patients remained in the study at week 9, and 31 patients remained at week 18.

Patients who reported their acute pain in the lower range of 0-4 had significantly less peripheral neuropathy after 18 weeks of treatment, compared with patients who rated their pain as 5-10. The neuropathy seen in all patients was primarily sensory neuropathy, as opposed to motor or autonomic neuropathy.

In patients with pain scores of 0-4 in the first cycle, compared with those who reported pain scores of 5-10, EORTC CIPN-20 scores were 7.8 points lower ($P = .0007$) on the autonomic subscale, 7.9 points lower ($P = .004$) on the motor subscale, and 11.3 points lower ($P = .001$) on the sensory subscale.

The largest differences were in numbness of the feet (17 points lower, $P = .001$) and numbness of the hands (16 points lower, $P = .002$).

Nonnarcotic pain medication was used by 46%-64% of the patients per week, and 23%-41% used opioids to manage both mild and severe pain.

“If we can determine who will develop peripheral neuropathy, there is a possibility of prevention. Right now, no one knows how to do this,” Dr. Reeves said in an interview. “The next question to answer is what can be done to prevent or reduce paclitaxel-associated acute pain syndrome,” she said.

Vitamin D Supplementation Prevents Breast Cancer Therapy-Related Bone Loss

MAJOR FINDING: 25(OH)D concentration increments due to supplementation prevent aromatase inhibitor-associated bone loss, independently of baseline 25(OH)D concentrations. Increasing levels of 25(OH)D concentrations at 3 months were inversely correlated to absolute bone loss (-0.004 g/cm², [-0.007 to -0.004], (P = .003), at 1 year.

DATA SOURCE: Prospective cohort study of 156 postmenopausal nonosteoporotic women using adjuvant aromatase inhibitors in early breast cancer.

DISCLOSURES: Dr. Sonia Servitja disclosed no relevant relationships. Chair and invited discussant Dr. Thomas J. Smith disclosed research funding from the American Cancer Society and the National Cancer Institute.

BY RICHARD HYER

Elsevier Global Medical News

The bone loss associated with aromatase inhibitors was significantly slowed with increasing supplements of vitamin D in a prospective cohort study of 156 postmenopausal women.

“The bone loss was less, the higher your vitamin D level was maintained,” said session chair Dr. Thomas J. Smith of Massey Cancer Center of Virginia Commonwealth University. “This is one of the first intervention studies,” he said. “And the results are pretty striking.”

Dr. Sonia Servitja of Hospital del Mar in Barcelona, and colleagues, assessed the association between 25-hydroxyvitamin D (25(OH)D) concentrations and bone loss at baseline, after 3 months of supplementation, and after 1 year, in patients receiving aromatase inhibitor therapy for early-stage breast cancer.

The 156 women in the prospective cohort had hormone-positive breast cancer and had initiated aromatase inhibitors from January 2006 to June 2009.

All patients received daily oral calcium (1 g) and vitamin D3 (800 IU). Patients with a baseline level of 25(OH)D less than 30 ng/mL received additional oral vitamin D3. The women were a mean age of 62 years with a mean age of menopause onset of 50 years.

The magnitude of the bone-loss prevention correlated with incremental increases in 25(OH)D concentrations.

Each 10-ng/mL increase in 25(OH)D concentration at 3 months appeared to be associated with a 0.55% decrease in bone loss, which was almost a third of the average bone loss experienced by these patients, according to the study findings, presented as a poster at the meeting.

The findings suggest that vitamin D supplementation at doses higher than the standard of 400 to 800 IU/day might be useful to minimize bone loss in women starting out on aromatase inhibitors and who are not eligible for bisphosphonate therapy according to current guidelines.

Patients who achieved 25(OH)D concentrations greater

than or equal to 40 ng/mL at 3 months experienced significantly reduced bone loss. In addition, 25(OH)D increases at 3 months were protective for relative bone loss (adjusted beta for each quintile 1.01%, P value less than .001).

Hepcidin Levels Predict ESA and IV Iron Responses

MAJOR FINDING: Forty-seven patients with lower serum hepcidin levels who received darbepoetin and four to five doses of intravenous iron had hemoglobin response rates of 92%-95% and required no red blood cell transfusions.

DATA SOURCE: Phase III MC04CC trial of 489 cancer patients with chemotherapy-associated anemia.

DISCLOSURES: The study was sponsored by Amgen. Dr. Steensma disclosed a consultant or advisory role with Amgen, maker of ESAs darbepoetin alfa and erythropoietin alfa. Dr. Ganz disclosed that her husband, Dr. Tomas Ganz, discovered hepcidin (Blood 2003;102:783-8), and that he has employment and stock ownership in Intrinsic LifeSciences, which is developing a test for hepcidin, has received research funding from Amgen, and has been a paid consultant to several companies including Ortho Biotech, which markets erythropoietin.

BY RICHARD HYER

Elsevier Global Medical News

Serum hepcidin levels may help predict which cancer patients would benefit from the combination of erythropoiesis-stimulating agents and supplemental iron in the treatment of chemotherapy-associated anemia, new data suggest.

Investigators found a positive association between serum hepcidin levels and clinical response to the combination of darbepoetin alfa (Aranesp) and intravenous iron in a planned analysis of 489 patients in a randomized, phase III trial. The original study did not find a benefit from the combination, but the new analysis showed it appeared to be effective with higher doses of intravenous iron in people who had lower levels of hepcidin.

Overall, the analysis showed that patients who received four or five 187.5-mg doses of intravenous iron were the most likely to achieve a hemoglobin response (80%, vs. 65% for placebo, vs. 67% for oral iron, vs. 56% for fewer than four doses of IV iron - all given in addition to darbepoetin). They also had the least need of red blood cell transfusions (9% vs. 13%-17% in the other groups).

The highest hemoglobin response rates in the study (92%-95%) occurred in 47 patients who had serum hepcidin levels below 64.3 ng/mL and received four to five doses of IV iron - and these patients required no red blood cell transfusions, Dr. David P. Steensma of Dana-Farber Cancer Institute, Boston, and his coauthors reported in a poster at the annual meeting of the American Society of Clinical Oncology.

“We found, interestingly, that patients who have lower hepcidin levels were much more likely to have positive re-

sponse to the IV iron plus darbepoetin combination,” Dr. Steensma said in an interview.

Hepcidin, a peptide made by hepatocytes, is a critical regulator of systemic iron homeostasis, and low serum hepcidin concentrations may predict iron deficiency, according to the poster.

This planned analysis followed a Mayo Clinic Cancer Research Consortium study which compared darbepoetin with darbepoetin plus oral iron vs. darbepoetin plus IV iron (ferrous sulfate) in two doses. The investigators reported that supplemental IV iron provided no additional benefit compared with oral placebo or oral iron in the trial (*J. Clin. Oncol.* 2011;29:97-105).

Serum hepcidin concentrations were measured from samples taken before treatment from 405 (83%) of the 489 eligible patients. Stratification by tertiles showed the lowest tertile had up to 20.2 ng/mL, the middle greater than 20 ng/mL to 64.3 ng/mL, and the highest greater than 64.3 ng/mL.

“The conclusions from this evaluation were that lower pretreatment serum hepcidin was associated with better clinical response. Serum hepcidin measurements may help predict response to ESAs plus supplemental iron in future trials,” Dr. Patricia Ganz of the University of California Los Angeles schools of medicine and public health said in an invited discussion of the study.

“The relative underdosing of IV iron in the [original] trial may explain the negative results, but the potential risks of higher doses of IV iron, e.g., iron overload, must also be considered,” she said.

Asked whether this research would change his clinical practice, Dr. Steensma said that no serum hepcidin assay is commercially available, but that one is in development.

“I think that in the future I’ll probably use serum hepcidin to help distinguish a subset of patients who may have relative iron deficiency, or who may benefit from IV iron, and perhaps use that to help target patients who should receive combination therapy, versus those [for whom] maybe an ESA alone would be just fine,” he said. “Especially if this is confirmed in other data sets.”

Flaxseed Bars Not Effective in Reducing Hot Flashes in Trial of 178 Postmenopausal Women

MAJOR FINDING: Mean hot flash scores decreased by 4.9 units (about 33%) in the flaxseed arm, and by 3.5 (about 29%) in the placebo arm ($P = .29$).

DATA SOURCE: A trial of 178 postmenopausal women randomized to flaxseed bars or placebo bars for 6 weeks.

DISCLOSURES: This study was funded by the National Cancer Institute. Dr. Pruthi reported having nothing to disclose.

BY RICHARD HYER

Elsevier Global Medical News

Eating bars rich in flaxseed failed to reduce hot flashes for postmenopausal women in a randomized, placebo-

controlled, phase III trial conducted by the North Central Cancer Treatment Group.

Mean hot flash scores fell comparably in both arms of the study, which enrolled breast cancer patients and women who never had the disease. Instead of relief from this troubling symptom, many participants reported GI distress.

“Our findings do not support the use of 410 mg of flaxseed lignans for the reduction of hot flashes. The gastrointestinal side effects seen in both groups were more likely due to the fiber content in the flaxseed and the placebo bars,” said Dr. Sandhya Pruthi of the Mayo Clinic in Rochester, Minn. She presented the results at the meeting.

“Because hot flashes can negatively impact quality of life for many women, there is increasing interest in the use of complementary therapies such as flaxseed,” Dr. Pruthi said, laying out the rationale for the trial.

Flaxseed is an annual plant, rich in lignans, which are a major class of phytoestrogens, she said. It is thought to have a weak estrogenlike effect, as well as estrogen antagonist effect.

In 2005, a pilot study of flaxseed was conducted in 30 women. They were given 400 mg of ground flaxseed, and investigators reported a 57% reduction in hot flash scores and a 50% reduction in hot flash frequency. This - along with a patient who claimed that flaxseed was successful in treating her hot flashes - led to the current trial, said Dr. Pruthi.

To be eligible, women with or without a history of breast cancer had to have more than 28 hot flashes per week. In all, 188 women were enrolled and 178 were randomized (88 to flaxseed bars containing 410 mg of lignans and fiber, and 90 to placebo bars containing protein and fiber, but no flaxseed, soy, or lignans). For 6 weeks, the participants were to eat one bar per day. The primary end point was a change from baseline in hot flash scores at week 6.

Of the entire group, 91 had a history of breast cancer but were without active disease. This group included women who were being treated with an aromatase inhibitor or tamoxifen.

Mean hot flash scores decreased by 4.9 units (33%) in the flaxseed arm, and 3.5 (29%) in the placebo arm ($P = .29$). “There was no significant difference in the reduction of hot flash scores between the two arms,” said Dr. Pruthi.

No statistically significant toxicity differences were experienced between study arms, but both groups reported substantial abdominal distention, gas, diarrhea, and nausea.

Although the results were disappointing, the trial does not leave women without remedies for hot flashes. Dr. Pruthi noted that venlafaxine and gabapentin were effective, and had been studied in randomized, placebo-controlled trials. “So we do have options for women who are not wanting to take hormonal therapies like estrogen or progesterone, especially with a history of breast cancer,” she said.

“However, there are side effects with those drugs. Patients need to balance between treating their symptoms and managing their side effects, which is why we need to do more studies in other complementary therapies that we think might have [fewer side effects] and still give us the benefit of treating hot flashes,” she said.

Laser Tx Cuts Oral Mucositis in Head and Neck SCC

MAJOR FINDING: The incidence of grade 3/4 oral mucositis was 6.4% among patients treated with low-level laser therapy vs. 48% among controls (P less than .001).

DATA SOURCE: Phase III prospective, double-blind phase III trial in 94 patients with head and neck squamous cell carcinoma.

DISCLOSURES: The authors reported no conflicts of interest. Dr. Murphy reported receiving research funding from Acto-GeniX, Amgen, and ImClone Systems.

BY PATRICE WENDLING

Elsevier Global Medical News

Up-front low-level laser therapy significantly reduces the oral mucositis that often derails patients with head and neck squamous cell carcinoma, according to data from a prospective, double-blind phase III trial of 94 patients.

The incidence of grade 3/4 oral mucositis was only 6.4% among patients receiving concurrent low-level laser therapy (LLLT) and chemoradiation, compared with 48% among controls receiving placebo laser and chemoradiation (P less than .001; hazard ratio, 0.13).

LLLT patients also had significantly less severe pain (P = .012), less opioid use (32% vs. 85%; P less than .001; HR, 0.33), and less need for gastrostomy (15% vs. 38%; P = .005; HR, 0.037). Dr. Héilton Spíndola Antunes reported in a late-breaking abstract at the meeting.

“LLLT should be the new standard of care in this setting,” Dr. Antunes, with the Instituto Nacional de Câncer, Rio de Janeiro, and his associates concluded.

LLLT has shown promise as a preventive therapy in squamous cell carcinoma of the head and neck (SCCHN), but definitive randomized trial data supporting its use has been lacking.

“I think the data is now accumulating that low-level laser light therapy may actually be effective, and we need to start taking this seriously,” said invited discussant Dr. Barbara A. Murphy, director of the Head and Neck Research Program at the Vanderbilt-Ingram Cancer Center in Nashville, Tenn.

Particularly noteworthy is that the study answers the “so-what” question, in that LLLT was shown to reduce not only mucositis, but the many sequelae that accompany it. “That’s pretty impressive,” she said. “[They’re] all going in the same direction.”

As for why it works, Dr. Murphy pointed to preclinical work supporting these mechanisms of action: local anti-inflammatory effects, effects on biochemical mediators, and a decrease in soft tissue edema and inflammatory cell infiltrate (Photomed. Laser Surg. 2006;24:158-68).

A total of 94 patients with SCCHN were evenly randomized to chemoradiation and placebo laser or diode InGaAlP laser therapy applied to the oral cavity for 5 consecutive days during chemoradiation. The laser therapy was applied in a punctual form, touching the mucosa for 10 seconds per point, outside the tumor area, totaling 9 points per region,

with 1 cm² each. Oral cavity regions included the upper and lower lip, buccal mucosa, ventral and lateral tongue, and floor of the mouth. The 660-nm wavelength laser had an output power of 100 mW, a spot size of 0.2375 cm², and an energy density of 4 J/cm².

All patients were treated with 70.2 Gy of radiation (1.8 Gy/day, 5 times per week), and concurrent cisplatin 100 mg/m³ was administered in three cycles every 3 weeks. Oral fluconazole 50 mg was given every 24 hours from day 6 to the last day of chemoradiation, and analgesics were given as needed.

The primary site was the oropharynx in 74 patients, nasopharynx in 9, and hypopharynx in 11. The patients’ mean age was 55 years, and 87% were male.

No LLLT or placebo patients had radiotherapy interruptions caused by oral mucositis. In the LLLT arm, 51% of patients did not have ulcers, compared with 17% in the placebo arm (P less than .001).

In all, 22 (47%) of the 47 control patients crossed over to LLLT because of mucositis grade 3 or more or ulcer area of 6 cm² or more.

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 showed a significant benefit with LLLT versus controls in physical and emotional functioning (mean scores of 82 vs. 66 and 62 vs. 47, respectively; P = .037 in both cases), fatigue (mean 29 vs. 47; P = .011), pain (mean 25 vs. 40; P = .043), and dyspnea (mean 6.7 vs. 17.6; P = .025).

On the EORTC QLQ-Head & Neck35, significant differences between the LLLT and control groups were observed in pain (mean score 23 vs. 43; P = .007), swallowing (mean 21.6 vs. 48; P = .001), and trouble with social eating (mean 30 vs. 43; P = .026).

“The patient feels better all over,” Dr. Antunes said in an interview, adding that he has been using laser therapy for 6 years, typically 10 minutes before radiation therapy.

Barriers to acceptance of LLLT use in head and neck patients have been the lack of sufficient level 1 evidence and a standardized protocol - both of which are nicely provided by the trial, Dr. Murphy said. Other barriers are the cost of equipment and reimbursement, as well as staffing time and training.

“I’m going to have to go back and really look at this, and think if this is something I need to start considering as an intervention in my patient population,” she said.



Scan the QR code with your smartphone to see Dr. Michael J. Fisch, Editor-in-Chief, discuss themes and trends in patient care

STATEMENT OF OWNERSHIP, MANAGEMENT and CIRCULATION (Required by 39 U.S.C. 3685). 1. Publication title: JOURNAL OF SUPPORTIVE ONCOLOGY.; 2. Publication No. 1544-6794.; 3. Filing date: October 1, 2011.; 4. Issue frequency: Bi-Monthly.; 5. No. of issues published annually: 6.; 6. Annual subscription price: \$334.00.; 7. Complete mailing address of known office of publication: International Medical News Group LLC, 60 Columbia Rd., Bldg. B, Morristown, NJ 07960.; 8. Complete mailing address of headquarters or general business office of publisher: International Medical News Group LLC, 60 Columbia Rd., Bldg. B, Morristown, NJ 07960; 9. Full names and complete mailing addresses of Publisher, Editor, and Managing Editor: President and Publisher, Alan J. Imhoff, International Medical News Group LLC, 60 Columbia Rd., Bldg. B, Morristown, NJ 07960 ; Editor, Mary Jo Dales, International Medical News Group LLC, 5635 Fishers Lane, Ste. 6000, Rockville, MD 20852, Managing Editor, Susan Hite, International Medical News Group LLC, 5635 Fishers Lane, Ste. 6000, Rockville, MD 20852; 10. Owner: Elsevier Inc., 360 Park Ave. South, New York, NY 10010. 11. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages or other securities: None.; 12. Tax Status: N/A; 13. Publication name: JOURNAL OF SUPPORTIVE ONCOLOGY.; 14. Issue date for circulation data below: September/October 2011; 15. Extent and nature of circulation: Average no. copies each issue during preceding 12 months: a. Total number of copies (net press run) 18,600; b. Legitimate paid and/or requested distribution (by mail and outside the mail) (1) Outside County Paid/Requested Mail subscriptions stated on PS Form 3541. 9,751; (2) In-County Paid/Requested Mail Subscriptions stated on PS Form 3541. 0; (3) Sales through dealers and carriers, street vendors, counter sales and other Paid or Requested Distribution Outside the USPS. 0; (4) Requested copies distributed by other mail classes through the USPS. 0; c. Total paid and/or requested circulation 9,751; d. Nonrequested distribution (by mail and outside the mail). (1) Outside County Nonrequested copies stated on PS Form 3541. 9,011; (2) In-County Nonrequested copies stated on PS Form 3541. 0; (3) Nonrequested copies distributed through the USPS by other classes of mail. 0; (4) Non requested copies distributed outside the mail. 75; e. Total nonrequested distribution. 9,086; f. Total distribution. 18,837; g. Copies not distributed. 89; h. Total. 18,927; i. Percent paid and/or requested circulation. 51.8%; No. copies of single issue published nearest to filing date. a. Total number of copies (net press run) 18,985; b. Legitimate paid and/or requested distribution (by mail and outside the mail) (1) Outside County Paid/Requested Mail subscriptions stated on PS Form 3541. 8,970; (2) In-County Paid/Requested Mail Subscriptions stated on PS Form 3541. 0; (3) Sales through dealers and carriers, street vendors, counter sales and other Paid or Requested Distribution Outside the USPS. 0; (4) Requested copies distributed by other mail classes through the USPS. 0; c. Total paid and/or requested circulation 8,970; d. Nonrequested distribution (by mail and outside the mail). (1) Outside County Nonrequested copies stated on PS Form 3541. 9,894; (2) In-County Nonrequested copies stated on PS Form 3541. 0; (3) Nonrequested copies distributed through the USPS by other classes of mail. 0; (4) Non requested copies distributed outside the mail. 0; e. Total nonrequested distribution. 9,894; f. Total distribution. 18,864; g. Copies not distributed. 121; h. Total. 18,985; i. Percent paid and/or requested circulation. 47.6%.; 16. Publication of Statement of Ownership for a Requestor Publication is required and will be printed in the November/December 2011 issue of this publication. 17. Signature and title of Editor, Publisher, Business Manager or Owner: Alan J. Imhoff, President, International Medical News Group LLC.