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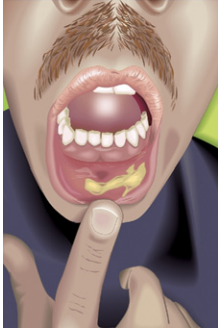
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Scientific Abstracts



**On the cover** Mucositis is a major acute complication and occurs in a large percentage of patients undergoing cytotoxic therapy. Can we use animal models to increase our understanding of the mechanisms of mucositis and translate new anti-mucotoxic agents into clinical trials?

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**A-1 2011 Annual Meeting Agenda**

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# Animal Models of Mucositis: Implications for Therapy

Joanne M. Bowen, PhD, Rachel J. Gibson, PhD, and Dorothy M. K. Keefe, MD, FRACP

**M**ucositis is a major acute clinical problem in oncology, caused by the cytotoxic effects of cancer chemotherapy and radiotherapy. The condition may affect the mucosa of the entire alimentary tract (AT), causing mouth and throat pain, ulceration, abdominal pain, bloating, vomiting, and diarrhea, depending on the target tissue.<sup>1</sup> Mucositis is extremely common, occurring in approximately 40% of patients following standard doses of chemotherapy and in almost all patients undergoing high-dose chemotherapy with stem-cell transplantation or head-and-neck radiation.<sup>2,3</sup> This represents a significant clinical and, importantly, economic burden in oncology. The presence of any mucositis during a cycle of cancer therapy significantly increases the risk of dose reduction, the frequency of infections and bleeding, and the length and cost of hospitalization.<sup>1,4</sup> Reductions in treatment doses lead to reduced survival.<sup>5</sup> Resource utilization by patients during episodes of mucositis is also significantly increased, with the need for nutritional adjuncts including fluid replacement, liquid diets, and total parenteral nutrition. Due to the association with infection, antibiotic therapy is also more common in patients with mucositis. Combined this translates to an incremental cost increase of US \$3,500 per cycle of standard-dose chemotherapy with mucositis<sup>4</sup> and US \$1,700–\$6,000 for radiation-induced oral mucositis depending on the grade.<sup>6</sup>

Despite the severity and prevalence of mucositis, there is currently no broadly effective preventative treatment available. Standard management is currently limited to pain relief, anti-diarrheal medication, and maintenance of good

**Abstract** Alimentary mucositis is a major acute complication in the clinical setting, occurring in a large percentage of patients undergoing cytotoxic therapy. One of the major problems with alimentary mucositis is that the underlying mechanisms behind its development are not entirely understood, which makes it extremely difficult to develop effective interventions. Animal models provide a critical source of knowledge when sampling from patients is unavailable or interventions are yet to be fully tested. This review focuses on the animal models used to increase our understanding of the mechanisms of mucositis and translate new antimucotoxic agents into clinical trials.

oral hygiene depending on the area of the tract affected. A large problem with determining the appropriate treatment for mucositis is that the mechanisms underpinning the condition are not fully elucidated. The entire AT has the same embryological route of development, with the differences observed being due to the cellular differentiation required in order to conduct specialized functions.<sup>7,8</sup> It is therefore highly likely that mucositis will be the same throughout the AT, with the specialized differences in local function offering an explanation for why different regions of the tract are more susceptible to “early” mucositis and others are more susceptible to “late” mucositis.<sup>7,8</sup> The true extent of the complexity of therapy-induced injury is still being realized, and one of the many issues yet to be fully understood involves the timing and sequence of injury events. A further challenge to elucidating the mechanism of mucosal injury is the relative difficulty and invasiveness of obtaining samples from sites within the AT. Therefore, in order to obtain longitudinal data from multiple sites, animal models are necessary. In addition, any new potential antimucotoxic agent must be first subjected to rigorous testing in animal models to prove efficacy and safety before translation to early clinical trials.

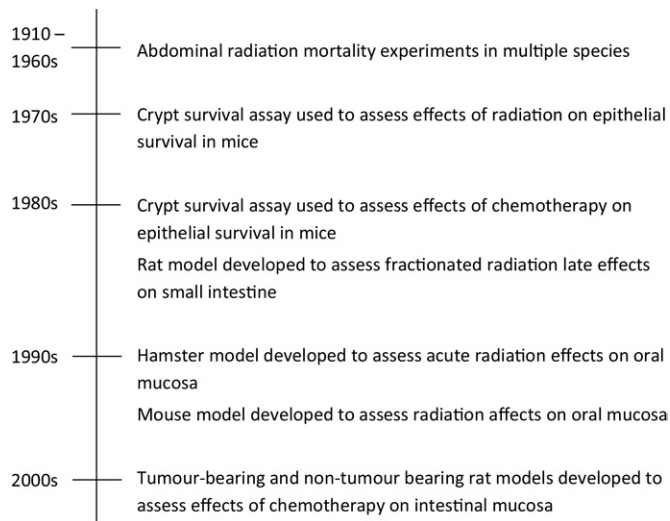
Animal models of mucositis have provided extensive information relating to mechanisms of cancer therapy-induced mucosal injury. There

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**Figure 1** Emergence of Animal Models to Study Cancer Therapy-Induced GI Toxicity and Mucositis

has been an increase in the variety and complexity of models over time, from basic survival end points to specialized biomarkers of damage. In line with this, a number of models have become routinely utilized for testing of new antimucotoxic agents. There have been too many experiments to name them all and their authors; however, a brief summary of the history of animal models of mucositis is given in Figure 1. Furthermore, it must be noted that animal models are highly dynamic, moving between injury-inducing agents and combinations of therapies over time. Below, we describe the most frequently published models arranged according to region inspected and damage-inducing agent.

### Oral Mucositis Animal Models

While there are a number of different animal models in oral mucositis research, two in particular have been studied extensively.

#### RADIATION MOUSE MODEL

Wolfgang Dorr and colleagues have developed a radiation model in mice, which involves irradiating the tongue and snout.<sup>9–13</sup> This model first emerged around 1990<sup>14</sup> to study epithelial repopulation. The mouse model of radiation uses inbred male and female C3H/Neu mice that originally came from the Dresden colony.<sup>9</sup> Over the years Dorr and colleagues have refined their radiation method, such that radiation damage to the lower tongue is induced via a combination of two techniques: the first is a percutaneous irradiation of the entire snout, with the second technique requiring local “top-up” radiation of the lower tongue.<sup>9</sup> Graded single doses of 25 kV X-rays are delivered as a 3 × 3 mm<sup>2</sup> area in the center of the lower tongue surface,<sup>15</sup> while fractionated radiation is given as 5 × 3 Gy/week for one or two weeks.<sup>16,17</sup> This treatment results in mucosal ulceration within the treatment field of the lower tongue surface, corresponding to confluent mucositis,

grade 3 of the classification of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC).

The mouse radiation model accurately assesses the mucosal response to treatment and has been used to test a variety of agents, including keratinocyte growth factor (palifermin),<sup>11,15,17–23</sup> sodium selenite,<sup>24</sup> and amifostine.<sup>25</sup> This model has also been used to investigate the effects of combining targeted therapy, with an epidermal growth factor (EGF) receptor tyrosine kinase inhibitor, and radiation on the mucosal response,<sup>26</sup> which is extremely important in the new era of combination therapies. The evolution of this model has also seen it used extensively to investigate the effects of combined chemotherapy and radiotherapy.<sup>18,27</sup> In addition, it has enabled detailed studies to be conducted comparing effects of single-dose and fractionated radiotherapy on the head.<sup>11,15,16,28,29</sup>

#### HAMSTER ORAL MUCOSITIS MODEL

Another model which has significantly advanced the understanding of the mechanisms of oral mucositis is the hamster model, which was first described in 1990<sup>30</sup> and has been used extensively by Stephen Sonis and colleagues. This model of mucositis uses male golden Syrian hamsters as, unlike other rodents, they have a buccal cheek pouch, which is susceptible to chemotherapy when scratched. Mucositis can be induced by the administration of 5-fluorouracil (5-FU) at 60 mg/kg for three days (days 0, 5, and 10). The buccal pouch mucosa is superficially irritated (mechanically scratched) on days one, two and three, resulting in mucositis in most of the animals.<sup>30</sup> The publication of this model revolutionized research into chemotherapy-induced mucositis. However, perhaps more importantly, the development of this model allowed for the current working five-phase hypothesis of mucositis to be developed.<sup>1,31–33</sup> Since the publication of this hypothesis, significant advances in mucositis research have occurred.

The hamster model has also been used in single-dose radiation,<sup>34–37</sup> fractionated radiation,<sup>38,39</sup> and chemoradiation-induced mucositis.<sup>39,40</sup> Mucositis in the radiation model is induced by everting the hamster’s left buccal pouch and applying a single focused dose of 40 Gy radiation, while the remainder of the animal is protected by a lead shield. This dose of radiation predictably elicits severe ulcerative mucositis. Clinically detectable mucositis generally occurs in this model by day six, with peak mucositis at about day 14–15. A fractionated dose is given as cumulative dose of 60 Gy radiation, partitioned into eight fractions of 7.5 Gy each on days 0–3 and 7–10, with a three-day rest period between days four and six. The chemoradiation model consists of 35 Gy radiation on day 0 and cisplatin (5 mg/kg) administered on day one to induce oral mucositis.<sup>39</sup> Another variation is two doses of 5-FU (60 mg/kg) on days –4 and –2, with 30 Gy radiation on day zero.<sup>40</sup>

This model has been used to test many agents, including EGF,<sup>41</sup> transforming growth factor  $\beta$  (TGF- $\beta$ ),<sup>42</sup> interleukin-11 (IL-11),<sup>43,44</sup> keratinocyte growth factor (KGF, palifer-

min), and velerfermin (fibroblast growth factor [FGF]-20),<sup>38,40</sup> among others.<sup>45</sup>

### Gastrointestinal Mucositis Animal Models

Few consistent animal models exist that investigate mucositis in the remainder of the gastrointestinal tract (GIT).

#### CHEMOTHERAPY MODELS

*The dark agouti rat mammary adenocarcinoma model of gastrointestinal mucositis.* Dorothy Keefe and colleagues, recognizing that gastrointestinal mucositis was a big problem, developed the dark agouti (DA) rat model of gastrointestinal mucositis in the mid-1990s.<sup>46</sup> This model is unique as it is capable of modeling the changes that occur in the human GIT following insult with chemotherapy.<sup>47</sup>

Using female inbred DA rats for the model of mucositis has allowed the Keefe laboratory to investigate a range of antimucotoxic agents, including palifermin,<sup>48,49</sup> velerfermin,<sup>50</sup> probiotics,<sup>51</sup> and IL-11,<sup>52</sup> and to study the mechanisms of damage induction by a number of cytotoxics, including methotrexate,<sup>53,54</sup> irinotecan,<sup>55–62</sup> and 5-FU.<sup>63,64</sup> The main advantage of the model is the isogenic tumor, which allows simultaneous assessment of tumor protection, a major fear with any potential antimucotoxic under development. All rats are subcutaneously implanted in each flank with mammary adenocarcinoma cells nine days before chemotherapy. There is excellent homogeneity between all animals in tumor growth and response to treatment.

The DA rat model of mucositis has also recently been modified to study fractionated radiotherapy and the occurrence of acute and subacute GIT injury. In a small pilot study, Ann Yeoh and colleagues developed a six-week fractionated radiotherapy course (total 45 Gy/18 fractions/6 weeks treating at radiation dose of 2.5 Gy/fraction).<sup>65</sup> They determined that fractionated radiotherapy induced gastrointestinal changes from as early as week one (i.e., 7.5 Gy), with severe injury seen in the small intestine at later time points.<sup>65</sup> Furthermore, many of the changes that were induced by fractionated radiotherapy were identical to those induced by chemotherapy,<sup>65</sup> adding considerable weight to the current hypothesis of mucositis.<sup>1,31–33</sup>

*Rat mucositis model of natural therapies.* The DA rat has also been used to study natural antimucotoxic agents in an adapted mucositis model from the laboratory of Gordon Howarth and colleagues since 1996.<sup>66</sup> Intestinal damage and bacterial translocation are induced in this non-tumor-bearing model by three times daily subcutaneous methotrexate.<sup>67–70</sup> Work carried out in TGF- $\alpha$  knockout mice has shed some light on the role of the EGF signaling pathway in the repair of methotrexate-induced gut damage.<sup>71</sup> The majority of work has been carried out to develop the potential antimucotoxic agent whey-derived growth factor extract,<sup>70,72,73</sup> a by-product of cheese production that is in clinical trials. Emu oil is another natural agent under investigation currently.<sup>74</sup> Howarth and colleagues have also investigated the mechanisms of damage following abdominal radiation in the DA rat. Radi-

ation enteritis is induced by a single dose of 10 Gy to the whole abdomen. Markers investigated four days later include growth curves, intestinal weight, and mucosal morphometry.<sup>75–77</sup>

#### RADIOTHERAPY MODELS

Radiation therapy for head and neck cancers results in 30%-60% of patients developing oral mucositis, while pelvic radiotherapy can lead to acute radiation damage to the anorectal region in up to 75% of patients.<sup>78</sup> These symptoms can be severe enough to interrupt the planned course of treatment in around 10% of patients.<sup>79</sup> Chronic injury is less common but has extreme long-term quality-of-life implications, with sometimes life-threatening complications.

*Mouse crypt survival model.* Chris Potten and colleagues have utilized and adapted the clonogen survival assay<sup>80</sup> for extensive experiments to determine aspects of sensitivity, timing, and dose dependence in the radiation response of intestinal crypt cells, particularly stem cells. Specifically, for the model, mice are killed four days after whole-body irradiation (or, in some experiments, chemotherapy), and the terminal ileum is fixed in Carnoy's fixative and prepared as gut bundles, where the intestine is cut into 10 segments and bundled together with micropore tape. Paraffin sections are stained with hematoxylin and eosin, and microcolonies are recorded by counting the surviving crypts per circumference of the 10 different transverse sections. Fifteen representative longitudinal sections of crypts from each mouse also have the width measured at the midpoint along the crypt to enable the data to be corrected for any variations in the size of the crypts between experimental groups.<sup>81</sup> Crypt survival curves are determined using computer-based curve-fitting programs. These results are supplemented by assays which specifically detect apoptosis and proliferation.

In 1983, the first intervention experiment for preventing radiation-induced gastrointestinal damage using streptomycin sulfate was conducted and showed a modest improvement in mortality but no significant improvement in survival of clonogens.<sup>82</sup> Next came investigating the effect of circadian rhythm on sensitivity to irradiation, which found that mornings were associated with a higher apoptotic response to treatment.<sup>83</sup> Similar results have been found in patients treated with morning vs. evening pelvic radiotherapy.<sup>84</sup> Further agents tested include KGF,<sup>85</sup> TGF- $\beta$ 3,<sup>86,87</sup> IL-11,<sup>88,89</sup> and teduglutide.<sup>90</sup> Ferrel et al<sup>85</sup> performed an experiment with the microcolony assay which provided evidence of the therapeutic potential of KGF (palifermin) for mucositis that translated into clinical trials. Palifermin remains the only Food and Drug Administration–approved drug for prevention and treatment of mucositis.

*Fractionated radiotherapy model of acute and chronic mucosal injury.* Martin Hauer-Jensen and colleagues first described an animal model of accelerated fractionation on radiation injury of the rat small intestine in the late 1980s.<sup>91</sup> The model was primarily designed to allow investigation of both acute damage at two weeks and chronic radiation damage at 26 weeks

**Table 1****Examples of Intervention Agents Tested in Animal Models of Mucositis or GI Toxicity**

INTERVENTION	MODEL SPECIES
KGF (palifermin)	Mouse, rat, hamster
FGF-20 (velafermin)	Mouse, rat, hamster
IL-11	Mouse, rat, hamster
EGF	Mouse, hamster
TGF- $\beta$	Mouse, rat, hamster
TGF- $\alpha$	Rat
WDGFE	Rat
Probiotics	Rat
Sodium selenite	Mouse
Amifostine	Mouse, rat
IB-367	Hamster
SCV-07	Hamster
ITF	Mouse
Glutamine	Mouse, rat

KGF, keratinocyte growth factor; FGF, fibroblast growth factor; IL, interleukin; EGF, epidermal growth factor; TGF, transforming growth factor; WDGFE, whey-derived growth factor extract; ITF, intestinal trefoil factor.

after completion of treatment. The animal model involves transposing a segment of the small intestine and fixing it to the scrotum following bilateral orchidectomy. The 4 cm intestinal loop can then be subjected to repeated irradiation at varying time points and doses.<sup>91</sup> By using this model of chronic radiation, Hauer-Jensen and colleagues have been able to demonstrate that the changes occurring in the acute phase of damage are associated with the severity of damage seen long term.<sup>91,92</sup> The most common dose regimens that have been investigated include 2.8 Gy in normal and accelerated fractionation schedules up to a total of 56 Gy and 4.2 or 5.6 Gy fractions to a total dose between 33.6 and 67.2 Gy.<sup>92–94</sup> In this model, relatively large doses can be delivered with few systemic problems, the only common adverse effect being local skin irritation. Examples of agents used in the various animal models of mucositis described are shown in Table 1.

*Targeted therapies model of GI mucositis.* The newest area of development for investigating GI toxicities of cancer therapy has been in small-molecule tyrosine kinase inhibitors (TKIs). Albino Wistar rats have been used to develop a model of lapatinib-induced diarrhea and mucosal injury to study mechanisms and potential interventions. This model gives daily oral lapatinib for four weeks, with or without concurrent weekly chemotherapy, and assesses changes along the length of the alimentary mucosa.<sup>95</sup> Wistar rats have an appropriate drug metabolic enzyme profile for investigating TKIs, which are metabolized predominantly through the CYP3A4 pathway. Many of the results to date are consistent with the clinical scenario. Emerging findings from this work indicate that intervention agents protecting the local small intestinal mucosa could prove effective at preventing TKI-induced diarrhea.

**Successes and Failures of Translated Agents**

Antimucotoxic agents progress from discovery to animal models to clinical trials in the hope of being the next palifermin. In animal models, palifermin was shown to protect against mucositis by improving weight loss and crypt survival,<sup>85</sup> protecting the oral mucosa,<sup>12,21,96</sup> and reducing diarrhea and mortality.<sup>48</sup> In the clinical setting, studies have consistently shown benefit in patients receiving palifermin with less severe and shorter-duration oral mucositis.<sup>97,98</sup> Palifermin is used clinically for patients receiving hematopoietic stem-cell transplantation for hematological malignancies, and more recently, it has been investigated in head-and-neck cancer<sup>99</sup> as well as sarcoma<sup>100</sup> patients, with generally positive results. However, palifermin has yet to be approved for standard multicycle chemotherapy and may be limited by oral mucosal thickening.

Many other agents have progressed from animal models of mucositis to early clinical trials with varying degrees of success. Just to name a few, these include VSL#3,<sup>101</sup> IL-11,<sup>102</sup> low-level lasers,<sup>103,104</sup> amifostine,<sup>105,106</sup> glutamine,<sup>107,108</sup> and various herb-based agents. While many are still under further investigation, a number of agents have failed at the clinical trial level by not adequately reaching clinical end points. One example is velafermin, a recombinant human FGF-20 that did not reach its primary end point (reduced incidence of severe oral mucositis) in its phase II dose-confirmatory trial of hematologic cancer patients receiving autologous stem-cell transplantation. Success in animal models does not always translate to the clinic, which may be due to a variety of issues, of which a few are outlined below.

**DIFFICULTIES OF ANIMAL MODELS IN MUCOSITIS RESEARCH**

While animal models undoubtedly have benefits, they also have difficulties and limitations. The Sonis hamster model has the confounding issue of wound healing. Hamsters have cheek pouches, and mucositis can be induced by either chemotherapy<sup>30,42–44</sup> or radiotherapy.<sup>44</sup> However, following administration of the chemotherapy, the cheek pouch needs to be “mechanically” scratched or irritated in order to induce ulcerated lesions. In humans, however, the oral mucosa does not need to be superficially irritated in order to induce mucositis, so this model is not exactly the same as the clinical setting. Additionally, superficial irritation may result in wound-healing mechanisms being initiated. Dose and scheduling issues are also important and cannot be overlooked. The doses used in rats do not automatically translate to humans: There may be species differences in susceptibility to different agents, and the traditional milligram per kilogram dosing of rodents is not often used in humans, where we tend to use (for reasons that are not always logical) body surface area dosing. Despite similarities, animal models are never identical to humans, and there will always be issues with translation from animal to human research. This does not, however, devalue animal research; it just adds an appropriate note of caution.

An added difficulty with animal models has been introduced with the development of monoclonal antibodies for treatment of human disease. Fully humanized monoclonal antibodies may not be active in animal models, and toxicities may not develop until translation occurs to the human situation.

Difficulties also arise in the DA rat model of mucositis. Unlike the hamster, in the rat visible oral mucositis does not occur due to the highly keratinized nature of the epithelium (D. Wilson and D. Keefe, personal communication) which makes it difficult to successfully investigate oral mucositis. Furthermore, higher doses of chemotherapy are required to induce mucosal injury in animal models, due to the resilience of the rat AT. Another difference is the presence of squamous epithelium in the rat stomach, which can lead to reduction in oral intake when KGF, a stimulator of epithelial growth, is used. Rats do not have an emetogenic reflex, and since some vomiting is a manifestation of mucosal injury, this is a disadvantage. However, it is possible to use pica as an indirect marker for nausea.<sup>109</sup>

The route of chemotherapy administration has important implications for drug metabolism. In the DA rat model of mucositis, intravenous administration of chemotherapeutic drugs is extremely difficult, with administration into the tail vein being made especially difficult due to the skin pigmentation. As a result, mucositis induced by drugs administered via this route is not routinely investigated. Although all chemotherapeutic drugs cause damage,<sup>110,111</sup> the mechanisms by which they do this may be different.

Other contributing factors also cause difficulties in animal research; including: stresses in the animals from isolation due to experimental procedures, the need to anesthetize animals on a regular basis and the effect that this has on mucosal homeostasis, and the efficacy of any investigative drugs on tumor load. Toxicities associated with cancer treatment include those that are localized or regional (ulcers, xerostomia, abdominal pain, malabsorption) and those that are more generalized systemic (fatigue, lack of appetite, nausea, cognitive impairment).<sup>112</sup> The recent realization of concurrent tissue-based and systemic toxicities has resulted in the new paradigm of toxicity clustering.<sup>113</sup> Interestingly, the proof-of-principle testing for this new way of thinking was carried out in cancer patients.<sup>113</sup> Translational research in the laboratory using animal testing is now occurring to examine in greater detail some of the initial findings. Looking at multiple toxicities in combination will add new knowledge in the area as well as uncover new challenges in applying the models.

The final issue in animal models is strain and sex differences in metabolic enzyme profiles for xenobiotics, particularly CYP family members<sup>114–117</sup> which can have a profound impact on drug clearance, and therefore toxicity, of agents at equivalent doses. Careful consideration of the animal model and the drugs to be administered are paramount for a successful animal trial.

## Future Use of Animal Models in Mucositis Research

With the constant application of drug screening and agent testing for potential cancer treatments and supportive agents to use in the clinic, the animal model of mucositis will continue to be a highly valuable tool. We are currently in an age where the biotechnology and pharmaceutical industry is progressing rapidly, offering exceptional new drugs for development. However, proper rigorous preclinical testing in appropriate and truly representative models needs to be carried out with each new antimucotoxic treatment to ensure that innovative treatment approaches are not introduced before the technology or its understanding has matured sufficiently to extract maximal benefit. Industry is only now beginning to realize the importance of toxicity testing of their agents. With the hype of targeted therapies, toxicity was not expected, so almost no testing was completed in some cases. Now, more agents are being tested earlier in development and with input from toxicity specialists.

## Impact

Over the next 20 years, due to the aging population, the global incidence of cancer will greatly increase and, with it, mucositis. There will also be an increase in consumerism in medicine, with better-informed and assertive patients seeking out novel therapies. For these reasons, the continued development of clinically useful therapies for mucositis is essential. However, the combination of complex factors including technological success, society's willingness to pay, and future health care–delivery systems will undoubtedly influence how preclinical models are designed and implemented.<sup>118</sup>

## Summary

Gastrointestinal mucositis is an extremely common side effect following cancer chemotherapy and radiotherapy, occurring in a large percentage of patients. Alleviating mucositis using antimucotoxics may lead to increased maximum tolerated doses of chemotherapy or radiotherapy and improve the quality of life for cancer patients both during and after treatment. Research needs to continue to focus on developing antimucotoxics that are both effective and safe. Identification of therapeutic targets and development of these novel agents requires well-validated and clinically relevant animal models to be employed. The future will see more antimucotoxic agents reach clinical trials in a broader range of therapeutic settings, in particular targeted therapies and multimodality regimens.

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# Translating Mucositis Research from Animal Models to Humans: Challenges and Opportunities

Rajesh V. Lalla, DDS, PhD, CCRP, DABOM

Commentary on “Animal Models of Mucositis: Implications for Therapy” by Joanne Bowen, Rachel Gibson, and Dorothy Keefe (page 161).

**A**limentary mucositis is an important complication of chemotherapy and/or radiation therapy, with significant implications for prognosis, nutrition, quality of life, and cost of care.<sup>1</sup> However, despite a significant amount of research, the clinical management of most patients with mucositis remains largely palliative.<sup>2,3</sup> Thus, there is an urgent need to better understand the pathogenesis of mucositis and to test promising new interventions based on this understanding. Animal models of mucositis are critical for such studies, aimed at identifying the best agents for evaluation in humans.

Bowen et al have prepared a well-written review that nicely summarizes the major animal models for oral and gastrointestinal mucositis. This group of investigators, led by Professor Keefe, is one of the worldwide leaders in mucositis research using animal models. The article also describes animal models developed by other leading groups under the direction of Professors Dorr, Hauer-Jensen, Howarth, and Sonis. Together the animal models developed by these and other groups have resulted in significant advances in our understanding of the pathogenesis of mucositis and the identification of promising therapeutic candidates.

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However, as Henry Wadsworth Longfellow wrote, “Into each life some rain must fall.” Indeed, animal models for mucositis have limitations that prevent them from exactly reproducing the human condition. Due to the multifactorial nature of the pathophysiology of mucositis, replication in an animal model can be challenging. As a result, several interventions that were extremely promising in animal models have turned out to be ineffective when tested in humans. Thus, there is a need for constantly adapting the animal models to better represent patients with mucositis, in addition to modifying them based on evolving cancer therapy regimens.

Ultimately, the best research model for mucositis is the human.<sup>4</sup> However, it is difficult to obtain sequential human tissue samples in mucositis patients for pathogenesis studies. Further, new compounds should be tested for safety and efficacy in animal models before human studies are undertaken. Therefore, animal models will continue to play a very important role in mucositis research. This article by Bowen et al provides an excellent description of the evolution, current status, and limitations of such animal models and sets the stage for further advances in this area.

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# The Quest for Effective Treatments of Mucositis

Stephen Sonis, DMD, DMSc

Commentary on “Animal Models of Mucositis: Implications for Therapy” by Joanne Bowen, Rachel Gibson, and Dorothy Keefe (page 161).

**R**egimen-related mucosal toxicity (mucositis) is a largely unsolved medical need associated with cancer treatment. Despite its long history, patients continue to suffer and clinicians are frustrated by the diffuse, painful ulcerative lesions of the mouth, esophagus, intestine, and rectal mucosa that are commonly induced by a range of chemotherapeutics and radiation therapies and which largely defy effective intervention. This review by Bowen and colleagues largely captures the past and current roles animal modeling plays in regard to our understanding of mucositis and the quest for effective treatments.

Until the late 1990s the biological complexity of mucositis was underappreciated. Prior to that time, the condition was considered to be solely the consequence of nonspecific direct damage to rapidly dividing epithelial “stem” cells. Any thoughts of intervention were focused on palliation or modifying proliferating normal cells. Attempts to better understand the pathogenesis were largely limited to the use of cadaveric material.<sup>1</sup> The introduction of animal models enabled studies in which mucositis could be investigated at the tissue, cellular, and genetic levels and revealed biological targets for possible treatment.

Chemotherapy-induced mucositis has been effectively studied in the mouse, hamster, and rat. Early studies by Farrell et al,<sup>2</sup> which combined 5-fluorouracil (5-FU) and methotrexate to induce lesions of the small intestine, were important in establishing the kinetics of intestinal injury. Although largely superseded by new

hamster models, the original 5-FU-induced mucositis model in that species was critical to providing insight into the pathogenesis of mucositis.<sup>3</sup> However, it was the advent and application of the acute radiation model in hamsters that provided the seminal data to support new mechanistic paradigms of mucositis biology at the cellular and genomic levels.<sup>4,5</sup> Importantly, the results of mechanistic and genomic studies in humans corroborated the original findings in hamsters.<sup>6–8</sup> The rat model introduced by Bowen and colleagues<sup>9</sup> has been instrumental in further defining the complex pathoetiology of chemotherapy-induced gastrointestinal mucositis.

With the completion of phase 2 and 3 clinical trials, assessment of the translational effectiveness of animal models is now attainable. Modeling of oral and intestinal chemotherapy- or radiation-induced mucositis by Farrell et al,<sup>2</sup> Dorr et al,<sup>10</sup> and Keefe et al<sup>11</sup> provided proof of concept for the clinical enablement of keratinocyte growth factor and confirmed information of value in establishing clinical dosing schedules. The hamster models of acute, fractionated, and chemoradiation-induced mucositis have proven to be predictive for the clinical response of at least two drugs and one biological: *N*-acetyl cysteine,<sup>12</sup> SCV-07,<sup>13</sup> and FGF-20.<sup>14</sup> In general, animal models have been most valuable in assessing potential efficacy and defining and optimizing treatment schedules.

As recognized in Keefe’s dark agouti mammary adenocarcinoma model, one cannot ignore tumor response when studying potential mucositis interventions.<sup>11</sup> Before any agent can go from animal to human, it is critical that it not only shows a mucosal protection benefit but also that it fails to undermine the antitumor effects of either radiation or chemotherapy.

The candor with which Bowen and colleagues note the shortcomings of animal models of mucositis should be appreciated. Without question, both the science of mucositis and steps toward effective treatments have been furthered by the application of animal modeling. Nonetheless,

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the best model is the human. Hopefully, the fruits of animal studies will continue to yield effective therapy options for patients at risk of regimen-related toxicities.

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# Understanding Bereavement: What Every Oncology Practitioner Should Know

Elizabeth Kacel, BA, Xin Gao, BS, and Holly G. Prigerson, PhD

**B**ereavement deserves special attention in oncology practices because of the frequency with which providers, patients, and their families encounter death. The biological, psychological, and sociocultural demands of a potentially terminal illness such as cancer put all involved parties at risk for experiencing grief at many points throughout the continuum of care, both before and after death. Grief may develop before a death as patients and their families experience the loss of physical abilities and roles, activities, relationships, or a sense of a future.<sup>1</sup> These losses may heighten a person's sense of loneliness, fear, anger, sadness, helplessness, and hopelessness.<sup>2</sup> Although grief typically decreases over time, the onset and expression of distress following a loss may vary among individuals, families, and cultures.<sup>3</sup>

A vast body of research has examined grief in terms of risk factors, clinical presentations, and treatment options. In this literature, many terms have been employed to discuss these aspects of the experience of loss. Typically, "bereavement" refers to the death of a significant other.<sup>4,5</sup> "Grief" represents the psychological reaction to the death and has been described as a feeling of "wanting what you cannot have."<sup>6</sup> Grief encompasses the distress, including related feelings, cognitions, and behaviors which occur as a result of this loss.<sup>1,5</sup> Finally, "prolonged grief disorder" (PGD) refers to a severe and protracted reaction to loss, which manifests as extreme emotional distress and mental or functional impairment.<sup>7-9</sup> Due to the unique relationship that often exists

**Abstract** Death and dying are ever-present in the practice of oncology. Oncology clinic staff regularly encounter terminally ill patients and grieving family members and, therefore, are well positioned to identify and intervene on behalf of those at risk for extreme psychological distress. It is important for oncology providers to understand grief, the factors that heighten the risk for maladjustment to the loss, and how best to ease the emotional pain and suffering of bereaved family members. This article highlights models of grief that examine early relationships, relationships at the time of the loss, cognitive processes, and cultural practices. We also discuss special circumstances of grief such as the loss of a child or parent and grief in young adults. Risk factors for severe grief reactions, specifically prolonged grief disorder, are examined, as are the efficacy of various interventions, including staff support, psychodynamic therapy, cognitive-behavioral therapy, interpersonal therapy, group therapy, and Internet interventions. Overall, the literature on treatment for grief has demonstrated mixed results, but some therapies have shown promise in treating particularly distressed families and individuals. We discuss the clinical significance of grief and the importance of recognizing the unique factors which contribute to individuals' abilities to cope with loss.

between a patient, the family, and the oncologist, providers have an opportunity to assist patients and families in adjusting to the many losses both will encounter. In particular, by encouraging the development of acceptance prior to the loss, providers may give family members a sense of predictability and comfort, which helps them to understand the dying process and decreases their distress.<sup>1,10,11</sup> This article addresses the practical needs of oncologists who are likely to encounter various presentations and morbid outcomes of grief and bereavement. We include a review of major theoretical models of grief, risk factors, clinical presentations (including pathological reactions), and special circumstances and conclude with a discussion of how oncology staff can best help patients and their family members by considering their losses holistically, in terms

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of their unique constellation of biological, psychological, and sociocultural traits.

## Theories of Grief

Grief has been examined extensively in terms of a variety of factors which impact an individual's psychological, biological, and sociocultural identity. Theoretical models of bereavement offer different perspectives on the development, maintenance, and treatment of grief. Understanding these models in conjunction with an appreciation for the uniqueness of various patient–family dynamics may contribute to a more refined approach to assisting individuals struggling with grief or to providing an appropriate outside referral. Putting these theoretical models to use in clinical care requires providers to remain open-minded about the various aspects of an individual's life which may help or hinder his or her ability to cope with the death of a loved one.<sup>12</sup>

One of the most widely acknowledged paradigms of loss is Bowlby's attachment theory. According to Bowlby,<sup>13</sup> the loss of a loved one may be the most devastating experience a person can endure in his or her lifetime. His theory is based on the concept of "attachment," the idea that early on, children form intense bonds with their caregivers in order to receive the care and nourishment they require to survive. A stable and consistent bond is referred to as "secure," while a less reliable relationship is termed "insecure." Bowlby<sup>13</sup> suggests that insecure attachment styles may be related to difficulties later in life including emotional distress, personality disorders, anxiety, depression, and emotional detachment. In addition, insecure attachments may contribute to greater difficulty in dealing with loss later in life, including a greater risk for severe grief reactions.<sup>9,14</sup> Individuals with secure attachments, however, may internalize memories of the deceased in a way that allows them gradually to accept the loss of a physical connection with that person.

Psychodynamic frameworks for understanding grief also focus on the importance of early mother–child relationships as internalized schemas for individuals' abilities to handle separation. In object relations theory, the initial separation between a child and his or her mother is seen as the foundation of reactions to emotional separations later in life. As with the attachment theory, a constant and reliable early relationship will impact an individual's ability to separate from a lost loved one in an autonomous, healthy manner. However, those individuals with more unpredictable early relationships may experience more distress in separating from the deceased.<sup>15</sup>

According to interpersonal theories of grief, the quality of relationships of those experiencing loss is significant. The concept of this theory is based on the way in which individuals interact with one another becomes a part of how they define themselves, regulate their emotions, and develop a sense of appropriate social roles. These interactions may impact their ability to recover and move on after losing a loved one.<sup>16</sup>

Other researchers suggest that cognitive processes are the key to understanding how individuals cope with loss.<sup>3,8</sup> Bereaved individuals may experience intrusive thoughts, frequent distractions, or catastrophic beliefs about the world.<sup>8</sup> In particular, cognitive-behavioral theories are based on the idea that a loss must be incorporated consciously into the bereaved individual's understanding of the world and his or her place in it.<sup>8</sup> Integrating a loss is often very challenging and may result in maladaptive thoughts, feelings, and behaviors which prolong the period of grief. Specifically, individuals who have this difficulty accepting the loss as a reality may also have particularly negative beliefs about the world, misinterpret their own reactions to the loss, and/or display anxious and avoidant strategies.<sup>8</sup> According to cognitive-behavioral theories, although individual personalities and mental health may play a role in a bereaved person's ability to cope with grief, maladaptive cognitions and behaviors may contribute to the development and maintenance of more serious grief reactions.<sup>8</sup>

Some models of grief focus on the sociological and cultural implications of an individual's background on his or her ability to handle loss. Rosenblatt<sup>12</sup> suggests that although the experience of grief may be common to all humans, there is no universal way of encapsulating the thoughts, feelings, and rituals of coping with grief. He suggests that clinicians and researchers who encounter or study grief must become familiar with the language and practices of people in a variety of societies in order to best understand and assist them.

Stroebe and Schut's<sup>17</sup> dual-process model is one of the most comprehensive theories of grief and suggests that bereavement consists of two kinds of coping: loss-oriented coping and restoration-oriented coping. Loss-oriented coping involves ruminating about the loss and yearning for life with the deceased, which may bring on both positive and negative emotions. Restoration-oriented coping centers on adjusting to life without the deceased person. As with loss-oriented coping, restoration-oriented coping may result in a variety of emotions. For example, a person may experience anxiety about creating a new lifestyle as well as pride or relief at succeeding at various tasks or accomplishments. The vacillation between rumination about the loss and conscious attempts to redefine life contributes to recovery from grief.<sup>17</sup>

Recent functional neuroimaging studies have begun to explore the neural basis of grief, identifying brain regions activated during the elicitation of grief with the ultimate goal of improving psychopharmacotherapy for PGD.<sup>18–20</sup> Grieving individuals exhibit increased activation of several brain regions involved in the processing and regulation of emotional pain, including the anterior cingulate cortex, insula, and amygdala. Freed et al<sup>19</sup> also identified differential patterns of activation between two symptoms commonly seen in PGD—intrusive and avoidant thoughts. Intrusive thoughts were associated with activations of the ventral amygdala and rostral anterior cingulate, while avoidant thoughts were associated with deactivation of the dorsal amygdala and dorsolateral prefrontal cortex. Extending neuroimaging research toward

PGD, O'Connor et al<sup>20</sup> found that while subjects with normal and prolonged grief exhibited similar activation of emotional pain-related regions, only those with PGD demonstrated activation of the nucleus accumbens. The increased activity in the nucleus accumbens correlates with higher levels of self-reported yearning for the deceased. Overall, these results suggest that grief is mediated by pathways involved in emotional pain, but PGD may involve abnormal activation of neural reward pathways that ultimately interferes with adaptation to the loss. While future studies should further explore these findings, the potential association between PGD and abnormalities in reward neurocircuitry holds significant implications for treatment.

## Clinical Presentations

Health-care professionals should recognize that grief may present in a variety of forms and at various times during a patient's illness and beyond. Grief may develop at the time of diagnosis (referred to as "anticipatory grief"), during and through death, and for months or even years after the loss. Recognition of grief symptoms in family members and caretakers may lead to earlier interventions, which may relieve suffering and prevent the development of pathological grief reactions.

## ANTICIPATORY GRIEF

Anticipatory grief describes grief symptoms experienced by both patients and their loved ones prior to death.<sup>21</sup> Although anticipatory grief symptoms may be similar to those experienced following loss, the term is useful in describing the grief which may begin far before death, when the patient and family first recognize the terminal prognosis of an illness. For some, the very diagnosis of cancer may be equated with terminal illness,<sup>1</sup> and anticipatory grief is often a normal response to the realization of major changes forthcoming. Patients and their families may experience fears regarding the loss of independent functioning and changing roles within the family. As a result, some families may encounter increasing dysfunction and conflict as family members react with hostility, anger, and poor expressiveness.<sup>22</sup> On the other hand, anticipatory grief may also be a positive experience. Families may become more cohesive through shared hardships, and anticipation of death forthcoming may offer patients and their loved ones time to emotionally prepare for the loss.

Predictors of anticipatory grief include female gender, adult children, high perceived stress, and difficulty coping.<sup>23,24</sup> Gilliland and Fleming<sup>23</sup> found that spousal anticipatory grief was characterized by higher levels of anger and loss of emotional control compared to grief following death and Smith<sup>25</sup> showed anticipatory grief predicted worse adjustment to the death. Similarly, adult children experiencing anticipatory grief were likely to report better adjustment to the death of their parent. However, these improved symptoms postloss may reflect relief from intense emotional and social turmoil surrounding the patient's illness, and relatively little is known

about the association between anticipatory grief and abnormal postloss grief reactions. Nevertheless, it is important that oncologists understand anticipatory grief and recognize symptoms that may begin in both patients and family members at the time of diagnosis. Anticipatory grief may produce intense emotional symptoms and holds key implications for postloss grief. It is critical for oncologists to deliver news with sensitivity and attempt to recognize dysfunctional reactions so that appropriate psychosocial resources can be made available.<sup>26</sup>

## GRIEF SURROUNDING TIME OF DEATH

A strong, trusting relationship among physician, patient, and family members is crucial at the end of life and promotes healthy adjustment for those who grieve. Informational materials regarding what to expect during these final moments may help alleviate anxieties and provide guidance for the upcoming hours or days. When death appears imminent, family members should be notified promptly and with utmost sensitivity. The health-care staff should be patient and respectful in taking time to adequately answer all questions.

Clinicians should offer support and encourage emotional expression rather than making efforts to minimize the loss.<sup>27</sup> Cultural and religious practices should be respected, and chaplaincy services may be offered when appropriate. Shortly following death, the clinical team may provide further assistance via psychosocial support and guidance regarding funeral arrangements. Moreover, clinicians may want to send a letter of condolence or make a phone call to the family to express sympathy for their loss and offer a debriefing meeting for the family.<sup>28</sup> Indeed, 50%–70% of bereaved caregivers of advanced cancer patients desire bereavement support after loss,<sup>29,30</sup> but the rate of bereavement follow-up reported by physicians remains low.<sup>31–33</sup> In one study, 33.3% of medical oncologists, radiation oncologists, and palliative care specialists reported that they usually or always make a telephone call, send a condolence card, or attend a funeral after a patient's death.<sup>33</sup> Families are often extremely appreciative of the care and support the oncologist has provided during the course of illness, and a consoling message provides a sense of closure for both families and clinicians.<sup>34</sup>

## MALADAPTIVE RESPONSES TO BEREAVEMENT

Although some form of sadness and anxiety is common, particularly right after the death of a loved one, most people tend to recover from their feelings of grief. However, extreme forms of prolonged distress resulting from grief that causes functional impairment are not considered normal.<sup>2</sup> Some individuals may develop separation anxiety, generalized anxiety disorder, phobias, or somatic symptoms.<sup>1</sup> In trying to understand the impact of grief on mental health, some researchers have suggested that bereavement-related depression does not differ from depression due to other stressful life events.<sup>35</sup> As a result, many patients may receive a diagnosis of major depressive disorder based on symptoms such as psychomotor retardation, feelings of worthlessness, extreme guilt, or suicidal ideation.<sup>9</sup> However, a variety of risk factors may

increase the likelihood that grief will result in clinically significant cases of depression, anxiety, or PGD. It is important to distinguish between sadness in the early months following a loss and more severe, protracted distress.

### PROLONGED GRIEF DISORDER

Although many individuals come to terms with loss over time and begin to feel a renewed sense of stability in their lives without the deceased, about 10%–20% demonstrate a severe and prolonged grief response.<sup>7,9</sup> Researchers have studied this potentially debilitating response to loss and developed empirically supported diagnostic criteria for PGD. Though PGD, anxiety, and depression may co-occur, an isolated set of symptoms specific to PGD has been identified. Bereaved individuals with PGD are “stuck” and unable to move on from their grief.<sup>9</sup> The experience of these individuals includes symptoms such as intense longing or yearning for the person who died, a sense of bitterness regarding the loss, rumination about the loss, social isolation, intense sorrow or regret, and a feeling meaningless.<sup>9</sup> Many of these symptoms and the impairing nature of the disorder may result from an unwillingness or inability to accept the loss of the deceased and to move toward a life without that person. This may contribute to the notion that an individual with PGD is “stuck” in a state of chronic mourning, unable to let go of the past shared life and picture a purpose or meaning in the world that can carry him or her forward.<sup>9</sup> Although symptoms may become evident at the time of death, one important feature of PGD is that a diagnosis cannot be determined until at least six months have elapsed since the loss. Given that normal grief tends to dissipate in six to thirteen months,<sup>36</sup> this time period is critical for clinicians to distinguish between individuals who are suffering and in need of treatment and those whose grief will likely resolve naturally.<sup>7</sup>

Research has offered evidence for the significant presence and distinct clinical picture of PGD compared to depression and posttraumatic stress disorder (PTSD).<sup>37</sup> PGD has been linked to an increased risk for broad, negative mental and physical health outcomes, life-threatening conditions, hospitalizations, symptoms of depression, increased stress, negative health behaviors, functional impairment, and suicidal thoughts.<sup>6,38–40</sup> Given the empirical evidence for PGD as a distinct mental illness, as well as the grave health outcomes which its symptoms predict, bereavement researchers have made the case for including PGD in the next edition of the *Diagnostic and Statistical Manual of Mental Disorders*.<sup>9</sup> Although other terms, such as “complicated” and “traumatic” grief, have been employed in past research, Prigerson et al<sup>9</sup> suggest that the use of the word “prolonged” is the most clear and accurate, as well as the least pejorative, way of describing this severe reaction to loss. Although previously discussed evidence exists for the uniqueness of the syndrome, some suggest that both “normal” and “abnormal” grief symptoms fall on a continuum which, if pathologized, may contribute to increased stigmatization or medicalization of the grieving process, which many view as a trying but expected part of life.

Prigerson and her colleagues maintain, however, that recognizing PGD as a distinct disorder will allow for more consistent and earlier recognition of bereaved individuals who require assistance and treatment.<sup>7,9,37</sup> In addition, among bereaved individuals who met the criteria for PGD, nearly all of them said they would be receptive to treatment; their families would be more understanding of their distress and relieved to know they had a recognizable syndrome.<sup>41</sup>

### RISK FACTORS FOR PGD

In a majority of individuals, the feeling of intense distress following a loss will gradually subside over the subsequent months. For certain individuals, this is not the case. Numerous risk factors for negative grief outcomes have been identified. Some factors relate to personal psychiatric vulnerabilities such as insecure attachment styles,<sup>42,43</sup> childhood abuse or neglect,<sup>44</sup> and history of psychiatric illnesses such as depression or childhood separation anxiety.<sup>14</sup> Other risk factors for experiencing extreme distress following a loss include the level of family cohesion and social support in the community. Moreover, the conditions of the death itself may also predispose individuals to pathological grief, depending on the family members’ perceived preparedness.<sup>11</sup>

Although many risk factors for PGD are difficult to change, early identification of the subset of individuals at risk for PGD is an important task for family members, oncology staff, psychiatrists, and primary-care physicians. Modifiable risk factors may be addressed and optimized early. In addition, health-care professionals may be in a unique position to recognize family members at high risk for pathological grief outcomes. Providing early psychosocial support for these individuals may prevent subsequent development of PGD and its sequelae.<sup>4</sup>

### Specific Circumstances

#### LOSS OF A CHILD

Childhood cancer is relatively uncommon and generally carries an encouraging prognosis, with 5-year survival rates of 81.5%.<sup>45</sup> However, when a child is lost to cancer, the grief reaction of parents is often more intense and prolonged than the grief which results from the loss of a spouse or a parent.<sup>46,47</sup> Parents may experience extreme feelings of guilt and failure as well as a sense that the natural order of the world has been upset when they have outlived their child. Kreicbergs et al<sup>48</sup> identified increased rates of anxiety and depression in parents who have lost a child to malignancy compared to nonbereaved parents, with a prolonged effect lasting seven to nine years postloss. Parents with unresolved grief experience increased physical and psychological morbidity, including disturbances in sleep, increased sick leave, and increased health-care utilization.<sup>49</sup> A Danish national follow-up study on child death from all causes found bereaved parents to have an increased risk for psychiatric hospitalization that was most pronounced during the first year postloss and significant for up to five years after the child’s death.<sup>50</sup> The same group also found bereaved mothers to have increased overall mortality

rates from both natural and unnatural causes throughout follow-up as well as increased mortality from unnatural causes in fathers at one to three years postloss.<sup>51</sup>

The physician–parent relationship is a critical aspect of care of the terminally ill child and may ultimately promote healthy grief resolution. A Swedish national survey of parents four to nine years following the loss of a child to cancer found those who had access to professional psychological support during the last month of their child’s life were more likely to report satisfactory grief resolution.<sup>52</sup> Higher degrees of grief resolution were also seen in parents who felt the health-care team was taking initiatives to offer counseling during the child’s illness and when parents had the opportunity to discuss their child’s condition with the attending physician. Oncology staff should be aware of the importance of communication with patients and their families and offer psychosocial services at the end of life. Studies have found parental perceptions of high-quality care to be associated with physicians providing news with care and sensitivity, giving clear information on what to expect during the end of life, and preparing the family for the circumstances surrounding the child’s death.<sup>53</sup> In addition, the physician should make attempts to communicate directly with the child, if he or she is old enough.<sup>53</sup> When psychiatric services are necessary, family-focused grief therapy may be effective at promoting support between parents and any remaining children.<sup>54</sup>

### **BEREAVEMENT DURING CHILDHOOD**

Loss of a parent during childhood often creates a void in the child’s life, a void that may begin long before the parent’s death as the remaining parent is occupied with caretaking activities. Household responsibilities are likely to change drastically as a result of parental loss, and children may experience fears about their own health and their security in the world.<sup>55</sup> Multiple studies have confirmed that children who experience parental death are at increased risk for anxiety and depression both later in childhood and as adults.<sup>56–58</sup> Bereavement during childhood represents a critical period during which clinicians and caretakers should be vigilant toward symptoms of depression, dysphoria, and conduct issues. Unfortunately, few studies have examined specific interventions in childhood grief. One recently published randomized controlled trial, discussed the effects of a family bereavement program entailing 12 group sessions for caregivers and youths and found this intervention to significantly reduce rates of externalization and internalization of problems as well as to lower rates of depression at their six-year follow-up.<sup>59</sup> Additional studies may better evaluate the efficacy of other supportive psychotherapies indicated for children after parental loss.

### **ADOLESCENTS AND YOUNG ADULTS**

Adolescents and young adults (AYAs, individuals 15–39 years old) live in a transition period characterized by a unique set of psychosocial factors,<sup>60</sup> which may affect their ability to cope with distress. The major task of adolescence involves the

formation of a coherent and personal identity,<sup>61</sup> while still retaining a connection to the family.<sup>62</sup> This process often continues into early adulthood, and as a result, loss of a loved one—particularly a parental figure—during this period is an aberrant life event that may disrupt identity formation. While clinicians and family members may typically interact with AYAs as adults during the grieving process, studies show that this group experiences an intensified set of emotions relative to older adults in grieving parental loss.<sup>63</sup> Similar to grief during childhood, grief during adolescence is a risk factor for chronic anxiety and depression.<sup>64</sup> Uniquely, AYAs may experience guilt or the necessity to return home during the terminal phase of illness and following death. On the other hand, AYAs who may have been the primary caretakers of the deceased may experience both grief as well as a sense of relief following the death. These responses may further trigger guilt and distress during an already fragile period. While empirical data are relatively sparse, current research suggests that AYAs represent a distinct psychosocial group who may benefit from more specific interventions directed at addressing their specialized needs.

### **Interventions and Treatments for Grief**

Although oncologists are likely to encounter patients or families experiencing various presentations of grief on a frequent basis, research on how to help these individuals has been mostly inconclusive. Several authors offer methodological arguments about why a large body of research on psychotherapeutic interventions has been inconsistent and difficult to interpret<sup>65–67</sup> and why most researchers have found small to moderate treatment effects. Some suggest that small effect sizes for bereavement interventions are a result of “diluting” the sample with less distressed bereaved persons from the start and the reduction of bereavement distress that occurs with time alone.<sup>68</sup> Some studies do indicate that those individuals with particularly severe grief symptoms may benefit from psychotherapeutic interventions<sup>23,65</sup> and/or psychopharmacological treatments.

### **CLINICAL SUPPORT FROM HOSPITAL STAFF**

There are many ways in which clinic staff members may offer support to individuals and families after a death. This may be particularly helpful and appreciated when the staff has developed a close relationship with a patient’s family prior to the loss. While the effort required may be as small as offering condolences over the phone or sending a sympathy card or more involved, such as visiting the family’s home, attending the funeral, or developing an annual commemoration service for the deceased and his or her family, preserving the connection that often develops during treatment may affect the loved ones’ experience of loss.<sup>1</sup>

### **PSYCHODYNAMIC AND INTERPERSONAL TREATMENTS**

Psychodynamic treatment approaches tend to be long-term and revolve around attempts to utilize knowledge of childhood experiences, object relations, and unconscious conflicts as a framework for understanding a patient’s grief response. Patients who would likely benefit most from psychodynamic therapy are those who have unresolved issues related to con-

flict and insecurity in their early relationships.<sup>1</sup> Interpersonal therapy (IPT) is one specific form of psychodynamic treatment that is manualized, time-limited, and focuses on relational conflicts, which are purported to maintain symptoms of distress. IPT was developed to treat depression but has since been utilized as a treatment for a variety of psychological disorders.<sup>1,65</sup> An inventory of relationships is developed to determine which of four common issues (grief, disputes, transitions, and deficits) contributes to the patient's struggles. Once this target area has been identified, the therapist works with the patient to improve communication and problem-solving abilities in order to alleviate the stress of relational conflicts. While some studies offer evidence for the effectiveness of IPT,<sup>1,65</sup> other results indicate that IPT alone does not significantly reduce bereavement-related major depressive episodes.<sup>69</sup>

### COGNITIVE-BEHAVIORAL THERAPY

Broadly conceptualized, cognitive-behavioral therapy (CBT) focuses on isolating and modifying automatic thoughts and catastrophic beliefs, which are often reinforced by maladaptive and/or avoidant behaviors. When considering grief in a cognitive-behavioral framework, Boelen and colleagues<sup>8</sup> suggest that individuals have a hard time accepting a loss as real and integrating the experience of the death into their internal self-narrative. Treatment within this conceptualization of grief may be especially helpful when individuals are experiencing excessive guilt or anger, which may be caused by distorted cognitions regarding the circumstances of the death or the relationship to the deceased.<sup>1</sup> Additionally, the behavioral component of CBT may be used to help bereaved individuals decrease their avoidant tendencies, which would result in a healthy interaction with reminders of the deceased and a recommencement of day-to-day activities.<sup>8</sup>

### GROUP-ORIENTED THERAPEUTIC APPROACHES

One of the most beneficial aspects of group therapy is that participating individuals can provide informed support to each other because of shared experiences. Group members can offer validation and normalization to one another regarding emotions and behaviors related to coping with the loss. Additionally, participants can share ways in which they have learned to cope with their grief. Studies have indicated that patients with PGD who were more extroverted, open, and conscientious with a history of social support and secure relationships would benefit most from group therapy.<sup>54,70,71</sup>

### FAMILY THERAPY

The understanding of a family's dynamics that often develops throughout the course of the deceased's treatment may lead clinicians to recommend family therapy. The aim of family-focused grief therapy<sup>22</sup> is to prevent unhealthy responses to bereavement by examining a family's ability to communicate, feel close to each other, and resolve conflict before a loss. The therapy is brief, focused, and time-limited. Families are screened before the patient has died, and if they demonstrate moderate struggles with communication, cohe-

sion, or conflict resolution, therapy begins at this time and continues after the loss. Beginning therapy before the patient's death gives clinicians the opportunity to view the way the illness impacts the family's functioning and provides a sense of continuity of care after the loss. Research has indicated that family-focused grief therapy has been modestly successful at reducing distress about a year after the loss but was most beneficial to families who were characterized as "intermediate" and/or sullen.<sup>22</sup> Identifying families before a loss who are already struggling to cope with the stress of cancer may provide clinicians with a valuable opportunity to intervene and help prevent additional distress.

### INTERNET-BASED THERAPY

Treatment interventions for grief found on the Internet have been demonstrated to be effective at reducing distress in the form of avoidance and depression.<sup>72</sup> There are a variety of reasons that Internet-based interventions may be successful and appealing to patients: they are cheaper, may be accessed in the comfort of an individual's home, may provide a greater sense of anonymity, and may allow the bereaved to avoid medical settings that remind him or her of the deceased's treatment and death.<sup>1</sup> Additionally, symptoms of psychiatric disorders (e.g., PGD, depression, and PTSD) may be reduced through Internet-based interventions.<sup>73,74</sup>

### COMBINED PSYCHOPHARMACOLOGICAL TREATMENTS

Bereavement-related depression may be treated with a combination of antidepressants and psychotherapy, similar to the treatment of major depressive disorder. Both selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) have shown efficacy at reducing depressive symptoms in the context of grief.<sup>66,75,76</sup> One open-label study found the SSRI paroxetine (Paxil, Pexeva) and the TCA nortriptyline (Aventyl, Pamelor) to be equivalently effective at reducing symptoms of both depression and complicated grief.<sup>73</sup> Other studies have found success in combining pharmacotherapy with psychotherapy. The most compelling evidence for this combined approach involves a double-blinded, randomized control trial of nortriptyline and interpersonal psychotherapy, which reduced depressive symptoms in 69% of treated patients following a median of 6.4 weeks of treatment compared to 56% in nortriptyline alone and 29% in psychotherapy alone.<sup>73</sup> In contrast to the open-label trial of paroxetine, however, the latter study found that neither nortriptyline nor interpersonal psychotherapy significantly reduced the symptoms of complicated grief. Therefore, while it appears that standard pharmacotherapies may be combined with psychotherapeutic approaches in treating bereavement-related depression, the intensity of grief symptoms may remain unchanged.

### TREATMENTS FOR PGD

Due to the complex nature of PGD, the disorder does not always respond effectively to typical treatments for bereavement-related depression.<sup>9,37</sup> Boelen et al<sup>77</sup> compared a CBT intervention for PGD to supportive counseling and found that CBT was

more effective at decreasing the pathological symptoms of PGD. Additionally, Shear et al<sup>78</sup> created complicated grief treatment, which combines psychoeducation with CBT methods. A randomized, controlled trial found that more patients responded quickly to complicated grief treatment than IPT.

### EFFECTS OF HOSPICE CARE

Hospice organizations and palliative care specialists are adept in the management of physical pain and emotional suffering at the end of life, and hospice staff may be able to play an important role in helping family members cope with loss. In addition to promoting a “good death,” most hospice programs provide grief and bereavement support for family members after the death, which may be helpful in reducing the severity of prolonged grief reactions. One prospective cohort study found that caregivers of patients enrolled in hospice for three or fewer days were at significantly increased risk of developing major depressive disorder compared to those with longer hospice enrollments.<sup>79,80</sup> This effect was found at six and thirteen months postloss after adjusting for confounding factors such as baseline major depressive disorder and caregiver gender, age, relationship to the patient, and burden. More importantly, a retrospective matched cohort study found hospice use at the end of life to be associated with reduced mortality during bereavement among widowed spouses.<sup>81</sup> Additionally, hospital deaths relative to hospice heightened the risk of PGD in bereaved family members.<sup>82</sup>

These studies suggest that hospice enrollment may be a preemptive intervention for those at risk for pathological grief, and enrollment status may be further used to identify those at risk for complicated grief. Additional research is certainly warranted to tease out the relationship between hospice use and postloss morbidity and mortality in caregivers. The available data suggest that physicians should consider engaging with the patient and family in a detailed discussion regarding the resources available through hospice organization.

### Conclusion

Although considerable government and private resources have been devoted for many years to finding a cure for cancer and many dramatic advances have been made, a significant proportion of the population is diagnosed with cancer every year. Many of these patients will not survive. The loss of a loved one can be, for many, one of life’s most devastating

experiences. While the experience of grief after a death may be thought of in terms of attachment, relationships later in life, intrusive thoughts, avoidance behaviors, or cultural background, oncology providers are likely to experience the suffering of their patients’ loved ones on a regular basis. Many of the theories of grief contain overlapping elements. These elements may be considered and integrated from within a biopsychosocial framework which takes into account the biological, psychological, and sociocultural ramifications of losing a loved one.

Many treatment models have been proposed for grief, and although the literature still suggests mixed results, further research into specific subgroups of bereaved individuals may be helpful in developing reliable and valid targeted interventions. Researchers will continue examining how therapies can help patients resolve conflict from early relationships, diffuse conflict in current relationships, and/or help patients accept the reality of the loss as part of their life story. Treatments which begin before the patient’s death, for both individuals and families, may facilitate greater acceptance and ability to deal with often inevitable role shifts and new responsibilities. Although some controversy about the treatment of grief exists in relation to the discussion of PGD as a distinct disorder, the empirical support for the distinctiveness of this disorder is strong and convinced the DSM-5 to recognize grief as an Axis I disorder, a form of adjustment disorder. We expect this development to stimulate research in epidemiology, neurobiology, and treatment of PGD.

Overall the literature indicates that the role of oncology staff in helping families cope with grief is immeasurable. Medically and psychologically, clinicians are well positioned to reach out to patients and prevent postloss suffering. Patients and their families often develop very close relationships with hospital staff and may benefit greatly from feeling as though their interactions with staff do not end the moment their loved one dies. Continuity of care, particularly in discussions of grief, must be continued even after the loss of a patient.

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# Take-Home Messages for the Oncology Practitioner

Noreen Carrington, LMFT, FT, and Charles F. von Gunten, MD, PhD

Commentary on “Understanding Bereavement: What Every Oncology Practitioner Should Know” by Elizabeth Kacel, Xin Gao and Holly Prigerson (page 172).

**K**acel and colleagues provide an exhaustive review of bereavement theory and practice.<sup>1</sup> However, as a consequence of the depth and structure, readers might miss the “take-home” messages that every oncology practitioner should know. In addition, every oncology practitioner needs to be able to recognize the grief responses in oncology practitioners themselves.

## What Every Oncology Practitioner Should Know

Every oncology practitioner, whether physician, nurse, pharmacist, radiation technician, or medical or clerical assistant, needs to know that grief is normal. Grief includes the emotional, physical, cognitive, and spiritual responses to loss. It is as normal as the flash of blood when starting an intravenous line or the pain of a bone marrow biopsy.

The manifestations of grief—what one is likely to see in the office or in the hospital—are varied: Crying, anger, emotional numbness, behaving as if nothing has changed are all common. The most important thing to know is that these relate to grief. People are not *trying* to be difficult; they are not *borderline* or *dysfunctional*. Eighty percent of the bereaved will get through it without professional help.<sup>2</sup> Most people do cope. While they may never feel “the same” as before, they will adapt to a new normal and carry on productive lives.

The response to grief from the oncology practitioner for those 80% should be the human response. The

development of new skills beyond that of the average caring health professional is not needed. When someone is crying, stop talking, sit down, and listen. When someone is angry, stop talking, sit down, and listen. When a survivor of a patient who died tearfully says that he or she hears the person’s voice or experiences a yearning for the presence of the deceased, sit down and listen. We are always surprised when it is the reception clerk in a busy oncology practice who seems the most skillful when confronted with a patient or family member expressing strong emotion. We speculate that it is because he or she has not unlearned the compassionate human responses that well-socialized adults demonstrate in such situations. We also observe that the expression of any strong emotion tends to upset oncology professionals, and those professionals tend to give the non-verbal signal to the person expressing the strong emotion to STOP IT!

For the 20% of patients or family members whose grief is associated with difficult adaptation, referral for specialized treatment is appropriate. There is no evidence that therapy from a psychiatrist versus a psychologist versus a social worker versus a marriage and family therapist is better or worse. The oncology practitioner needs to know what is available in his or her environment and to use it.

Bereavement care for the family is provided by all accredited hospice programs in the United States. Hospice programs screen for complicated grief risk as part of routine care. For this reason, and many others, referral for hospice care represents the completion of comprehensive cancer care.<sup>3</sup> The evidence is strong enough to assert that every patient with a prognosis of less than six months if the disease runs its usual course should be referred for hospice care from an accredited hospice program. If there is a choice of hospice programs, the oncology practitioner is in the position of being able to refer to the hospice that he or she thinks provides the best care; if grief is a concern, choose the one with the most extensive mental health staff.

Bereavement counselors learn things even the best oncology professionals do not learn even if the

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therapeutic relationship has been strong and productive. They see the bereaved over time when there is no reason to return to the oncology practice. In addition, the relationships between patient/family and the oncology practice are complex. Some have called it a love relationship. In any loving relationship, there are things one partner does not tell the other. Yet, those "secrets" can have a profound impact on the course of grief.

### Grief in the Oncology Practitioner

Nothing inoculates oncology practitioners against grief. In fact, prevailing patterns of coping with sequential loss may have a negative impact on the practitioner and the cancer care provided. This is not confined to just the physicians—everyone in an oncology practice can be expected to experience grief related to patient care.

Expect to cry sometimes. Expect to be angry sometimes. Expect to need "a break" from work for vacations. Recognize when intrusive thoughts about patients interfere with your

otherwise normal life. Recognize when relationships outside of work are affected. Be open to the observations of your colleagues to notice when you are "different" and need to talk. Know where you can get professional help when the usual approaches do not return you to the loving, caring oncology professional you usually are.

*Conflict of Interest Disclosures:* No potential conflicts of interest were reported.

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# Recognizing Grief in Oncology Patients and Their Caregivers

Judith Lacey, MD, FACHPM

Commentary on “Understanding Bereavement: What Every Oncology Practitioner Should Know” by Elizabeth Kacel, Xin Gao and Holly Prigerson (page 172).

*Health-care professionals should recognize that grief may present in a variety of forms and at various times during a patient’s illness and beyond.*

—Kacel, Gao, and Prigerson, “Understanding Bereavement: What Every Oncology Practitioner Should Know”

**R**ecognizing and addressing the psychological distress of patients and their families often falls to the oncologist. We know that up to 50% of patients with cancer have identifiable psychiatric disorders, such as anxiety, depression, delirium, and demoralization.<sup>1</sup> But when it comes to patient grief, how do we diagnose this and differentiate it from other complaints? Which patients are more susceptible? How do we identify the family with anticipatory grief or at risk of prolonged grief disorder (PGD)? Are there interventions during the course of the illness trajectory that can improve the well-being of both patient and family? This article provides an overview of what the oncologist should know about bereavement.

As clinicians working with patients with advanced cancer, we are aware that many of our patients do not want to be perceived as a burden to their family and want to know that their family members and loved ones are supported. Patients

wish to ensure that the impact of their disease and dying will not result in long-term emotional, social, or physical family member morbidity. Identifying family members’ psychosocial and coping concerns is therefore an integral part of patient care.<sup>2</sup>

As people live longer with a diagnosis of incurable cancer and all its uncertainty, researchers remind us to consider anticipatory grief. Both patient and family can be grieving - a process that may begin at any time from the moment of a cancer diagnosis. Cultural background, personality, past history, and family function contribute to how one grieves. In a recent publication in *Death Studies*, the complex nature of grief in the patient with advanced cancer is explored further, recognizing the overlap of symptoms with major depression.<sup>3</sup> The interesting question is whether interventions introduced for the advanced cancer patient to address existential and psychosocial distress may also be useful for the grieving patient.

From Kacel, Gao, and Prigerson’s article we have learned that clinicians have the opportunity to aid in reducing postloss and potentially pre-loss suffering. We need to identify those patients and family members who are at risk of developing PGD, think about the possibility of anticipatory grief, refer those requiring intervention, and refer early to palliative care (hospice) as it improves bereavement outcome. We need to be aware of the significant positive impact good patient–doctor, parent–doctor, and family–doctor communication can have on reducing PGD and long-term morbidity.

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# Guiding Patients Facing Decisions about “Futile” Chemotherapy

Erin Alesi, MD, Barton Bobb, RN, MSN, and Thomas J. Smith, MD

## Case Presentation

Ms. G is a 71-year-old woman with metastatic gastric adenocarcinoma recently diagnosed after an extensive surgical resection for a small bowel obstruction (SBO). She was admitted from the surgery clinic with intractable nausea and vomiting. An abdominal computerized tomographic (CT) scan revealed a partial SBO and peritoneal carcinomatosis. Given her recent surgery, the extent of her disease, and high likelihood of recurrent SBO, the surgical team decided that Ms. G was no longer a surgical candidate. When her symptoms did not improve with conservative measures, both oncology and palliative medicine were consulted to assist with symptom management and goals of care. The oncology team stated that Ms. G was still a chemotherapy candidate and suggested that she attend her new patient evaluation in oncology clinic the following week. The palliative medicine team then met with the patient to discuss management options and her preferences for care. The palliative care team explained ways to control her nausea and vomiting without using a nasogastric tube, and the patient agreed to transfer to their service for symptom management. The palliative team explained that her cancer was incurable but that chemotherapy options existed to help control her disease and possibly prolong her life. They also explained that the chemotherapy has side effects and that the patient would need to decide if she wanted to undergo treatment and accept potential side effects for the possibility of prolonging her life by weeks to months and improving her symptoms. As an alternative, she was told that she could focus solely on symptom control with medications and allow her disease to take its natural course. Ms. G was asked to think about how she wanted to spend the time she had left. Prior to discharge, as her symptoms improved, Ms. G was evaluated by another oncologist, who, after consulting the expert gastrointestinal cancer team, explained to her that the current chemotherapy options available for metastatic gastric cancer were rarely, if ever, successful at reversing malignant obstruction. With this information, the patient decided to be discharged home with hospice and spend time with her family. She died peacefully at her home approximately two weeks later.

## Futile Is as Futile Does

**W**hen deciding whether or not chemotherapy is “futile,” the concept of medical futility must be explored.<sup>1</sup> Though it remains difficult to adequately define, the qualitative and quantitative descriptions offered by Schneiderman et al<sup>2</sup> are widely used. Qualita-

tively, futile treatment “merely preserves permanent unconsciousness or cannot end dependence on intensive medical care.” More precisely, it is a medical treatment “that in the last 100 cases . . . has been useless.”<sup>2</sup> A useful, albeit imprecise, definition of futile *chemotherapy* is that in which the burdens and risks outweigh the benefits. As an example, studies on chemotherapy for advanced non-small-cell lung cancer (NSCLC) have shown that patients with poor performance status or chemotherapy-unresponsive disease receive little benefit in terms of response rates and survival.<sup>3,4</sup> A retrospective analysis by Massarelli et al<sup>3</sup> showed dismal response rates for third- and fourth-line NSCLC chemotherapy of 2.3% and 0%, respectively. Additionally, an observational

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**Table 1****Questions to Discuss with the Patient when Chemotherapy May Be Futile**

QUESTION	LEADING PROMPTS	COMMENT
What is the patient's current understanding of the disease?	How much do you know about your cancer at this point? How much do you want to know?	Be sure the patient is ready to discuss this issue and that you have enough time for discussion. Ask if there are others who should receive this information simultaneously, afterward, or instead of the patient.
What are the patient's goals?	Knowing that we can't cure your cancer, what are your goals, wishes, or hopes for the future?	Treatment decisions may be impacted greatly by a patient's personal goals (eg, patient wants to live to child's graduation or patient wants to be as comfortable as possible).
If chemotherapy is an option and the patient is interested, is he or she aware of potential risks and benefits?	Although everyone responds differently, these are the likely side effects and outcomes of this treatment ...	Be specific in terms of likelihood of response, type of response (palliation instead of cure, extent of life prolongation expected, symptom relief, etc) and how likely it is that treatment will help achieve patient's goals. Discuss potential symptom burden from treatment in detail. Patient needs to be able to make informed decision about risks vs. benefits involved in potential treatment.
If the patient declines chemotherapy, treatment is not indicated, or treatment fails, what other options are available?	Let's talk about options to make sure that you are comfortable and enjoy the highest quality of life possible in the time that you have left.	Focus on pain and symptom management. Discuss hospice options (home vs. inpatient) and make referrals when appropriate. Stress that you will continue your relationship with the patient (possibly as a hospice provider) and that you will ensure that his or her symptoms are managed, either directly or through hospice nurses.

study by Zietemann and Duell<sup>4</sup> showed that 40% and 50% of patients receiving second- and third-line chemotherapy for NSCLC die during or soon after treatment, respectively, and that over 20% receive chemotherapy within 14 days of death. Neither study commented on quality of life experienced by patients. However, a recent study by Temel et al<sup>5</sup> demonstrated that NSCLC patients receiving concurrent palliative care and standard oncologic care had better quality of life and even longer survival than patients receiving only standard oncologic care, despite being less likely to receive aggressive end-of-life care. Though limited to patients with NSCLC, these studies illustrate that chemotherapy in advanced cancer is often futile, especially when less aggressive care can improve quality of life as well as survival.

Addressing the futility of chemotherapy with patients is challenging for most oncologists. Although defining treatments as "futile" is suitable in the medical literature, it is a word that may carry negative connotations, such as hopelessness or abandonment, to patients. A more descriptive and less negative term, "nonbeneficial," may be used when discussing futile chemotherapy with patients. The point when chemotherapy becomes nonbeneficial, and thus futile, is different for each patient and might even change over time. Addressing the patient's definition of nonbeneficial chemotherapy regularly during treatment ensures that the patient's goals are clear and allows the oncologist to direct conversation toward alternative options, such as palliative and hospice care, when chemotherapy cannot provide the benefits sought by the patient. This can be as simple as asking the patient, "Do you think the chemotherapy is giving you enough benefit to continue?"

### Palliative Care: It's Not Just Giving Up on People

Both the physician and the patient face several decisions when considering whether or not to pursue chemotherapy for advanced cancer. First of all, the patient must decide how much information he or she wants from the oncologist. If the patient is the decision maker, he or she must choose to accept chemotherapy that is palliative, not curative. After a frank discussion about the anticipated outcomes and symptoms associated with chemotherapy, the patient must consider whether he or she can accept the burden of treatment for the potential of prolonging life by days, weeks, or months. On the other hand, the oncologist must decide if chemotherapy should even be offered, based on patient performance status, known therapeutic outcomes, and patient values and goals. The oncologist can reassure patients that the best available data show that patients who use hospice for even one day actually live longer than those who do not.<sup>6</sup> Once informed about what palliative care and hospice offer, the patient may determine whether or not alternatives to chemotherapy are more favorable. If the patient qualifies for clinical trials, he or she must decide to accept treatment with uncertain outcome. When reflecting upon such difficult issues, both the patient and oncologist should involve others to help guide decision making. Oncologists can consult trusted colleagues for their expertise and to ensure that they are using the best information available. Patients should involve loved ones whom they trust to help make decisions in their best interest. **Table 1** provides key questions that the oncologist faces when making these decisions and how to approach them.

As an alternative to addressing the above issues with the patient independently, oncologists may involve a palliative

**Table 2****Things that Help Oncologists and Their Patients**

ITEM	HOW IT HELPS	COMMENTS
Early discussion of palliative and hospice care when chemotherapy may no longer help.	Hospice (and eventual death) will not come as a complete surprise.	“We will do our best to help you with this cancer, but at some point there may not be any treatments known to help.” “Remember the conversation we had when we first met?”
Reassurance that the oncologist will not abandon the patient if concurrent care is given.	This major fear may keep oncology patients at the same practice they have known for years—it is familiar—when they would be better served by transition.	There are now at least four randomized trials showing that most patients will accept concurrent palliative care if offered and that outcomes are equal or better at less cost. <sup>6,13–15</sup>
Legal documents such as advance medical directives, durable medical power of attorney.	Reinforces the seriousness and “now” aspect of care.	These are readily available in all states at no cost. They are not the final word on how to live one’s remaining time but will get the conversation started.
Best nationally recognized information showing that further chemotherapy will not help due to 3 prior failures or is not indicated due to poor performance status. <sup>9,10</sup>	The oncologist can point to the right page and say, “The best national guidelines call for a switch away from chemo . . . because it will do no good and will cause harmful side effects.”	Readily accessed from the Internet.
Use decision aids, similar to Adjuvant!	Increases the amount of truthful information given, even when the news is bad, and helps with transition points.	An increasing number of these are available <sup>16–19</sup> and will soon be offered as smart-phone applications (apps).

care specialist to facilitate this conversation.<sup>7</sup> Particularly in cases where the oncologist decides that chemotherapy is no longer a viable option, it may be easier, from both the patient and the provider perspectives, for the palliative care specialist to have this discussion. In a recent survey of patients on our oncology ward, the great majority did not want to discuss advance directives (ADs) with their oncologist—these patients thought ADs were important and should be discussed but were more comfortable discussing them with the admitting provider than the oncologist.<sup>8</sup> Patients may feel that they are disappointing their oncologist by being unable to take further treatment or by admitting that treatment has failed them. Similarly, oncologists might view having this discussion as an admission of their failure as a provider. The palliative care specialist, on the other hand, has no responsibility for chemotherapy and possibly no prior relationship with the patient, thus alleviating this type of emotional association between provider and patient. Furthermore, the conversation about nonbeneficial chemotherapy provides a segue for the palliative care provider to discuss with patients what he or she does best: establishing goals of care, managing symptoms, and maintaining comfort. For the palliative care specialist, providing symptom management and the best possible quality of life for patients are the fundamental goals. Death is generally not viewed with a sense of failure when palliation is the focus of care.

### Oncology: Palliative Care Is Giving Up

We still hear from oncologists like ourselves the dreaded words “What do you want me to do, give up on the patient?” or, to the patient, “What, are you giving up? I thought you’d keep fighting!” We would argue that current best practices include knowing when the risks and harms of chemotherapy

outweigh any potential chance of benefit. Physicians and patients should follow current National Comprehensive Cancer Network (NCCN) guidelines for solid tumors such as breast<sup>9</sup> and lung<sup>10</sup> cancer and stop chemotherapy when the chance of success is minimal. If the doctor cannot describe a specific, substantial benefit that outweighs the toxicity, he or she should not recommend it.<sup>11</sup> And all the relevant guidelines call for considering a switch to nonchemotherapy palliative care when the patient’s performance status is Eastern Cooperative Oncology Group (ECOG)  $\geq 3$ , defined as “3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.”<sup>12</sup> Such a simple threshold could dramatically reduce the use of chemotherapy at the end of life and lessen downstream toxicities.

Oncologists can implement several strategies to help facilitate the transition from aggressive care to comfort care (Table 2). For patients with incurable cancer, oncologists can hold early discussions about palliative and hospice options that will need to be implemented when chemotherapy is no longer able to control their disease. This discussion introduces palliative medicine as part of the care plan for incurable disease and allows the patient to anticipate such a transition. Oncologists can also provide reassurance that they will continue to be involved in their patient’s care and to support them, even if the patient does not undergo further chemotherapy. There are at least four studies that show equal<sup>13</sup> or better<sup>6</sup> survival, smoother transitions to hospice when death is inevitable, less intensive end-of-life care, and superior patient and family outcomes with concurrent palliative care.<sup>14,15</sup> By helping patients establish legal documents, such as ADs and power of attorney, oncologists and palliative care specialists can alleviate some of the stress related to the end

of life and make the transition to comfort care easier. Finally, oncologists can review guidelines such as those from the NCCN and American Society of Clinical Oncology, which call for a switch to palliative care when the cancer has grown on three regimens or the patient's ECOG performance status is three or above.<sup>11,12</sup>

Communication tools, such as the National Cancer Institute's Oncotalk and EPEC-O, are useful for oncologists seeking to further enhance their communication skills.

## Take-Home Messages

Guiding patients in making decisions about nonbeneficial, or futile, chemotherapy presents a challenge for many oncologists as well as their patients and families. Though futility is difficult to define, oncologists and their patients can decide through regular, open discussion if the burdens of chemotherapy outweigh the benefits and whether or not chemotherapy can achieve the reasonable benefits desired by the patient. *"Your cancer is advancing despite our best efforts to keep it from growing. Let's talk about what options we have at this point and see what will work best for you."* To make such decisions, oncologists must obtain the most current information and convey it to patients (or their designated decision makers) as clearly as possible. *"Based on the latest evidence, there is a 20% chance that the cancer will shrink or stay the same size with this treatment and*

*an 80% chance that it will continue to grow despite treatment."* Both oncologists and their patients should involve those whom they trust to help with decision making. In cases where chemotherapy is nonbeneficial, oncologists may prefer to involve palliative and hospice care specialists to discuss the transition to comfort care with the patient. *"At this time, I do not have any treatments that are likely to help you live longer or more comfortably, but I want to make sure that we get the most out of the rest of your life. I have asked a palliative care specialist to help us make this possible."* In order to ease the transition from aggressive or curative care to comfort care, oncologists can employ approaches such as early discussion of palliative and hospice care, assuring the patient of continued involvement in their care, and helping patients with ADs. These approaches not only benefit patients and their families but also strengthen the relationship between the oncologist and the patients and their families.<sup>1</sup>

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# Olanzapine Versus Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting: A Randomized Phase III Trial

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**C**hemotherapy-induced nausea and vomiting (CINV) is associated with a significant deterioration in quality of life and is perceived by patients as a major adverse effect of the treatment.<sup>1</sup> The use of 5-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>) receptor antagonists plus dexamethasone has significantly improved the control of acute CINV.<sup>2</sup> Recent studies have demonstrated additional improvement in the control of acute CINV and delayed CINV with the use of three new agents: palonosetron, a second-generation 5-HT<sub>3</sub> receptor antagonist;<sup>3</sup> aprepitant, the first agent available in the drug class of neurokinin-1 (NK-1) receptor antagonists;<sup>4,5</sup> and olanzapine, an antipsychotic which blocks multiple neurotransmitters in the central nervous system.<sup>6-8</sup>

Palonosetron is a second-generation 5-HT<sub>3</sub> receptor antagonist which has antiemetic activity at both central and gastrointestinal sites. In comparison to the first-generation 5-HT<sub>3</sub> receptor antagonists, it has a higher potency, a significantly longer half-life, and a different molecular interaction with 5-HT<sub>3</sub> receptors.<sup>9,10</sup> These differences may explain palonosetron's efficacy in delayed CINV compared to the first-generation receptor antagonists.<sup>3</sup> A high level of efficacy and an excellent safety profile have been demonstrated in a number of studies.<sup>3,9,11-14</sup> Based on these studies, palonosetron is recommended by multiple international antiemetic guidelines<sup>15-17</sup> for the prevention of acute nausea

## Abstract

**BACKGROUND:** The purpose of the study was to compare the effectiveness of olanzapine (OLN) and aprepitant (APR) for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy.

**METHODS:** A phase III trial was performed in chemotherapy-naive patients receiving cisplatin  $\geq 70$  mg/m<sup>2</sup> or cyclophosphamide  $\geq 500$  mg/m<sup>2</sup> and doxorubicin  $\geq 50$  mg/m<sup>2</sup>, comparing OLN to APR in combination with palonosetron (PAL) and dexamethasone (DEX). The OLN, PAL, DEX (OPD) regimen was 10 mg of oral OLN, 0.25 mg of IV PAL, and 20 mg of IV DEX prechemotherapy, day 1, and 10 mg/day of oral OLN alone on days 2-4 postchemotherapy. The APR, PAL, DEX (APD) regimen was 125 mg of oral APR, 0.25 mg of IV PAL, and 12 mg of IV DEX, day 1, and 80 mg of oral APR, days 2 and 3, and 4 mg of DEX BID, days 2-4. Two hundred fifty-one patients consented to the protocol and were randomized. Two hundred forty-one patients were evaluable.

**RESULTS:** Complete response (CR) (no emesis, no rescue) was 97% for the acute period (24 hours postchemotherapy), 77% for the delayed period (days 2-5 postchemotherapy), and 77% for the overall period (0-120 hours) for 121 patients receiving the OPD regimen. CR was 87% for the acute period, 73% for the delayed period, and 73% for the overall period in 120 patients receiving the APD regimen. Patients without nausea (0, scale 0-10, MD Anderson Symptom Inventory) were OPD: 87% acute, 69% delayed, and 69% overall; APD: 87% acute, 38% delayed, and 38% overall. There were no grade 3 or 4 toxicities. CR and control of nausea in subsequent chemotherapy cycles were equal to or greater than cycle 1 for both regimens. OPD was comparable to APD in the control of CINV. Nausea was better controlled with OPD.

**DISCUSSION:** In this study, OLN combined with a single dose of DEX and a single dose of PAL was very effective at controlling acute and delayed CINV in patients receiving highly emetogenic chemotherapy. CR rates were not significantly different from a similar group of patients receiving highly emetogenic chemotherapy and an antiemetic regimen consisting of APR, PAL, and DEX.

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and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy (HEC) and for the preven-

tion of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

Aprepitant is an NK-1 receptor antagonist which blocks the emetic effects of substance P.<sup>4,5,18</sup> When combined with a standard regimen of the corticosteroid dexamethasone and a 5-HT<sub>3</sub> receptor antagonist, aprepitant is effective at preventing CINV in patients receiving HEC.<sup>5,18</sup> This regimen is recommended in the guidelines of multiple international groups for the control of CINV in patients receiving HEC.<sup>15-17</sup>

Palonosetron and aprepitant have been combined with dexamethasone for the prevention of CINV in a phase II study of 58 patients who received MEC.<sup>19</sup> This three-drug antiemetic regimen was found to be safe and highly effective at preventing CINV in the acute, delayed, and overall periods.

Olanzapine is a Food and Drug Administration–approved antipsychotic that blocks multiple neurotransmitters: dopamine at D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> brain receptors; serotonin at 5-HT<sub>2a</sub>, 5-HT<sub>2c</sub>, 5-HT<sub>3</sub>, and 5-HT<sub>6</sub> receptors; catecholamines at  $\alpha_1$ -adrenergic receptors; acetylcholine at muscarinic receptors; and histamine at H<sub>1</sub> receptors.<sup>20,21</sup> Common side effects are sedation and weight gain,<sup>22,23</sup> as well as an association with the onset of diabetes mellitus.<sup>24</sup> Olanzapine's activity at multiple receptors—particularly at the D<sub>2</sub>, 5-HT<sub>2c</sub>, and 5-HT<sub>3</sub> receptors, which appear to be involved in nausea and emesis—suggests that it may have significant antiemetic properties.

A recent phase II trial demonstrated that olanzapine, when combined with a single dose of dexamethasone and a single dose of palonosetron, was very effective at controlling acute and delayed CINV in patients receiving both HEC and MEC.<sup>7</sup> There was excellent control of nausea without the use of multiple days of dexamethasone. A recent phase III study showed that addition of olanzapine to the 5-HT<sub>3</sub> receptor antagonist azasetron and dexamethasone improved delayed CINV in patients receiving HEC or MEC.<sup>8</sup>

Dexamethasone has been a very effective antiemetic at controlling both acute and delayed CINV, but concern has been expressed over the potential toxicity of the use of multiple-day dexamethasone to control CINV.<sup>25</sup> Patients receiving dexamethasone as a prophylactic treatment for CINV reported moderate to severe problems with insomnia, hyperglycemia, indigestion–epigastric discomfort, agitation, increased appetite, weight gain, and acne.<sup>25</sup> Dexamethasone might be decreased or eliminated in an antiemetic regime if other agents effective in both the acute and delayed periods are employed.

The purpose of this study was to compare the efficacy of olanzapine vs. aprepitant, each combined with palonosetron and dexamethasone, in the prevention of CINV in patients receiving HEC.

## Patients and Methods

### PATIENT SELECTION

Eligible patients were  $\geq 18$  years of age with histologically or cytologically confirmed malignant disease who were chemotherapy-naïve and scheduled to receive HEC (cisplatin

$\geq 70$  mg/m<sup>2</sup>, cyclophosphamide  $\geq 600$ – $1,000$  mg/m<sup>2</sup> and doxorubicin  $\geq 50$ – $60$  mg/m<sup>2</sup>). Patients were treated at three outpatient oncology treatment centers with three participating medical oncologists at each site. A similar number of patients in each arm were seen at each site.

### INCLUSION/EXCLUSION CRITERIA

The inclusion/exclusion criteria consisted of the following: patients had to be without nausea in the 24 hours prior to beginning chemotherapy; serum creatinine  $\leq 2.0$  mg/dL; serum bilirubin  $\geq 2.0$  mg/dL; serum glutamic-oxaloacetic transaminase (SGOT) or serum glutamic-pyruvic transaminase (SGPT) less than or equal to three or more times the upper limits of normal; absolute neutrophil count  $\geq 1,500$  mm<sup>3</sup>; patients of childbearing potential (male and female) had to consent to use adequate contraception throughout the protocol therapy; females of childbearing potential had to have a negative urine pregnancy test; no severe cognitive compromise; no known history of central nervous system disease (e.g., brain metastases, seizure disorder); no treatment with another antipsychotic agent such as risperidone, quetiapine, clozapine, phenothiazine, or butyrophenone for 30 days prior to or during the protocol therapy; chronic phenothiazine administration as an antipsychotic agent was not allowed, but patients may receive prochlorperazine and other phenothiazines as rescue antiemetic therapy; no concurrent use of amifostine (Ethyol); no concurrent abdominal radiotherapy; no concurrent use of quinolone antibiotic therapy; no chronic alcoholism (as determined by the investigator); no known hypersensitivity to olanzapine; no known cardiac arrhythmia, uncontrolled congestive heart failure, or acute myocardial infarction within the previous six months; and no history of uncontrolled diabetes mellitus.

### INFORMED CONSENT

All patients gave written informed consent, and the study was approved by the institutional review committee of each participating site.

### STUDY DESIGN AND TREATMENT REGIMEN

All patients eligible for the study were randomized to either the olanzapine, palonosetron, and dexamethasone (OPD) regimen or the aprepitant, palonosetron, dexamethasone (APD) regimen according to a computer-generated random assignment schedule created by a statistician not involved with the study. Patients were further stratified according to gender and to the chemotherapy regimen (cisplatin or doxorubicin/cyclophosphamide).

All patients who received the OPD regime received on the day of chemotherapy, day 1, an antiemetic regimen consisting of dexamethasone 20 mg IV and palonosetron, 0.25 mg IV, 30–60 minutes prior to chemotherapy administration. Patients also began olanzapine 10 mg PO on the day of chemotherapy (day 1) and continued 10 mg PO daily for days 2–4 following chemotherapy administration. Patients received no other antiemetic treatment on days 2–4.

All patients who received the APD regimen received on the day of chemotherapy, day 1, an antiemetic regimen consisting of dexamethasone 12 mg IV, palonosetron 0.25 mg IV, and aprepitant 125 mg PO, 30–60 minutes prior to chemotherapy. Postchemotherapy, patients received oral aprepitant 80 mg/day on days 2 and 3 and oral dexamethasone 4 mg BID on days 2–4.

Protocol therapy continued with each chemotherapy cycle until discontinuation of the same regimen of chemotherapy or at the discretion of the treating investigator up to a maximum of six cycles. Patients were permitted to take rescue therapy of the treating investigator's choice for nausea and/or emesis or retching based on clinical circumstances. Patients who required rescue therapy were permitted to continue on the study at the discretion of the treating investigator in consultation with the patient.

### STUDY VISITS AND ASSESSMENT PROCEDURES

In the prestudy period, all pertinent demographics (age, gender, height, weight) and medical data (site and stage of disease, Eastern Cooperative Oncology Group [ECOG] rating, laboratory values, medications and present therapies including present oncologic therapy) were recorded. For the purposes of this study, the M.D. Anderson Symptom Inventory (MDASI)<sup>26</sup> was utilized to allow for simple, expedient measures of key symptom variables being examined daily for the entire study period. The main purpose of the use of the MDASI in this study was to determine if there were any major or minor toxicities related to the antiemetic regimens.

The MDASI is a flexible system for the assessment of symptoms experienced by patients with cancer. It consists of 13 core symptom items that are rated based on their presence and severity and six symptom interference items that are rated based on the level of symptom interference with function.<sup>26</sup>

Beginning with the first day of chemotherapy (day 1) and daily through day 5, patients were asked to record daily episodes of vomiting/retching (number and time), the daily intensity of symptoms utilizing the MDASI, and the utilization of rescue therapy.

Patients were also asked to record daily episodes of nausea using a visual analogue scale from 0 to 10, with 0 indicating no nausea and 10 indicating a maximal level of nausea. A nurse/research coordinator contacted each patient each day (days 2–5) to remind the patient to complete forms and to query toxicities.

### STATISTICAL METHODS

The primary end point in the study was complete response (CR) (no emetic episodes and no use of rescue medication) for the overall period (0–120 hours postchemotherapy). Secondary end points were CR in the acute (0–24 hours postchemotherapy) and delayed (days 2–5 postchemotherapy) periods and no nausea in the acute, delayed, and overall periods. The study was powered with a sample size to detect a 15% difference between the two antiemetic regimens. With a tol-

erance of 15%, 111 subjects were needed in each arm to obtain a 0.80 power at a Type I error level of 0.05.

The total number of patients was elevated to account for a 10% dropout rate.

Demographic data and patient characteristics were examined descriptively.

The frequencies of severe toxicities and adverse events were calculated.

The percentage of patients with CR for the acute period, the delayed period, and the overall period was calculated. The percentage of patients with no nausea (MDASI score 0) was calculated.

The mean, median, and standard deviation of the maximum MDASI symptom scores over days 1–5 were calculated for cycle 1. A repeated-measures analysis of variance was performed to test for a change in symptom scores across cycles and over days within cycles. Since 19 analyses of variance were performed, the level of significance was lowered to 0.01 as an adjustment for multiple comparisons.

### Results

Figure 1 is a flow diagram of the distribution and randomization of the study patients. Two hundred fifty-one patients were assessed for eligibility; four were excluded due to nausea 24 hours prior to treatment. Two hundred forty-seven patients were randomized. Three patients were excluded in each arm due to loss to follow-up or not completing or discontinuing the assigned treatment. A very small and equal number of patients in each arm was lost to analysis after randomization. The remaining patients in each arm were adequate in number to complete the planned analysis.

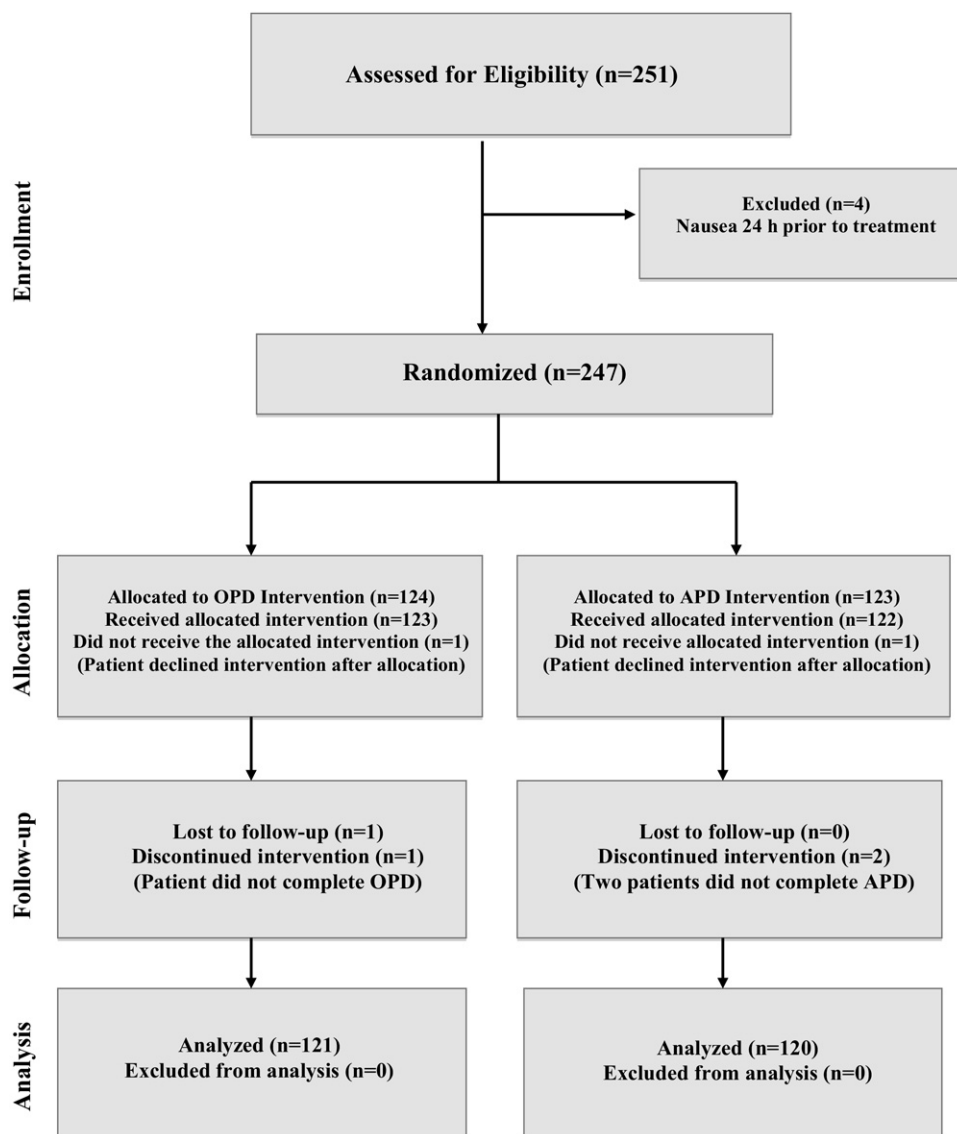
### PATIENT CHARACTERISTICS

Demographic data and patient characteristics are presented in Table 1. Two hundred forty-one patients received at least one cycle of chemotherapy and completed the assigned antiemetic regimen; 217 patients (90.1%) received two cycles, 197 (81.7%) received three cycles, 157 (65.1%) received four cycles, 92 (38.2%) received five cycles, and 88 (36.5%) received six cycles. There were very few patients who experienced weight gain or glucose elevation from day 1 to day 5 in cycle 1, and there was no difference in the study groups.

### PRIMARY EFFICACY PARAMETERS

The CR for the acute period, the delayed period, and the overall period in 121 patients receiving the OPD regimen and in 120 patients receiving the APD regimen is shown in Figure 2. The four patients in the OPD group who did not have a CR in the acute period required rescue without emesis. Twenty-eight patients in the OPD group did not have a CR in the delayed period. Eighteen had emesis on days 2 and 3, and all required rescue. Nine had emesis on day 4, and two required rescue. One patient had emesis without rescue on day 5.

The 16 patients in the APD group who did not have a CR in the acute period all had emesis, and three required rescue in the first 24 hours postchemotherapy. There were 32 patients in the APD group who did not have a CR in the delayed period.



**Figure 1** Distribution and Randomization of Study Patients

OPD, olanzapine + palonosetron + dexamethasone; APD, aprepitant + palonosetron + dexamethasone

On day 2, 10 patients had emesis without rescue and four patients had emesis with rescue. On day 3, eight patients had emesis without rescue and six patients had rescue without emesis. On day 4, two patients had rescue without emesis; and on day 5, two patients had emesis with rescue.

There were no significant differences ( $P > 0.05$ ) in the CR between the OPD regimen and the APD regimen for the acute, delayed, and overall periods.

The control of nausea for the acute period, the delayed period, and the overall period in 121 patients receiving the OPD regimen and in 120 patients receiving the APD regimen is shown in Figure 3. There were 16 patients in the OPD group who experienced nausea ( $>0$ , scale 0–10, MDASI) in the acute period. The 37 patients in the OPD group who experienced nausea in the delayed period consisted of 18 on day 2, 17 on day 3, and two on day 4. Sixteen patients in the APD group had nausea in the acute period. The occurrence of nausea in the

delayed period for the APD group was 32 patients on day 2, 28 on day 3, 10 on day 4, and four on day 5.

There was no significant difference ( $P > 0.05$ ) for the control of nausea between the OPD regimen and the APD regimen for the acute period. There were significant differences ( $P < 0.01$ ) between the OPD regimen and the APD regimen for the delayed and overall periods.

The CR and control of nausea for patients receiving either the OPD regimen or the APD regimen in subsequent cycles of chemotherapy were not significantly different from cycle 1 and were not significantly different for gender or type or stage of disease.

#### ADVERSE EVENTS

There were no grade 3 or 4 toxicities attributable to the study drugs in any of the patients for any of the cycles of chemotherapy.

**Table 1**  
Demographic Data and Patient Characteristics

	OPD	APD
Patients (n)	121	120
Age range (years)	39–77	42–81
Median age (years)	63	61
Gender (n)		
Female	81	83
Male	40	37
ECOG (n)		
0	93	94
1	23	22
2	5	4
Diagnosis (n)		
Bladder	8	4
Breast	60	66
Lung (non-small cell)	42	40
Malignant lymphoma	11	10
Chemotherapy regimen (n)		
Cisplatin ( $\geq 70$ mg/m <sup>2</sup> )	50	44
Doxorubicin ( $\geq 50$ – $60$ mg/m <sup>2</sup> ) and cyclophosphamide ( $\geq 600$ – $1,000$ mg/m <sup>2</sup> )	71	76
Initial measurements (mean)		
Height (inches)	68	69
Weight (lb)	145	149
Body mass index	23.0	23.3
Weight gain, day 1 to day 5, cycle 1 (n)		
>5%	5	6
>10%	1	2
Glucose elevation, day 1 to day 5, cycle 1 (n)		
>5%	10	11
>10%	5	7

OPD, olanzapine + palonosetron + dexamethasone; APD, aprepitant + palonosetron + dexamethasone.

The symptom scores as measured by the MDASI for cycle 1 are recorded in Table 2. Nine of the 17 symptom scores significantly differed between cycles at the 0.01 level of significance. Pain, fatigue, disturbed sleep, distress, shortness of breath, lack of appetite, sadness, general activity, and mood significantly decreased over the cycles.

Problems remembering, drowsiness, and dry mouth significantly increased over days in some individual cycles but were not increased among cycles and did not result in any grade 3 or 4 toxicities. There were no significant changes between the OPD and the APD regimens for any of the symptom scores.

## Discussion

In this study, olanzapine combined with a single dose of dexamethasone and a single dose of palonosetron was very effective at controlling acute and delayed CINV in patients receiving HEC. The CR rates were not significantly different from a similar group of patients receiving HEC and an antiemetic regimen consisting of aprepitant, palonosetron, and dexamethasone. The two antiemetic regimens were compa-

rable in CR in the acute, delayed, and overall periods. In addition, the CR rates were similar to previous studies which used the same olanzapine antiemetic regimen<sup>7</sup> and the commonly employed aprepitant regimen.<sup>27–31</sup> This aprepitant antiemetic regimen has been the recommended regimen of various international associations' antiemetic guidelines for patients receiving HEC.<sup>15–17</sup> The OPD and APD antiemetic regimens were very well tolerated with no grade 3 or 4 toxicities, and there was no major severity noted among a wide range of 17 symptoms as measured by the MDASI.

A dexamethasone dose of 20 mg was used in the OPD regimen since this is the recommended dose for patients receiving HEC by the various antiemetic guidelines.<sup>15–17</sup> A dexamethasone dose of 12 mg was used in the APD regimen since this is the recommended dose to be used with aprepitant due to the possibility of hyperglycemia.<sup>27,29</sup>

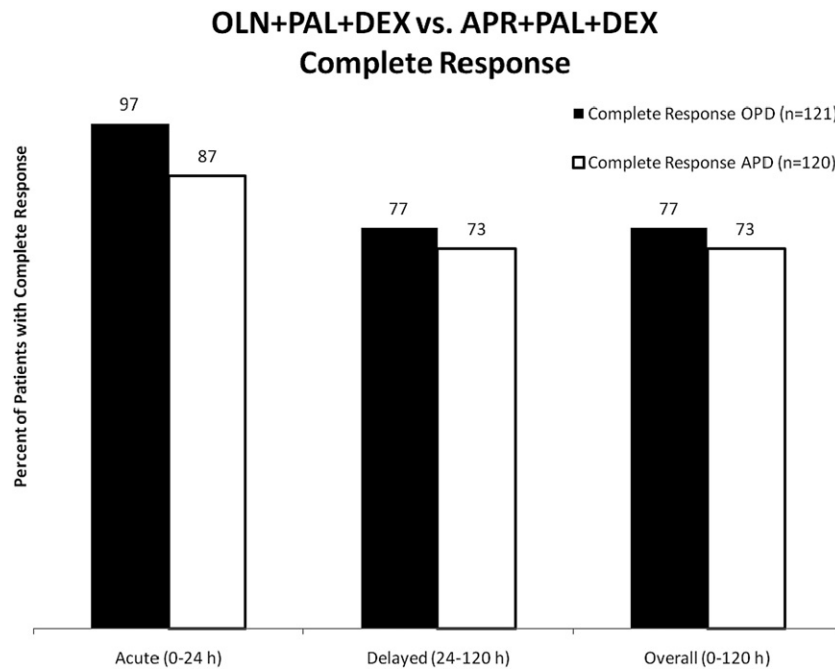
The control of nausea was also similar for the two antiemetic regimens in the acute period for this group of patients but was significantly better for the OPD regimen in the delayed and overall periods. The effectiveness of olanzapine in the control of nausea has been demonstrated in one recent phase III study,<sup>8</sup> two previous phase II studies,<sup>6,7</sup> a retrospective study<sup>32</sup> and a case report.<sup>33</sup> Nausea has not been significantly improved by the use of aprepitant in two phase III studies of patients receiving cisplatin<sup>27,34</sup> and in two phase III studies of patients receiving an anthracycline and cyclophosphamide.<sup>31,35</sup>

The high level of CR in the acute period for patients receiving HEC observed in this study was most likely an important aspect in controlling delayed CINV. The importance of the control of acute nausea and vomiting on the control of delayed nausea and vomiting has been discussed in detail in the literature.<sup>36</sup>

There were patients, however, who had a CR and good control of nausea in the acute period and subsequently developed emesis and nausea in the delayed period, suggesting differences in the mechanisms of acute and delayed CINV. The main period of failure in CR or control of nausea in the delayed period in this study was day 2 or 3, which is consistent with a number of previous studies.<sup>18,28</sup>

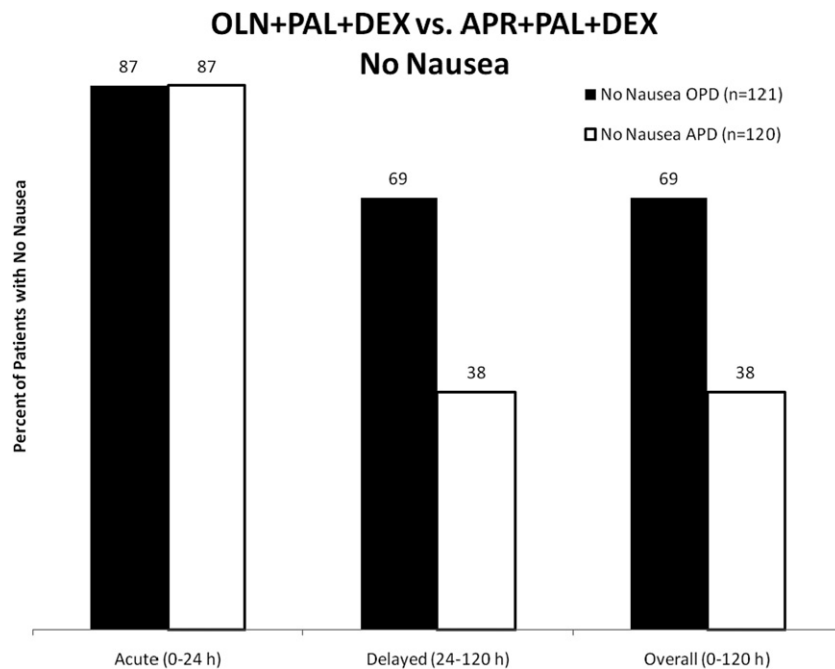
One hundred fifty-seven of the 241 patients received at least four cycles of chemotherapy, and the high level of CR, the level of control of nausea, and the lack of adverse events noted in cycle 1 were maintained over the multiple cycles of chemotherapy for each of the antiemetic regimens.

The high level of control of CINV in the delayed period in this study appears to be due to the combination of olanzapine and palonosetron. Olanzapine has been shown in previous studies to be an effective agent at controlling delayed CINV.<sup>6–8</sup> A recent study<sup>14</sup> demonstrated that when administered with dexamethasone before HEC, palonosetron exerts better efficacy against CINV than granisetron in the delayed phase. The high level of control of delayed CINV in this study was achieved without the use of dexamethasone in the delayed period, potentially eliminating the short- and long-term toxicities of dexamethasone experienced by some patients.<sup>25</sup>



**Figure 2** Percent of Patients with a Complete Response (No Emetic Episodes and No Use of Rescue Medication) for Patients Receiving Highly Emetogenic Chemotherapy in Cycle 1

OLN, olanzapine; PAL, palonosetron; DEX, dexamethasone; APR, aprepitant; OPD, OLN + PAL + DEX; APD, APR + PAL + DEX;  $P > 0.05$  for acute, delayed, and overall



**Figure 3** Percent of Patients with No Nausea (No Nausea, 0 on Scale of 0–10, MDASI) for Patients Receiving Highly Emetogenic Chemotherapy in Cycle 1

OLN, olanzapine; PAL, palonosetron; DEX, dexamethasone; APR, aprepitant; OPD, OLN + PAL + DEX; APD, APR + PAL + DEX;  $P > 0.05$  for acute,  $P \leq 0.01$  for delayed and overall

Olanzapine blocks the neurotransmitters dopamine and serotonin, which are known mediators of CINV.<sup>20,21</sup> Olanzapine appears to have activity in controlling both acute and delayed emesis and nausea and may exert much of its anti-

emetic effect in the central nervous system at multiple cortical receptors, although a peripheral effect may also exist. Olanzapine blocks the serotonin-mediated 5-HT<sub>2C</sub> receptor, which has been shown to mediate antiemetic activity in

**Table 2**

MDASI Scores (0–10) Over Days 1–5 in Patients Receiving Highly Emetogenic Chemotherapy in Chemotherapy Cycle 1

SYMPTOM	OPD REGIMEN (N = 121)		APD REGIMEN (N = 120)	
	DAY 1	DAY 5*	DAY 1	DAY 5**
Pain	1.5	1.2	1.1	1.6
Fatigue	4.1	4.2	3.0	3.5
Disturbed sleep	2.1	2.6	3.3	3.0
Distress	1.5	2.0	2.2	2.4
Problems remembering	1.5	1.6	2.1	2.2
Shortness of breath	1.9	2.2	2.5	2.3
Lack of appetite	1.9	1.8	2.2	1.9
Feeling drowsy	3.3	3.7	2.8	2.6
Dry mouth	3.5	3.8	3.3	3.5
Feeling sad	1.9	2.2	3.0	2.8
Numbness	0.9	1.2	2.1	1.7
General activity	2.1	2.2	2.1	2.3
Mood	0.5	1.3	2.0	1.7
Work	2.3	3.0	3.0	2.7
Relations	1.8	1.7	1.7	1.5
Walking	1.9	2.1	2.1	2.3
Enjoyment	1.5	2.1	3.1	2.8
Sedation	1.1	1.9	1.3	2.1

OPD, olanzapine + palonosetron + dexamethasone; APD, aprepitant + palonosetron + dexamethasone.

\* $P > 0.05$  for all symptoms in OPD regimen, \*\* $P > 0.05$  for all symptoms in APD regimen.

animal models (ferret cisplatin-induced emesis and cisplatin-induced anorexia in the hypothalamus of rats).<sup>37,38</sup> The effect of olanzapine on this receptor as well as other dopamine and serotonin receptors may explain its efficacy in CINV.

The relative contribution of the effects of various antiemetics at central and peripheral sites to the control of acute and delayed nausea and emesis cannot be determined at this time based on available studies.<sup>2,4</sup> In this study, for the doses given (10 mg daily for 4 days), olanzapine was not associated with significant sedation, weight gain, or induction of significant hyperglycemia. These effects have been associated with olanzapine given for longer periods of time.

There are also economic benefits of olanzapine. The 4-day treatment with olanzapine is approximately 10%–20% of the cost of the 3-day aprepitant treatment.<sup>39</sup>

The results of this study demonstrate that in patients receiving HEC, the OPD regimen is equivalent to the APD regimen in controlling emesis and the use of rescue medication but that the OPD regimen is significantly better at controlling nausea.

The trial arms in the study were not blinded. It is unlikely that the lack of blinding in the trial would affect the trial outcome since all of the patients in the study were chemotherapy-naïve and none had previously received either of the antiemetic regimens.

Future investigations may explore the efficacy of olanzapine with or without dexamethasone in the delayed period for clinical situations such as multiday chemotherapy or high-dose chemotherapy and stem cell transplantation.

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October 27-29, 2011

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Seventh Annual

# Chicago Supportive ONCOLOGY c o n f e r e n c e

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Associate Professor, Oncology  
Mayo Clinic  
Rochester, MN  
Associate Editor: *The Journal of Supportive Oncology*

## PROGRAM OVERVIEW

The overall purpose of the Seventh Annual Chicago Supportive Oncology Conference is to provide participants with the latest information on supportive care issues. The goal is to enable health care professionals to deliver state-of-the-art medical care, improve patient outcomes, and enhance the quality of life of patients with cancer. These activities will help reduce the barriers that prevent the integration of therapies into practice and support adherence to current guidelines.

## INTENDED AUDIENCE

This conference is designed for physicians, nurses, nurse practitioners, physician assistants, residents, and fellows who will gain important insights into practical management issues in the palliative and supportive care of patients with neoplastic diseases.

## EDUCATIONAL GAPS

Literature reviews, surveys, and evaluations from previous activities indicate that clinicians feel only somewhat competent in handling supportive care issues such as communicating with patients and families, staying current with trial data and translating them into clinical practice, and integrating evidence-based guidelines into patients' plans of care.

## FACULTY

### Amy P. Abernethy, MD

Duke University Health System

### Donald I. Abrams, MD

University of California, San Francisco

### Anthony L. Back, MD

University of Washington

### Susan Block, MD

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### J. Mark Sloan, MD\*

Boston University School of Medicine

### John L. Shuster, Jr, MD

Vanderbilt University

### Bradley H. Stuart, MD

Sutter VNA and Hospice

### \*Conference Advisory Board

## LEARNING OBJECTIVES

After participating in this activity the learner should be better able to:

- Employ assessment tools and treatment options for depression in patients with cancer.
- Manage select symptoms in the patient with cancer, including fatigue, sleep disturbances, refractory nausea and vomiting, and mucositis.
- Communicate with the patient and family members regarding difficult clinical decisions such as hydration and nutrition, and family conflict.
- Describe the role of clinical trials in supportive care.
- Summarize the role of lymphedema rehabilitation and hormone replacement therapy in the care of the patient with breast cancer.
- Summarize the potential use of genomic markers in cancer care.
- Articulate the current evidence for the use of select integrative medicines in supportive care: medical marijuana, acupuncture, and compounding pharmacies.
- Explain issues in cancer pain management including opioid toxicities and management of pelvic pain.
- Discuss select neurologic issues in the patient with cancer: CNS malignancies and chemotherapy-induced peripheral neuropathies.
- Discuss the issues surrounding survival prediction in supportive care in patients with selected diseases.

## CONTINUING EDUCATION

### Accreditation

**Physicians.** This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Boston University School of Medicine and Global Academy for Medical Education. Boston University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Boston University School of Medicine designates this live activity for a maximum of 17.25 AMA PRA Category 1 Credit(s)<sup>™</sup>.

Physicians should only claim credit commensurate with the extent of their participation in the activity.

**Nurses.** This activity for 17.3 contact hours, which includes 4.0 hours of pharmacy content, is provided by the Meniscus Educational Institute.

The Meniscus Educational Institute is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

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### Certificate of Credit

Participants who successfully complete this activity (including completion and online submission of the evaluation form) will be issued a statement of credit via e-mail or US mail within 4 weeks.

*Faculty disclosures will be made known on the day of the program.*

# AGENDA

## THURSDAY, OCTOBER 27, 2011

- 7:30 AM Registration / Continental Breakfast / Exhibits
- 8:15 AM **Opening Remarks**  
Jamie H. Von Roenn, MD
- 8:20 AM **PLENARY: Challenges for Palliative Care Integration**  
Larry D. Cripe, MD
- 9:00 AM INTERACTIVE PANEL DISCUSSION

### Psychology

- 9:15 AM **Communication and Advanced Care Planning**  
Susan Block, MD
- 9:45 AM **Depression and Use of Medications**  
John L. Shuster, Jr., MD
- 10:15 AM INTERACTIVE PANEL DISCUSSION
- 10:30 AM Break and Visit Exhibits

### Symptom Management

- 11:00 AM **Fatigue**  
Debra Barton, PhD, RN, AOCN, FAAN
- 11:30 AM **Sleep Disturbance**  
Gary R. Morrow, PhD
- 12:00 PM **Refractory Nausea and Vomiting**  
Mellar Davis, MD
- 12:30 PM INTERACTIVE PANEL DISCUSSION
- 12:45 PM Lunch on Your Own
- 2:00 PM **PLENARY: Succeeding to Research**  
Anthony L. Back, MD
- 2:40 PM INTERACTIVE PANEL DISCUSSION

### Communications

- 3:00 PM **Discussing Hydration and Nutrition: to Feed or Not to Feed**  
Timothy J. Moynihan, MD
- 3:30 PM Break and Visit Exhibits
- 3:45 PM **Communicating with Families**  
Anthony L. Back, MD

### Breast Cancer

- 4:15 PM **Lymphedema Rehabilitation Care**  
Gail L. Gamble, MD
- 4:45 PM INTERACTIVE PANEL DISCUSSION
- 5:15 PM Poster and Networking Reception\*

## FRIDAY, OCTOBER 28, 2011

- 7:30 AM Continental Breakfast / Exhibits
- 8:00 AM **Welcome Back**
- 8:05 AM **PLENARY: Clinical Trials and Palliation**  
Amy P. Abernethy, MD
- 8:45 AM INTERACTIVE PANEL DISCUSSION

\*CME/CNE credit not provided for these sessions

### Neurology

- 9:00 AM **Chemotherapy-induced Neuropathy: Natural History, Prevention and Treatment**  
Charles L. Loprinzi, MD
- 9:30 AM **Patients with Malignancies**  
Stuart A. Grossman, MD
- 10:00 AM INTERACTIVE PANEL DISCUSSION
- 10:30 AM Break and Visit Exhibits

### Complementary and Alternative Medicine

- 11:00 AM **Acupuncture: Best Evidence**  
Dawn L. Hershman, MD, MS
- 11:30 AM **Compounding Medications**  
Mike Riepl, RPH
- 12:00 PM INTERACTIVE PANEL DISCUSSION
- 12:30 PM Lunch on Your Own

### Pain

- 1:30 PM **Opioid Toxicity**  
Judith A. Paice, PhD, RN, FAAN
- 2:00 PM **Pelvic Pain**  
Lois M. Ramondetta, MD
- 2:30 PM INTERACTIVE PANEL DISCUSSION
- 3:00 PM Break and Visit Exhibits

### Breast Cancer

- 3:15 PM **Is There a Role for HRT?**  
Richard J. Santen, MD
- 3:45 PM **Complementary & Alternative Medicine: Medical Marijuana**  
Donald I. Abrams, MD
- 4:15 PM **ASCO Review**  
Michael J. Fisch, MD, MPH
- 4:45 PM INTERACTIVE PANEL DISCUSSION
- 5:15 PM Session Ends

## SATURDAY OCTOBER 29, 2011

- 7:30 AM Continental Breakfast / Exhibits
- 7:55 AM **Welcome Back**
- 8:00 AM **PLENARY: The Promise of Genomic Markers**  
Christine Miaskowski, PhD, RN, FAAN
- 8:40 AM INTERACTIVE PANEL DISCUSSION

### Prognosis

- 9:00 AM **Cardiology**  
Bradley H. Stuart, MD
- 9:30 AM **Nephrology**  
Jean L. Holley, MD
- 10:00 AM **Cancer**  
Paul A. Glare, MD
- 10:30 AM **Mucositis Treatment**  
Barbara Murphy, MD
- 11:00 AM INTERACTIVE PANEL DISCUSSION
- 11:30 AM CSOC 2011 Concludes-See you in 2012

# Scientific Abstracts\*

Seventh Annual Chicago Supportive Oncology Conference

Chicago, Illinois

October 27-29, 2011

\*CME/CNE credit not provided for abstracts or conference poster session.

## PAIN, FATIGUE AND SLEEP DISORDERS

### Abstract PA-1: Exploring the Potential Association Between Carnitine Deficiency and Pediatric Cancer-Related Fatigue: A Cross-Sectional Study

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**BACKGROUND:** Fatigue is one of the most prevalent symptoms reported by cancer patients of all ages and can negatively impact quality of life. There are few evidence-based effective treatments for cancer-related fatigue available, especially for pediatric patients. Deficiency of carnitine, a micronutrient required for fatty-acid metabolism and energy production, has been reported in pediatric and adult cancer patients and has been associated with fatigue. Preliminary studies of adult cancer patients have also shown the potential for carnitine to improve fatigue. This study will provide further information on the prevalence of carnitine deficiency and the potential role of carnitine deficiency in fatigue among pediatric cancer patients. **OBJECTIVES:** 1) To determine the prevalence of carnitine deficiency in pediatric cancer patients receiving treatment (Group 1) or who have completed therapy (Group 2). 2) Further establish the prevalence of fatigue in these two groups of pediatric cancer patients treated at Children's Memorial Hospital. 3) Explore the relationship of carnitine deficiency with fatigue and other selected variables. **METHODS:** Patients, ages 8 to 18 years, are asked to complete measures of fatigue, the Pediatric Functional Assessment of Chronic Illness-Fatigue (pedsFACIT-F), The Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale and give a numeric rating of their fatigue according to the National Comprehensive Cancer Network (NCCN) Cancer-Related Fatigue Screening. Blood samples for carnitine testing are obtained. The patients' medical records are reviewed for collection of additional pertinent data. **RESULTS:** Of the anticipated 150 patients to be enrolled, 68 patients have participated and data are available for 63. Of the 63 patients, 36 patients were on therapy and 27 were off therapy. Mean NCCN screen-

ing scores for on therapy patients were  $2.4 \pm 0.6$  and  $4.7 \pm 2.9$  for ages 8-12 (N = 20) and >12 years (N = 16) respectively. Mean NCCN screening scores for off therapy patients were  $1.7 \pm 0.6$  and  $3.4 \pm 2.8$  for ages 8-12 (N = 11) and >12 years (N = 16) respectively. Mean pedsFACIT-F scores for on therapy patients were  $14.6 \pm 4.9$  and  $17.3 \pm 6.7$  for ages 8-12 and >12 years respectively. Mean pedsFACIT-F scores for off therapy patients were  $12.7 \pm 4.6$  and  $14.4 \pm 6.2$  for ages 8-12 and >12 years respectively. Mean PedsQL total scale scores for on therapy patients were  $68.4 \pm 12.0$  and  $58.5 \pm 19.1$  for ages 8-12 and >12 years respectively. Mean PedsQL total scale scores for off therapy patients were  $76.0 \pm 11.3$  and  $69.6 \pm 21.1$  for ages 8-12 and >12 years respectively. Of the 63 patients, 15 (23.8%) had abnormal carnitine panels by interpretation. Ten (66.7%) patients reported moderate to severe fatigue on NCCN screening. Mean pedsFACIT-F score was  $14.7 \pm 6.0$  and mean PedsQL total scale score was  $67.31 \pm 20.3$  for these 15 patients. These results may or not be statistically significant. Further statistical analysis, including correlates of fatigue, is pending completion of study enrollment. **LIMITATIONS:** Tests of statistical significance and further statistical analysis have not been performed. As this is a cross-sectional study, a causal link between fatigue and carnitine status cannot be determined. In this study, there is no direct comparison to healthy subjects. This study does not include non-English-speaking patients. **CONCLUSIONS:** Preliminarily, the study results indicate that on therapy patients have higher mean scores of fatigue than off therapy patients. For both on therapy and off therapy patients, older patients (> 12 years) have higher mean scores of fatigue than younger patients (ages 8-11). In this partial sample, 23.8% of patients had an abnormality of carnitine panel by interpretation. The actual significance of these findings and of fatigue correlates may be further elucidated with enrollment of additional patients and further data analysis. **KEYWORDS:** Fatigue, carnitine, cancer, cancer-related fatigue, pedsFACIT-F, PedsQL, NCCN.

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**CONFLICTS OF INTEREST:** The corresponding author has no conflicts of interest to report.

**ACKNOWLEDGEMENTS:** This research project is supported by a grant from SurvivorVision, a not-for-profit charitable organization.

## Abstract PA-2: Evaluating a Novel Device for the Treatment of Chemotherapy-Induced Peripheral Neuropathy

Pachman DR, MD<sup>1</sup>, Barton DL, RN, PhD<sup>2</sup>, Linquist BM, RN<sup>2</sup>, Fee-Schroeder KC, RN<sup>2</sup>, Lachance DH, MD<sup>3</sup>, Loprinzi CL, MD<sup>2</sup>

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**BACKGROUND:** Chemotherapy-induced peripheral neuropathy (CIPN) is a common and dose limiting side effect of chemotherapy. Multiple therapies have been investigated for the treatment of CIPN, however, there are no proven effective interventions. Scrambler therapy (MC5-A) is designed to treat pain via non-invasive cutaneous electrostimulation. The device substitutes “pain” information with “non-pain” information by generating 16 different current patterns, which simulate nerve action potentials. Five small trials have reported the efficacy of MC5-A in the treatment of various forms of neuropathic and cancer-related pain. One pilot trial assessed efficacy of scrambler therapy in CIPN. Patients treated with 10 sessions of scrambler therapy had a decrease in pain score of 59%. However, scrambler therapy has never been tested against a sham therapy and there is still much to learn about its clinical effects and mechanism of action. **OBJECTIVE:** Two pilot trials will be done to obtain prospective pilot experience with MC5-A with regard to treatment efficacy, compared to a sham, and tolerability. **METHODS:** Each pilot trial will involve 10 patients with CIPN. Inclusion criteria include symptoms of peripheral neuropathy  $\geq 1$  month, and pain, numbness, or tingling rated  $\geq 4/10$  during the prior week. Sham therapies include: 1) electrodes placed on the back compared to the legs, and 2) a TENS machine on the lower extremities. **RESULTS:** This poster will provide an overview of a novel potential therapy (MC5-A), showing pictures of the device and treatment algorithm. **LIMITATIONS:** These studies are in progress. **CONCLUSION:** Strong preliminary data support further investigation of scrambler therapy. **KEYWORDS:** chemotherapy-induced peripheral neuropathy, pain, neuropathy, scrambler therapy, neurocutaneous stimulation

**CORRESPONDING AUTHOR:** Deirdre R. Pachman, MD

**CONFLICTS OF INTEREST:** The corresponding author has no conflicts of interest to report.

## PSYCHO-ONCOLOGY

### Abstract PA-3: Understanding the Psychosocial Needs of Young Adults with Cancer: Identifying Targets for Clinical Intervention

Trevino KM, PhD<sup>1,2,3</sup>, Maciejewski PK, PhD<sup>1,2,3</sup>, Fasciano K, PsyD<sup>1,2,3</sup>, Greer J, PhD<sup>2,4</sup>, Partridge A, MD, MPH<sup>1,2,3</sup>, Kacel EL, BA<sup>1</sup>, Block S, MD<sup>1,2,3</sup>, Prigerson HG, PhD<sup>1,2,3</sup>

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**BACKGROUND:** The NCI has recognized the unique burden of cancer for young adults (YAs) and called for specialized services to address their needs. Few studies have investigated the nature of distress in YAs, making development of targeted psychosocial interventions difficult. **OBJECTIVE:** The present study advances understanding of YA psychosocial needs by examining correlates of quality of life, suicidal ideation, and disruption of work, social, and family life in patients with advanced cancer. **METHODS:** Structured clinical interviews were conducted between 4/10 and 1/11 with 40 YA advanced cancer patients (age range 20-40 years, M=35.2, SD=5.16) receiving care at Dana-Farber Cancer Institute. Validated measures assessed quality of life (e.g. Global McGill Quality of Life Questionnaire), psychopathology, grief over cancer-related losses, coping methods, and psychosocial variables of clinical interest. Quality of life scores were regressed individually on grief, psychopathology, illness acceptance, patient-oncologist therapeutic alliance, social support, and coping methods. Significant bivariate associations were entered into multivariate models to identify the most significant set of influences. The same set of independent variables was used in models of life disruption and suicidal ideation. **RESULTS:** In bivariate analysis, grief, illness acceptance, therapeutic alliance, social support, depression, and coping methods were associated with quality of life ( $P < .05$ ). In multivariate analysis, less grief ( $B = -.54$ ,  $SE = .43$ ,  $df = 29$ ,  $P < .01$ ) and more social support ( $B = .32$ ,  $SE = .62$ ,  $df = 29$ ,  $P < .05$ ) remained significant predictors of better quality of life. In multivariate analysis, more grief predicted more suicidal ideation ( $B = .54$ ,  $SE = .036$ ,  $df = 29$ ,  $P < .01$ ) and less illness acceptance predicted more life disruption ( $B = .51$ ,  $SE = .31$ ,  $df = 29$ ,  $P < .01$ ). **LIMITATIONS:** This study is limited by a cross-sectional design and small sample size. In addition, the measures used were not designed for or validated on YA samples, a limitation characteristic of all psychosocial research in YA oncology at this time. The sample for this study was restricted to YAs with advanced disease and included a broad age range that captures multiple developmental transitions. **CONCLUSIONS:** For YAs with advanced cancer, grief, social support, and illness acceptance are critical to quality of life, functionality, and will to live. Clinical interventions that reduce grief, promote illness acceptance, and enhance social support may address the unique psychosocial needs of YA cancer patients. **KEYWORDS:** young adult, cancer, psychological stress, grief, quality of life, suicidal ideation

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## QUALITY-OF-LIFE ISSUES

**Abstract PA-4: Using Regression Analyses to Determine Predictors of Life Quality Among Oral Cancer Patients with Orthopedic Trauma**Chang Chi-Chang<sup>1</sup>, Huang Shi-Feng\*<sup>2</sup>, Cheng Sun Long<sup>3</sup><sup>1</sup>School of Applied Information Sciences, Chung Shan Medical University and Information Technology Office, Chung Shan Medical University Hospital, Taichung, Taiwan<sup>2</sup>School of Applied Information Sciences, Chung Shan Medical University, Taichung, Taiwan<sup>3</sup>Chung Shan Medical University Hospital, Taichung, Taiwan

**BACKGROUND:** Little is known about the clinical consequences of psychological morbidity associated with orthopedic trauma among oral cancer patients. **OBJECTIVE:** The objective of this study was to investigate the extent of psychological symptoms that patients experience following orthopedic trauma and whether these are associated with quality of life. **METHODS:** All oral cancer patients attending orthopedic clinics at Chungshan Medical University Hospital between November 2010 and January 2011 were screened for study eligibility. All consenting patients completed a baseline assessment form, the SCL-90-R depression and somatization subscores. In addition, we conducted regression analyses to determine predictors of quality of life among oral cancer patients. **RESULTS:** Of the patients, 50 were eligible, and 45 agreed to participate. Patient Physical Component summary scores were associated with older age ( $\beta = -0.3$ ,  $P < 0.001$ ) and Positive Symptom Distress Index (i.e., the intensity of psychological symptoms;  $\beta = -0.06$ ,  $P = .003$ ). The proposed model predicted 21% of the variance in patients' SCL-90-R scores. Somatization was an important psychological symptom negatively associated with SCL-90-R scores. In a prospective study of 45 patients, 1 in 5 met the threshold for psychological distress. **DISCUSSION:** Psychological symptoms were significantly associated with both SF-36 Physical Component and SCL-90-R scores. Future research is necessary to determine whether oral cancer patients would benefit from early screening and intervention to address comorbid psychopathology. **KEYWORDS:** oral cancer, quality of life, orthopedic trauma, SCL-90-R, SF-36

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**CONFLICTS OF INTEREST:** There are no conflicts of interest to report.**Abstract PA-5: Linking Quality Metrics to Outcomes Through Prospective, Point-Of-Care Quality Data Collection in Community-Based Palliative Cancer Care**<sup>1</sup>Kamal AH, MD, Bull J, MD, Zhong X, <sup>2</sup>Abernethy AP, MD<sup>1</sup>Duke Cancer Institute, Durham, NC<sup>2</sup>Duke University Medical Center, Durham, NC

**BACKGROUND:** Quality metrics in oncology are often developed using expert consensus as evidence to inform development is lacking. We created Quality Data Collection Tool (QDACT), an electronic quality monitoring system for community-based palliative care, to document care quality and link metrics to outcomes in palliative cancer care. **OBJECTIVE:** Demonstrate an association between quality metric conformance and quality of life in palliative cancer care. **METHODS:** We reviewed metric conformance to selected metrics from QOPI, Cancer-ASSIST, and PEACE and correlated this with patient-reported quality of life (QOL), focusing on cancer patients enrolled in QDACT 1/08-3/11 among 4 participating community palliative care practices in North Carolina. Statistical associations were assessed using Fisher's exact test. **RESULTS:** Data on 460 cancer patients informed conformance to 18 unique quality measures. Between measures, conformance ranged 2%-99%, indicating heterogeneity in practice. Adherence to metrics varied by year, signifying annual changes in care delivery. Significant associations were found between conformance and better QOL for 5 metrics (all  $P < .05$ ). These involved a documented plan of care for moderate/severe pain, mandatory screening for symptoms including fatigue and constipation, and assessment of emotional well-being. The strongest association ( $P < .001$ ) was between "screening of symptoms during the first visit" and QOL. There was a trend towards improved QOL with early constipation intervention ( $P = .06$ ). **LIMITATIONS:** Data are retrospective and taken from one time point, limiting conclusions on changes in QOL with changes in metric conformance. **CONCLUSIONS:** Quality metrics can be prospectively monitored in community-based palliative care patients with cancer using data systems that simultaneously measure quality and document outcomes. Conformance to 5 key metrics improves QOL, focusing on timely symptom assessment and management and emotional assessment. Quality measurement can inform priorities for care to improve the patient experience with advanced cancer. **KEYWORDS:** palliative cancer care, quality, quality measurement, quality metrics, quality of life, data collection

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**Abstract PA-6: Longitudinal Health-Related Quality of Life Assessment: Implications for Prognosis in Stage IV Pancreatic Cancer**

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**BACKGROUND:** Several studies have demonstrated the predictive significance of baseline health-related quality of life (QoL) on survival in cancer. **OBJECTIVE:** We investigated whether longitudinal changes in QoL could predict survival in stage IV pancreatic patients treated with an integrative model of care. **METHODS:** 186 stage IV pancreatic cancer patients treated at our institution between Jan 2001 and Dec 2009 who were available for a minimum follow-up of 3 months. QoL was evaluated at baseline and after 3 months of treatment using EORTC-QLQ-C30. Cox regression with bootstrap re-sampling was performed to evaluate the prognostic significance of baseline and change in QoL scores after adjusting for age, gender and treatment history. **RESULTS:** Mean age at diagnosis was 55.1 years; 121 were male, 65 female. 127 patients were newly diagnosed while 59 were previously treated. Median overall survival was 8.9 months (95% CI: 7.8-10 months). For baseline QoL analysis, every 10-point increase in global QoL score was associated with a 12% decreased risk of death (HR, 0.88; 95% CI, 0.81 to 0.95;  $P = .001$ ). For change in QoL score analysis, an 11% lower risk of death was independently associated with a 10-point improvement in cognitive function at 3 months (HR, 0.89; 95% CI, 0.79 to 0.99;  $P = .04$ ). **DISCUSSION:** This exploratory study provides preliminary evidence to suggest that baseline global QoL as well as change in cognitive function score after 3 months of treatment provide useful prognostic information in advanced pancreatic cancer. **KEYWORDS:** quality of life, pancreatic cancer, prognosis

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### Abstract PA-7: Development of A Palliative Care Intervention For Patients With Lung Cancer and Their Family Caregivers

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**BACKGROUND:** Patient education is essential to support coping with multiple physical symptoms, psychological and social concerns, and spiritual issues in lung cancer. **OBJECTIVE:** This NCI-funded interdisciplinary Program Project (P01) focuses on palliative care, QOL, and symptom control. This study tests usual care versus a palliative care intervention encompassing a four component patient and family caregiver education intervention. **METHODS:** In addition to conducting 2 pilot studies, a rigorous review of the literature and available resources served as the basis for the patient

intervention. Information was organized by QOL domains (physical, psychological, social, spiritual). Included is the patient's Action Plan completed by the patient and nurse. Teaching conducted by the Advanced Practice Nurse (APN) is tailored to the patient's needs and priorities. The family caregiver intervention follows the same format. APNs spent 2 months training for the intervention through role playing and mock teachings. In addition, an Interdisciplinary Case Conference (ICC) plan is developed and discussed at the weekly interdisciplinary working group meeting to receive feedback regarding the patient's needs. This feedback serves to further tailor the patient's teaching intervention. **RESULTS:** The study ends in 2014 and outcomes of this project include assessment of the impact of the education on patient symptoms, QOL, and supportive resource use as well as family caregiver outcomes. **LIMITATIONS:** This study is limited to one institution. **DISCUSSION:** This project will provide important comprehensive education interventions and resources for lung cancer patients and their family caregivers. **KEYWORDS:** lung cancer, palliative care, quality of life, symptom control, Patient Intervention Action Plan, Interdisciplinary Case Conference Plan

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### Abstract PA-8: Patient Expectation and Satisfaction With Outpatient Palliative Care Services

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**BACKGROUND:** Palliative care (PC) has been shown to improve quality of life for cancer patients, but how consults should be ideally delivered remains unclear. Efforts to evaluate content of PC visits and to assess patients' symptoms systematically may improve overall patient care and improve patient-reported quality of life outcomes. **OBJECTIVE:** To determine patient satisfaction with regard to outpatient palliative care services. In particular, to determine what patient expectations regarding such an appointment are and whether physical examination had any bearing on satisfaction level. **METHODS:** To understand patient expectations and assess satisfaction, pre- and post-visit surveys were provided to 20 consecutive patients (completed by 14 patients) in our outpatient PC clinic. Questions focused on patient perceptions regarding PC consultation, including perceived fears, expectations, and satisfaction. **RESULTS:** Symptom management was the primary reason patients provided for referral. Referrals from primarily oncologists and primary care physicians predominated, with pulmonologist, cardiologist, nephrologist, and other specialists also represented. Half of patients indicated the physical exam performed exceeded their expectation, half indicated it met their expectation, and two did not answer the question. Table 1 details results of questions. **LIMITATIONS:** 1. Population size. 2. Generalizability to other practices. **CONCLUSION:** Several important points are notable. First, patients were highly satisfied with the outpatient PC services they received. Next, patients reported little

anxiety or fear related to the visit. Most importantly, patients had a high level of satisfaction with the encounter. Though physical exam is often less a part of the assessment versus psychosocial interventions, referral for procedures, or medication adjustment, this was not perceived negatively by patients. Though data are pilot in nature, they suggest that PC services can be tailored to patient-specific symptomatology, which further permits time to focus on sensitive, patient-specific concerns. **KEYWORDS:** palliative care, outpatient, satisfaction, expectation

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Question	Average (5=strongly agree; 3=neutral 1=strongly disagree)	Standard deviation
Your palliative care visit met your initial expectations.	4.93	0.27
The goals for which you were referred for palliative care were met by today's visit.	4.93	0.27
Your feelings and concerns were appropriately and adequately addressed by today's visit.	4.93	0.27
The service provided by the Palliative Care Clinic was valuable.	4.93	0.27
You would encourage other patients to be seen in the Palliative Care Clinic.	4.96	0.13
The physical examination your provider performed on you was adequate to assess your symptoms.	4.88	0.43

## TREATMENT-RELATED SIDE EFFECTS

### Abstract PA-9: "ABH GEL" (Ativan®, Lorazepam; Benadryl®, Diphenhydramine; Haloperidol, Haldol®, Gel) Is Not Absorbed From the Skin of Normal Volunteers

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**BACKGROUND:** Lorazepam (Ativan), diphenhydramine (Benadryl), haloperidol (Haldol) ("ABH") topical gel is currently widely used

for nausea in hospice due to perceived efficacy and low cost, and has been suggested for cancer chemotherapy. However, there are no studies of absorption, a prerequisite for effectiveness. **OBJECTIVE:** The rationale for a trial of drug absorption is to determine which drugs are absorbed. This is thought to be critical in designing effective treatments, and determining use of the absorbed drugs for other conditions, e.g. lorazepam for seizures, or haloperidol for agitation/delirium. **METHODS:** 10 volunteers applied the standard 1.0 ml dose (2 mg of lorazepam, 25 mg of diphenhydramine, and 2 mg of haloperidol in a pluronic lecithin organogel) rubbed on the volar surface of the wrists by the subject. Blood samples were obtained at 0, 30, 60, 90, 120, 180 and 240 minutes. Plasma concentrations were analyzed for each drug. **RESULTS:** No lorazepam (A) or haloperidol (H) was detected in any sample from any of the 10 volunteers down to a level of 0.05 ng/ml. Diphenhydramine (B) was found in multiple plasma samples at concentrations >0.05 ng/ml in 3 patients, with the highest concentration 0.30 ng/ml in 1 person at 240 minutes. Overall, 5 of 10 patients exhibited detectable B in one or more samples supporting limited absorption. No subject noted any side effects. **LIMITATIONS:** Could other effects be causing symptom control, such as pressure point, placebo? The efficacy of ABH gel should be confirmed in randomized trials before its use is recommended. (This is underway at our institution at this time.) **CONCLUSION:** As commonly used, none of the lorazepam (A), haloperidol (H) or diphenhydramine (B) in ABH gel is absorbed in sufficient quantities to be effective in the treatment of nausea and vomiting. Diphenhydramine (B) is erratically absorbed at sub-therapeutic levels. **KEYWORDS:** Ativan, Haldol, benadryl, ABH gel, skin absorption, topical medications, compounded medications

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### Abstract PA-10: Effects of Age, Body Mass Index, and Tricep Skinfold Thickness on the Pharmacokinetics of Granisetron Transdermal System

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**BACKGROUND:** Sancuso® (granisetron transdermal system [GTDS]) is indicated for chemotherapy-induced nausea and vomiting in patients receiving moderately or highly emetogenic chemotherapy for up to 5 consecutive days. **OBJECTIVE:** Data from a single-center, open-label, phase 1 study (NCT00868764) were analyzed to determine effects of age, body mass index (BMI), and tricep skinfold thickness (TST) on GTDS pharmacokinetics. **METHODS:** GTDS (3.1 mg/24 h) was applied for 7 days; pharmacokinetic testing occurred 8 hours after application on day 1 and for ≤9 days thereafter. Analysis of variance, Pearson correlations, Wilcoxon tests, and t-tests were applied (significance  $P < .05$ ).

**RESULTS:** Sixty healthy volunteers were divided by age  $\geq 65$  years ( $n=24$ ) and  $\geq 18-45$  years ( $n=6$ ) and BMI  $< 19.5$  kg/m<sup>2</sup> in men or  $< 18.5$  kg/m<sup>2</sup> in women ( $n=12$ ), 30.0-39.9 kg/m<sup>2</sup> ( $n=12$ ), and 20.0-24.9 kg/m<sup>2</sup> ( $n=6$ ). The analysis comprised 58 subjects, median age 54 (range 18-84) years, BMI 25 (16-39) kg/m<sup>2</sup>, and TST 10 (2-20) mm. No significant correlations were noted with age ( $P = .08$ ,  $P = .14$ ,  $P = .12$ ) or BMI ( $P = .97$ ,  $P = .86$ ,  $P = .80$ ) for maximum granisetron plasma concentration (C<sub>max</sub>), area under the concentration-time curve (time 0 to timepoint of last quantifiable concentration, AUC<sub>0-z</sub>), or average granisetron plasma concentration (C<sub>avg</sub>(24-168)); age and BMI were not predictive of these parameters. No significant correlation was found between TST and C<sub>max</sub> ( $P = .36$ ), AUC ( $P = .28$ ), or C<sub>avg</sub> ( $P = .33$ ); TST was not predictive of these parameters. **LIMITATIONS:** Single-center, open-label study; small patient numbers. **CONCLUSIONS:** No GTDS dose adjustments are needed for age, BMI, or TST, as these factors did not affect GTDS pharmacokinetics. **KEYWORDS:** granisetron transdermal system, chemotherapy-induced nausea and vomiting, pharmacokinetics, effect of age, effect of body mass index, effect of skin-fold thickness

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### Abstract PA-11: The Evaluation of Flaxseed for Hot Flashes, Results of a Randomized, Controlled Trial, NCCTG Study N08C7

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**BACKGROUND:** Hot flashes are a common symptom, during the menopause transition or following breast cancer treatment, that can negatively impact the quality of life for many women. **OBJECTIVE:** Preliminary data suggest that flaxseed, a rich source of dietary lignans, may be a potentially effective treatment for hot flashes. A phase III randomized, placebo controlled trial was conducted to evaluate the efficacy of flaxseed in reducing hot flashes.

**METHODS:** Postmenopausal women experiencing at least 28 hot flashes per week were randomly assigned to a flaxseed bar (providing 410 mg of lignans) for 6 weeks versus a placebo bar. Participants completed daily prospective, self report hot flash diaries during the baseline week and then began eating one study bar per day for 6 weeks, while continuing to record their daily hot flashes. The intra-patient difference in hot flash activity between baseline and the last treatment week was the primary endpoint. Side effects of the bars were evaluated through self report and CTC assessment. **RESULTS:** Between October and December, 2009, 188 women were enrolled in this trial. Mean hot flash scores were reduced by 4.9 units in the flaxseed group and 3.5 in the placebo group ( $P = .29$ ). In both groups, a little over a third of the women received a 50% reduction in their hot flash scores. Only one side effect was significantly different between groups, that being grade 1 pruritis, which was more common (7%) in the placebo group versus 1% in the flaxseed group. Both groups reported increased abdominal distension, flatulence, diarrhea and nausea. Adherence and ability to detect treatment assignment did not differ between groups. **LIMITATIONS:** Fiber content in placebo and flaxseed bar resulted in gastrointestinal side effects that contributed to non-compliance. **CONCLUSION:** The results of this trial 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 likely due to the fiber content in the flaxseed and placebo bars. **KEYWORDS:** menopause, breast cancer, hot flashes, flaxseed, anti-estrogen, lignans, phytoestrogens

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### Abstract PA-12: Cognitive Function in Women Receiving Taxane Therapy

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**BACKGROUND:** Cognitive impairment is well documented in breast cancer patients receiving chemotherapy, commonly affecting domains of executive function and verbal learning/memory. Taxanes have been shown to cross the BBB and cause cytokine dysregulation, both potential mechanisms for impairment. **OBJECTIVE:** Our primary aim was to explore whether breast cancer patients who receive a regimen including a taxane experience more impairment compared to regimens that do not and compared to normal aging women. **METHODS:** 51 postmenopausal women were divided into a control group, and breast cancer patients receiving either adriamycin/cyclophosphamide or adriamycin/cyclophosphamide+taxane. Each group underwent neuropsychological testing prior to chemotherapy(T0), immediately following chemotherapy(T1), and 6-months post-chemotherapy(T2). **RESULTS:** In the control group, 41% were

impaired at baseline, with a decrease to 28% at T2. In the AC group, 35% were impaired at baseline, with a decrease to 9% at T2. In the AC-T group, 24% were impaired at baseline, with an increase to 46% at T2.

Impairment analysis by cognitive domain:					
		Executive function	Visual learning/memory	Psychomotor efficiency	Mental flexibility
T0	Control	23%	23%	0%	0%
	AC	17%	17%	12%	0%
	AC-T	12%	18%	0%	0%
T2	Control	14%	13%	0%	0%
	AC	0%	0%	9%	0%
	AC-T	15%	0%	23%	15%

**DISCUSSION:** Baseline cognitive impairments occurred in the domains of executive function and verbal learning/memory across all groups, but improved with time, suggesting practice effects. In the AC-T group, a significant percentage of women experienced decline in psychomotor efficiency and mental flexibility suggesting an association between taxane therapy and impairment in these domains. **KEYWORDS:** cognitive impairment, breast cancer, taxane, executive function, verbal learning, mental flexibility, supportive oncology

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### Abstract PA-13: Paclitaxel-Associated Acute Pain Syndrome (P-APS) and Its Association with The Development of Peripheral Neuropathy: NCCTG Trial N08CI

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**BACKGROUND:** Paclitaxel is well known to cause an acute pain syndrome that has been referred to as arthralgias and myalgias. It has been hypothesized that this pain might actually be neurologic in origin (Loprinzi et al; Cancer J 2007; 13:399-403). A recent prospective cohort study evaluating the natural history of this paclitaxel-associated acute pain syndrome supported an association ( $P = .0017$ ) between the degree of paclitaxel-associated acute pain severity and the subsequent development of peripheral sensory neuropathy (J Clin Oncol. 2011 Apr 10;29(11):1472-8). **OBJECTIVE:**

This study was the second of four cohorts aimed at evaluating the natural history of the paclitaxel-associated acute pain syndrome and the association, if any, with the development of peripheral neuropathy. **METHODS:** Adult patients receiving at least 175 mg/m<sup>2</sup> of paclitaxel every three weeks, with concomitant carboplatin, participated in this study. Patients completed questionnaires for 7 days following each dose of paclitaxel. They were asked to judge, on each day, pain that was new and that they thought was related to chemotherapy (graded on a scale of 0 to 10 with 10 being worst). They also completed questionnaires (EORTC CIPN-20 instrument) to collect neuropathy data at the beginning of each weekly cycle of therapy and monthly after chemotherapy completion. Descriptive statistics were utilized for study endpoints.

**RESULTS:** Eighty-five patients were accrued. Eighty-eight percent experienced pain, most prominent in the hips and lower extremities, which peaked at day 4 after the first paclitaxel cycle. Subjects who experienced less acute pain (scores of 0-4) with the first paclitaxel cycle had less neuropathy over 18 weeks of treatment than did patients with 5-10 pain score severities. **LIMITATIONS:** In this cohort, patients received paclitaxel in combination with another neurotoxic agent, carboplatin. Subjects were followed over 18 weeks of treatment, with successively fewer patients remaining by the end of the study. **CONCLUSIONS:** In conjunction with our earlier data, this study suggests that there is a correlation with the paclitaxel-associated acute pain syndrome and the development of peripheral neuropathy, with those experiencing more severe pain with the first paclitaxel cycle developing more eventual peripheral neuropathy. **KEYWORDS:** Paclitaxel associated acute pain syndrome, peripheral neuropathy

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