

Symptom Control Trials: A 20-Year Experience

Charles L. Loprinzi, MD, Debra L. Barton, RN, PhD, Aminah Jatoi, MD, Jeff Sloan, PhD, Jim Martenson, MD, David Steensma, MD, Ravi Rao, MD, Paul Novotny, MS, Amit Sood, MD, Axel Grothey, MD, Lori Minasian, MD, and Harold Windschitl, MD

In 1985, a report in the literature noted that an allopurinol mouthwash appeared to decrease 5-fluorouracil (5-FU)-induced oral mucositis,¹ and this proposed remedy became accepted as standard practice by some.² Coincidentally, the US National Cancer Institute (NCI) Community Clinical Oncology Program (CCOP), while in its infancy, mandated that CCOP participant institutions be involved with cancer control trials in addition to cancer treatment trials. In response to this stand, a study was developed both to fulfill CCOP requirements and to address the question of whether an allopurinol mouthwash could reduce 5-FU-induced mucositis.³ Thus began a symptom control program, which, over the past 2 decades, has been involved with the conduct of more than 65 protocols. This work has been the combined effort of the investigators in both the North Central Cancer Treatment Group (NCCTG) and the Mayo Clinic. Thirteen symptoms and symptom complexes related to cancer and/or cancer therapy have been studied in this program (Table 1).

Symptoms

MUCOSAL TOXICITY

In 1986, the mucositis prevention program was initiated. Trials studying ways to inhibit 5-FU-induced mucositis revealed that there was no suggestion of benefit for an allopurinol mouthwash,³ a chamomile mouthwash,⁴ glutamine,⁵ or sucralfate.⁶ Oral cryotherapy, given for 30 minutes around each dose of bolus 5-FU, in contrast, did decrease

Abstract Symptoms related to cancer and/or cancer therapy are a prominent consideration in cancer patients; multiple options have been proposed to alleviate these problems. The US National Cancer Institute (NCI) Community Clinical Oncology Program (CCOP) has mandated that CCOP participant institutions be involved with cancer control trials in addition to cancer treatment trials. Through such efforts, scientifically sound symptom control clinical trials are being conducted to determine the effectiveness of promising agents. In this article, the authors provide an update of clinical trial outcomes regarding 13 symptom and symptom complexes related to cancer and/or cancer therapy, emphasizing that publication of both positive and negative study results is important to separate what works from what does not.

mucositis by about 50%.⁷ This finding was collaborated by another group who reported virtually identical results when they repeated the study.⁸ A subsequent trial, designed to compare 60 versus 30 minutes of oral cryotherapy, did not reveal any improvement with the longer study duration.⁹ Cochrane reports at one time concluded that cryotherapy was the only evidence-based intervention for preventing 5-FU-induced mucositis.¹⁰

With regard to radiation-induced oral mucositis, chlorhexidine was associated with net harm, causing increased mouth pain and no suggestion of a reduction in mucositis.¹¹ An oral antibiotic lozenge appeared to be of borderline benefit,¹² whereas a capsaicin lozenge did not provide any benefit.¹³ For radiation-induced esophagitis, sucralfate caused toxicity but no suggestion of any benefit.¹⁴

Radiation-induced lower gastrointestinal tract mucosal toxicity has also been studied. While ol-salazine was being studied for the prevention of radiation-induced diarrhea, it actually was discovered that this drug was associated with increased diarrhea compared with placebo.¹⁵ Sucralfate (associated with some toxicity), glutamine, and a somatostatin analog did not reduce radiation-induced

Drs. Loprinzi, Jatoi, Rao, and Grothey are from the Division of Medical Oncology; Dr. Barton is from the Cancer Center; Dr. Sloan and Mr. Novotny are from the Department of Cancer Center Statistics; Dr. Martenson is from the Department of Radiation Oncology; Dr. Steensma is from the Division of Hematology; and Dr. Sood is from the Division of General Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Dr. Minasian is from the Community Oncology and Prevention Trials Research Group, National Cancer Institute, Bethesda, Maryland. Dr. Windschitl is from CentraCare Clinic, St. Cloud, Minnesota.

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Correspondence to: Charles L. Loprinzi, MD, Division of Medical Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905; telephone: (507) 284-8964; fax: (507) 284-1803; e-mail: clopinzi@mayo.edu

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Table 1

Symptoms Related to Cancer and/or Cancer Therapy

SYMPTOM	DATE OF INITIATION OF FIRST STUDY
Mucosal toxicity	1986
Anorexia/cachexia	1987
Pain	1988
Hot flashes	1989
Skin toxicity	1990
Sexual symptoms	1992
Neuropathy	1993
Lymphedema	1994
Anemia	1997
Cognitive dysfunction	2000
Osteoporosis	2001
Insomnia	2004
Fatigue	2005

diarrhea in placebo-controlled trials.^{16–18} Table 2 provides a summary of this program.^{3–7,9,11–18}

In total, this mucositis program has demonstrated that purported agents are as likely to cause net harm as they are to result in benefit. Thus, proper scientific evaluation of these agents is appropriate before employing them in clinical practice.

ANOREXIA/CACHEXIA

The anorexia/cachexia program was initiated in 1987, after the late Dr. Charles Moertel, one of the first oncologists ever to conduct a symptom control trial,¹⁹ noted that patients with carcinoid cancers gained weight when treated with the serotonin antagonist cyproheptadine.²⁰ This led to a randomized placebo-controlled clinical trial to evaluate this agent,²¹ the first in a long line of cancer anorexia/cachexia trials illustrated in Table 3.^{21–35}

These clinical trials demonstrate that megestrol substantially improves appetite and leads to non-fluid weight gain. The NCCTG conducted the largest and first-published placebo-controlled trial to test megestrol for cancer anorexia/cachexia and establish this progestational agent as one of the most effective therapies available for palliating cancer anorexia/cachexia.²² A large number of other trials have followed, confirming the original findings from the NCCTG.³⁶

Building on this initial observation of efficacy, the NCCTG pursued a series of other studies to better define the role of megestrol in palliating cancer anorexia/cachexia. One trial demonstrated that megestrol has a dose-response effect on appetite, with doses of 800 mg/d providing maximal improvement.²³

In terms of improving appetite, megestrol is relatively equivalent to dexamethasone, but the latter is associated with an adverse-event profile that includes myopathy and gastritis. For this reason, megestrol is thought to be a better choice for therapy that is planned to be administered for months, as opposed to just weeks.²⁸

Following the demonstration that megestrol could improve cancer anorexia/cachexia, a placebo-controlled trial was de-

Table 2

Mucosal Toxicity Studies

TREATMENT TRIAL	DATE INITIATED	# OF SUBJECTS	RESULTS
5-FU–induced oral mucositis			
Allopurinol mouthwash vs placebo ³	1986	77	Negative study
Oral cryotherapy vs control ⁷	1988	95	50% reduction in mucositis
Oral cryotherapy duration (30 vs 60 min) ⁹	1989	178	No benefit for 60 min of cryotherapy over 30 min
Chamomile mouthwash vs placebo ⁴	1990	164	Negative study
Sucralfate solution vs placebo ⁶	1992	50	Negative study, but sucralfate associated with toxicity
Glutamine vs placebo ⁵	1995	134	Negative study
Radiation-induced oral mucositis			
Chlorhexidine vs non-absorbable antibiotics vs placebo ¹¹	1992	52	Chlorhexidine associated with net harm
Chlorhexidine vs non-absorbable antibiotics vs placebo (same trial as the one above) ¹²	1992	112	Antibiotics of minimal benefit
Capsaicin lozenge vs placebo ¹³	1996	18	Negative study
Esophagitis			
Sucralfate vs placebo ¹⁴	1992	97	Negative study, but sucralfate associated with toxicity
Diarrhea			
Olsalazine vs placebo ¹⁵	1991	58	Olsalazine associated with net harm
Sucralfate vs placebo ¹⁶	1994	123	Sucralfate associated with toxicity but no benefit
Glutamine vs placebo ¹⁷	1996	129	No benefit from glutamine
Somatostatin analog vs placebo ¹⁸	2000	129	No benefit from early use of somatostatin analog

veloped to determine whether the early initiation of megestrol might be beneficial. Patients with newly diagnosed extensive-stage small cell lung cancer were randomized to receive megestrol versus placebo. Unfortunately, megestrol was not associated with an improvement in tumor response rate, tumor response duration, or patient survival,²⁵ observations that suggest this agent is best used for palliation.

Comparative studies have helped to define the role of megestrol in the context of newer, emerging agents. Fluoxymesterone,²⁸ dronabinol (Marinol),²⁹ and an eicosapentaenoic acid (EPA) nutritional supplement³⁰ did not perform as well as megestrol as an anti-anorexia agent. Pentoxifylline²⁴ and hydrazine^{26,27} were tested in separate trials and proved no better than placebo.

Clinical translational studies have demonstrated that

megestrol does lead to a true increase in body mass, consisting of fat, not lean tissue.³¹ Laboratory-based studies revealed that megestrol causes adrenal suppression, leading to an increased clinical awareness of this phenomenon.³² Other translational, laboratory-based investigations have shown that there was no apparent effect of megestrol on circulating interleukin-6 (IL-6) concentrations,³⁵ that neuropeptide Y (an orexigenic hormone) appears depressed in cancer patients with anorexia,³⁴ and that the proteolysis-inducing factor (PIF; a previously touted mediator of the anorexia/cachexia syndrome) is not associated with changes in weight, anorexia, or survival in patients with metastatic gastric/esophageal cancer.³³

HOT FLASHES

Since the first hot flash study was initiated in 1989, a large number of such trials have been performed (Table 4).³⁷⁻⁵⁴ The results of one of the randomized studies have demonstrated that clonidine decreases hot flashes to a moderate degree but is associated with bothersome toxicity, limiting its utility.³⁷ Similar results were reported by another group.⁵⁵

The newer antidepressants have been moderately effective in managing hot flashes, with positive placebo-controlled trials being demonstrated with venlafaxine (Effexor) and fluoxetine.^{41,42} A comparison of venlafaxine and medroxyprogesterone acetate (MPA) revealed that venlafaxine did not reduce hot flashes as prominently as did MPA.⁴³ Megestrol did substantially reduce hot flashes, to the degree that would be expected with estrogen.³⁸ Vitamin E was of borderline benefit.³⁹ Although a pilot trial of black cohosh appeared promising,⁴⁴ in a subsequent placebo-controlled study, it failed to demonstrate any suggestion of efficacy against hot flashes.^{40,54}

CHEMOTHERAPY-INDUCED NEUROPATHY

Chemotherapy-induced neuropathy studies began in 1993 (Table 5).⁵⁶⁻⁵⁹ Individual trials evaluating the treatment of established chemotherapy-induced neuropathy with nortriptyline,⁵⁶ gabapentin,⁵⁷ and lamotrigine⁵⁸ have been completed. All three of these trials provided negative study results. A trial of glutamine for preventing paclitaxel-induced acute pain (often labeled as arthralgias/myalgias but which might actually be pain from a nerve injury) revealed that it provided no benefit.⁵⁹

Administering protective agents at the time of chemotherapy to prevent neuropathy is being evaluated through the use of calcium/magnesium for oxaliplatin (Eloxatin) in one study and vitamin E in another study to determine whether these agents can prevent chemotherapy-induced neuropathy from a variety of cytotoxic drugs.

OSTEOPOROSIS

Studies regarding the alleviation of osteoporosis-related troubles in patients with cancer were initiated in 2001 (Table 6), examining means of alleviating bone loss problems in patients with cancer treated with hormonal therapy or chemotherapy. All patients on these osteoporosis trials have been given calcium and vitamin D as standard therapy. These trials are evaluating

Table 3

Anorexia/Cachexia Trials

TRIALS	YEAR INITIATED	# OF SUBJECTS	RESULT
Randomized trials			
Cyproheptadine vs placebo ²¹	1987	293	Minimal benefit noted
Megestrol vs placebo ²²	1988	133	Positive study
Megestrol dose-response trial ²³	1989	342	Dose response benefit noted up to a dose of 800 mg/d
Pentoxifylline vs placebo ²⁴	1991	70	Negative trial
Megestrol vs placebo in small cell lung cancer ²⁵	1989	243	Improvement in appetite, weight, and nausea but no benefit for survival, quality of life, or tumor response
Hydrazine vs placebo/lung cancer ²⁶	1989	119	Negative study
Hydrazine vs placebo/colon cancer ²⁷	1989	127	Negative study
Megestrol vs dexamethasone vs fluoxymesterone ²⁸	1991	475	Relatively equivalent results with megestrol and dexamethasone, both of which appeared superior to fluoxymesterone
Megestrol vs dronabinol vs both ²⁹	1995	469	No benefit for dronabinol instead of, or in addition to, megestrol
EPA vs megestrol vs both ³⁰	1998	421	No benefit for EPA compared with or in addition to megestrol
Etanercept vs placebo	2000	66	Manuscript pending
Infliximab vs placebo in lung cancer	2000	67	Results pending
Zinc vs placebo for radiation dysgeusia	2001	173	Manuscript pending
Creatine vs placebo	2004	210+	Accrual ongoing
Pilot studies			
Neuropeptide Y	2001	7	Results pending
Etanercept	2001	13	Results pending
Laboratory-based studies			
Body composition changes with megestrol ³¹	1990	12	Megestrol increased fat mass
Megestrol effect on adrenal function ³²	1990	16	Megestrol decreased adrenal production of cortisol
Tumor necrosis factor polymorphisms in weight, anorexia, or survival ³³	2002	41	Urine PIF is not associated with changes
Neuropeptide Y ³⁴	2001	73	This hormone appears depressed in patients with cancer anorexia/cachexia
Megestrol regulation of IL-6 ³⁵	1996	85	No change in IL-6 concentrations after treatment with megestrol

Abbreviations: EPA = eicosapentaenoic acid; PIF = proteolysis-inducing factor; IL-6 = interleukin-6

Table 4
Hot Flash Trials

TRIALS	YEAR INITIATED	# OF SUBJECTS	RESULTS
Randomized trials			
Clonidine vs placebo ³⁷	1989	110	Mild improvement in hot flashes but associated toxicity bothersome
Megestrol vs placebo ³⁸	1990	163	Substantial reduction in hot flashes in both men and women
Vitamin E vs placebo ³⁹	1995	104	Borderline benefit
Soy phytoestrogen vs placebo ⁴⁰	1996	177	Negative study
Fluoxetine vs placebo ⁴¹	1997	81	Moderate reduction in hot flashes
Venlafaxine dose-response placebo-controlled trial ⁴²	1997	191	Moderate reduction in hot flashes
MPA vs venlafaxine ⁴³	1999	188	MPA with a more marked reduction in hot flashes than venlafaxine
Gabapentin dose-response, placebo-controlled trial in men	2000	223	Study ongoing
Black cohosh vs placebo ⁴⁴	2001	107	Negative study
Gabapentin alone or in combination with an antidepressant in antidepressant failures	2003	118	Study analysis ongoing
Pilot studies			
Venlafaxine ^{45,46}	1997	28	Promising results
Bupropion ⁴⁷	2000	21	Promising results
Mirtazapine ⁴⁸	2000	20	Negative trial
Mirtazapine ⁴⁸	2000	22	Promising results
Gabapentin ⁴⁹	2000	20	Promising results
Citalopram ⁵⁰	2000	18	Promising results
Nefazodone	2000	9	Study stopped early as drug was pulled from the market
Paroxetine in men ⁵¹	2001	22	Promising results
DHEA ⁵²	2002	22	Promising results
Citalopram in venlafaxine failures ⁵³	2000	22	Promising results
Black cohosh ⁵⁴	2000	21	Promising results
Desipramine	2002	26	Study analysis ongoing
Aprepitant	2003	25	Study analysis ongoing
Flax seed	2004	30	Study analysis ongoing
Levetiracetam	2005	19+	Study analysis ongoing

Abbreviations: MPA = medroxyprogesterone acetate; DHEA = dehydroepiandrosterone

men with prostate cancer who were receiving androgen ablation therapy, premenopausal women with breast cancer who were being treated with adjuvant chemotherapy, and postmenopausal

Table 5
Chemotherapy-induced Neuropathy Trials

TRIALS	YEAR INITIATED	# OF SUBJECTS	RESULTS
Treatment			
Nortriptyline ⁵⁶	1993	51	Negative trial
Gabapentin ⁵⁷	2000	115	Negative trial, manuscript in preparation
Lamotrigine ⁵⁸	2001	130	Negative trial, manuscript in preparation
Prevention			
Calcium/magnesium vs oxaliplatin	2005	50+	Patient accrual ongoing
Vitamin E	2005	1+	Patient accrual ongoing
Paclitaxel-induced acute pain			
Glutamine vs placebo ⁵⁹	1999	36	Negative study

Table 6
Osteoporosis-Prevention Trials

TRIALS	YEAR INITIATED	# OF SUBJECTS	RESULTS
Estrogen vs risedronate vs both vs placebo in prostate cancer	2001	71	Results pending
Risedronate vs placebo for premenopausal women receiving chemotherapy	2002	216	Results pending
Zoledronic acid vs control for women starting letrozole	2003	558	Results pending
Zoledronic acid for women with established osteopenia starting letrozole	2005	35+	Study ongoing

women with breast cancer receiving an aromatase inhibitor. The results of all of these trials are currently pending.

ANEMIA

In 1997, the NCCTG initiated its first study of means to alleviate chemotherapy-induced anemia (Table 7).^{60,61} Results from this program have demonstrated that weekly erythropoietin (40,000 U subcutaneous [SQ]) is better than weekly placebo for improving hemoglobin levels and decreasing transfusions in patients with cancer-associated anemia.⁶⁰ A subsequent trial looked at erythropoietin weekly for 4 doses followed by continuation of 40,000 U of erythropoietin weekly versus 120,000 U of erythropoietin every 3 weeks (Q3W). Relatively equivalent results were seen.⁶¹

An ongoing trial is evaluating darbepoetin alfa (Aranesp) in patients with chemotherapy-associated anemia. These pa-

Table 7
Anemia Trials

TRIALS	YEAR INITIATED	# OF SUBJECTS	RESULTS
Erythropoietin vs placebo ⁶⁰	1997	333	Improved hemoglobin and decreased transfusions
Erythropoietin QW vs Q3W following a week loading course ⁶¹	2002	360	Relatively equivalent results seen with QW vs Q3W erythropoietin
Darbepoetin alfa with IV iron vs oral iron vs oral placebo	2004	155+	Study accrual ongoing
Erythropoietin Q3 vs Q3W vs darbepoetin alfa Q3W	2006	Pending	Study being developed

Abbreviations: QW = every week; Q3W = every 3 weeks

Table 8
Skin Toxicity Trials

TRIALS	YEAR INITIATED	# OF SUBJECTS	RESULTS
Radiation-induced toxicity			
Aloe vera vs placebo for chest wall radiation therapy ⁶²	1990	191	Negative results
EGFR inhibitor-induced rash			
Tetracycline vs placebo	2005	65	Study results being analyzed
Sunscreen vs placebo	2006	19+	Study accruing
Capecitabine-induced hand-foot syndrome			
Vitamin B ₆ vs urea cream vs both vs placebo	2006	19+	Study accruing

Abbreviation: EGFR = epidermal growth factor receptor

tients are randomized to receive intravenous iron versus oral iron versus an oral placebo. Lastly, a trial is in development to assess erythropoietin weekly (40,000 U SQ) versus Q3W (120,000 U vs 80,000 U) compared with darbepoetin alfa Q3W (500 µg).

SKIN TOXICITY

The first study of treatment-induced skin toxicity (Table 8) found that an aloe vera gel did not improve radiation-induced chest wall toxicity.⁶² Results are currently pending from a study that examined whether tetracycline prevents or lessens the severity of epidermal growth factor receptor (EGFR) inhibitor-induced dermatitis. A subsequent study is accruing patients to look at a sunscreen as a means of treating EGFR inhibitor-induced dermatitis. In addition, a current clinical trial is examining vitamin B₆ versus a urea-based cream versus both versus placebo for alleviating the hand-foot syndrome (palmar-plantar dysesthesia) commonly associated with capecitabine (Xeloda) therapy.

Table 9
Sexual Health Trials

TRIALS	YEAR INITIATED	# OF SUBJECTS	RESULTS
Vaginal dryness			
Replens vs a nonspecific vaginal lubricant ⁶³	1992	45	Both a polycarbophil-based moisturizer and a nonspecific vaginal lubricant appeared to alleviate vaginal dryness
Pilocarpine vs placebo	2006	Pending	Study in development
Libido in women			
Testosterone cream vs placebo ⁶⁴	2002	132	Negative study

Table 10
Fatigue Trials

TRIALS	YEAR INITIATED	# OF SUBJECTS	RESULTS
Ginseng vs placebo	2005	290	Study analysis ongoing
Concerta vs placebo	2006	Pending	Study under development

SEXUAL SYMPTOMS

The initially evaluated symptom related to sexual health (Table 9) was vaginal dryness.⁶³ In this trial of a polycarbophil-based moisturizer (Replens) versus a nonspecific vaginal lubricant control, both study arms appeared to decrease vaginal dryness. A subsequent vaginal dryness study is evaluating pilocarpine, based on data from patients with Sjögren syndrome.⁶⁴ A recently completed study evaluated a testosterone cream preparation for cancer survivors who believed they had impaired sexual desire; data from this study do not support its routine use.⁶⁵

FATIGUE

A placebo-controlled trial has been initiated to determine whether American ginseng can alleviate cancer fatigue. A subsequent trial is under development to examine a long-acting methylphenidate preparation versus placebo (Table 10).

COGNITIVE DYSFUNCTION

One study has completed its accrual goals to evaluate ginkgo biloba versus placebo in the prevention of cognitive dysfunction in patients with breast cancer who are receiving adjuvant chemotherapy. A total of 226 patients were enrolled in this study, which should be mature in 2007.

PAIN

Trials of cancer pain⁶⁶⁻⁷¹ (Table 11) have demonstrated the following results: 1) the pharmacokinetics of sublingual morphine are equivalent to those of oral morphine⁶⁶; 2) a

Table 11**Pain Trials**

TRIALS	YEAR INITIATED	# OF SUBJECTS	RESULTS
Morphine route pharmacology study ⁶⁶	1988	6	Oral morphine pharmacokinetics equivalent to sublingual morphine
A randomized crossover evaluation of methylphenidate in cancer patients receiving strong narcotics ⁶⁷	1989	43	Not much benefit
Pilot evaluation of systemically administered local anesthetics (flecainide and mexiletine) for treatment of cancer pain ⁶⁸	1991	20	Negative trial
An open-label pilot study of transdermal fentanyl for cancer pain ⁶⁹	1991	35	Positive pilot trial
Capsaicin cream for alleviating postsurgical neuropathic pain ⁷⁰	1991	99	Substantially better than placebo
Topically administered local anesthetic (EMLA cream 5%) to relieve procedural pain ⁷¹	1992	47	Positive study results
Lidocaine patch for alleviating postsurgical neuropathic pain	2004	30	Study analysis ongoing

capsaicin cream was substantially better than was placebo for decreasing postsurgical neuropathic scar pain (50% pain reduction at 8 weeks versus 17%)⁷⁰; 3) a topically administered local anesthetic (EMLA cream 5%) relieved pain during central venous port accesses in children with cancer⁷¹; 4) methylphenidate did not appear to provide much benefit in cancer patients receiving strong narcotics⁶⁷; 5) transdermal fentanyl (Duragesic) appeared to be helpful for the

management of cancer pain in ambulatory patients⁶⁹; and 6) the systemically administered local anesthetics, flecainide and mexiletine, did not appear to be helpful for treating cancer pain.⁶⁸

LYMPHEDEMA

In 1994, a trial was conducted to evaluate the use of coumarin to alleviate lymphedema in women after surgery for breast cancer. This trial, which enrolled 150 women in 1 month, did not show any benefit but did show that coumarin was associated with hepatotoxicity.⁷²

INSOMNIA

A double-blinded, placebo-controlled, randomized trial is currently accruing participants to evaluate the herb *Valeriana officinalis* for sleep disturbances after a cancer diagnosis. More than 200 patients have been enrolled on this trial to date.

Conclusion

As evidenced by the large numbers of patients accrued in the previously described trials, symptoms related to cancer and/or cancer therapy are prominent in patients suffering from cancer. Multiple treatments have been proposed for alleviation of a number of these symptoms. Through the efforts of a dedicated core group of individuals, scientifically sound clinical trials, as illustrated in this article, can be conducted to determine whether promising agents are effective or not. Many of the trials provide negative results, as is common in clinical research. Publication of both the negative and positive results from these trials is important to distinguish what works from what does not, so effective evidence-based practice can be employed and further research developed. Clinical trial outcomes can help patients and providers to avoid toxicities from unhelpful agents and can move science forward to discover effective therapies. Moreover, these trials may actually play a role in improving survival by making cytotoxic therapy less toxic and therefore more acceptable to patients and physicians.

References

PubMed ID in brackets

- Clark PI, Slevin ML. Allopurinol mouthwash and 5-fluorouracil induced oral toxicity. *Eur J Surg Oncol* 1985;11:267–268. [4029407]
- Marini G, Simoncini E, Zaniboni A, et al. 5-Fluorouracil and high-dose folic acid as salvage treatment of advanced breast cancer: an update. *Oncology* 1987;44:336–340. [3500441]
- Loprinzi CL, Cianflone SG, Dose AM, et al. A controlled evaluation of an allopurinol mouthwash as prophylaxis against 5-fluorouracil-induced stomatitis. *Cancer* 1990;65:1879–1882. [2180557]
- Fidler P, Loprinzi CL, O'Fallon JR, et al. Prospective trial of a chamomile mouthwash for prevention of 5-FU-induced oral mucositis. *Cancer* 1996;77:522–525. [8630960]
- Okuno SH, Woodhouse CO, Loprinzi CL, et al. Phase III controlled evaluation of glutamine for decreasing stomatitis in patients receiving fluorouracil (5-FU)-based chemotherapy. *Am J Clin Oncol* 1999;22:258–261. [10362332]
- Loprinzi CL, Ghosh C, Camoriano J, et al. Phase III controlled evaluation of sucralfate for alleviating stomatitis in patients receiving 5FU (fluorouracil-based chemotherapy). *J Clin Oncol* 1997;15:1235–1238. [9060567]
- Mahood DJ, Dose AM, Loprinzi CL, et al. Inhibition of 5-fluorouracil-induced mucositis by oral cryotherapy. *J Clin Oncol* 1991;9:449–452. [1999715]
- Cascinu S, Fedeli A, Fedeli SL, Catalano G. Oral cooling (cryotherapy), an effective treatment for the prevention of 5-fluorouracil-induced stomatitis. *Eur J Cancer B Oral Oncol* 1994;30B:234–236. [7950836]
- Rocke LK, Loprinzi CL, Lee JK, et al. A randomized clinical trial of two different durations of oral cryotherapy for prevention of 5-fluorouracil-related stomatitis. *Cancer* 1993;72:2234–2238. [8374882]
- Clarkson JE, Worthington HV, Eden OB. Prevention of oral mucositis or oral candidiasis for patients with cancer receiving chemotherapy (excluding head and neck cancer). *Cochrane Database Sys Rev* 2000;2:CD000978. [10796567]
- Foote RL, Loprinzi CL, Frank AR, et al. Randomized trial of chlorhexidine mouthwash for alleviation of radiation-induced mucositis. *J Clin Oncol* 1994;12:2630–2633. [7989938]
- Okuno SH, Foote RL, Loprinzi CL, et al. A randomized trial of a nonabsorbable antibiotic lozenge given to alleviate radiation-induced mucositis. *Cancer* 1997;79:2193–2199. [9179067]
- Okuno SH, Foote RL, Olmscheid MA, et al. Evaluation of an oral capsaicin lozenge for preventing radiation-induced mucositis. *J Cancer Integr Med* 2004;2:179–183.
- McGinnis WL, Loprinzi CL, Buskirk SJ, et al.

Placebo-controlled trial of sucralfate for inhibiting radiation-induced esophagitis. *J Clin Oncol* 1999;15:1239–1243.

15. Martenson JA, Hyland G, Moertel CG, et al. Olsalazine is contraindicated during pelvic radiation therapy: results of a double-blind, randomized clinical trial. *Int J Radiat Oncol Biol Phys* 1996;35:299–303. [8635937]

16. Martenson JA, Bollinger JW, Sloan JA, et al. Sucralfate in the prevention of treatment-induced diarrhea in patients receiving pelvic radiation therapy: a North Central Cancer Treatment Group phase III double-blind placebo-controlled trial. *J Clin Oncol* 2000;18:1239–1245. [10715293]

17. Kozelsky TF, Meyers GE, Sloan JA, et al. Phase III double-blind study of glutamine versus placebo for the prevention of acute diarrhea in patients receiving pelvic radiation therapy. *J Clin Oncol* 2003;21:1669–1674. [12721240]

18. Martenson JA, Sloan JA, Deming RL, et al. Phase III double-blind study of depot octreotide versus placebo in the prevention of acute diarrhea during pelvic radiation therapy: results of North Central Cancer Treatment Group protocol N00CA. *J Clin Oncol* 2006;24(18S):8506.

19. Moertel CG, Schutt AJ, Reitemer RJ, et al. Corticosteroid therapy of preterminal gastrointestinal cancer. *Cancer* 1974;33:1607–1609. [4135151]

20. Moertel CG, Kvols LK, Rubin J. A study of cyproheptadine in the treatment of metastatic carcinoid tumor and the malignant carcinoid syndrome. *Cancer* 1991;67:33–36. [1985720]

21. Kardinal CG, Loprinzi CL, Schaid DJ, et al. A controlled trial of cyproheptadine in cancer patients with anorexia and/or cachexia. *Cancer* 1990;65:2657–2662. [2187585]

22. Loprinzi CL, Ellison NM, Schaid DJ, et al. A controlled trial of megestrol acetate in patients with cancer anorexia and/or cachexia. *J Natl Cancer Inst* 1990;82:1127–1132. [2193166]

23. Loprinzi CL, Michalak JC, Schaid DJ, et al. Phase III evaluation of four doses of megestrol acetate as therapy for patients with cancer anorexia and/or cachexia. *J Clin Oncol* 1993;11:762–767. [8478668]

24. Goldberg RM, Loprinzi CL, Mailliard JA, et al. Pentoxifylline for treatment of cancer anorexia and cachexia? a randomized, double-blinded, placebo controlled trial. *J Clin Oncol* 1995;13:2856–2859. [7595749]

25. Rowland KM Jr, Loprinzi CL, Shaw EG, et al. Randomized double blind placebo controlled trial of cisplatin and etoposide plus megestrol acetate/placebo in extensive stage small cell lung cancer. *J Clin Oncol* 1996;14:135–141. [8558188]

26. Loprinzi CL, Goldberg RM, Su JQ, et al. Placebo-controlled trial of hydrazine sulfate in patients with newly diagnosed non-small cell lung cancer. *J Clin Oncol* 1994;12:1126–1129. [8201374]

27. Loprinzi CL, Kuross SA, O'Fallon JR, et al. Randomized, placebo-controlled evaluation of hydrazine sulfate in patients with advanced colorectal cancer. *J Clin Oncol* 1994;12:1121–1125. [8201373]

28. Loprinzi CL, Kugler JW, Sloan JA, et al. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *J Clin Oncol* 1999;17:3299–3306. [10506633]

29. Jatoi A, Windschitl HE, Loprinzi CL, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group Study. *J Clin Oncol*

2002;20:567–573. [11786587]

30. Jatoi A, Rowland K, Loprinzi CL, et al, for the North Central Cancer Treatment Group. An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: a North Central Cancer Treatment Group and National Cancer Institute of Canada collaborative effort. *J Clin Oncol* 2004;22:2469–2476. [15197210]

31. Loprinzi C, Schaid D, Dose AM, Burnham N, Jensen M. Body composition changes in patients who gain weight while receiving megestrol acetate. *J Clin Oncol* 1993;11:152–154. [8418227]

32. Loprinzi CL, Jensen MD, Jiang NS, Schaid DJ. Effect of megestrol acetate on the human pituitary-adrenal axis. *Mayo Clin Proc* 1992;67:1160–1162. [1469926]

33. Jatoi A, Foster N, Wieland B, et al. The proteolysis-inducing factor: in search of its clinical relevance in patients with metastatic gastric/esophageal cancer. *Dis Esophagus* 2006;19:241–247. [16866854]

34. Jatoi A, Loprinzi CL, Klee GG, Sloan J. Neuropeptide Y, leptin, and cholecystokinin 8 in patients with advanced cancer and anorexia: a North Central Cancer Treatment Group investigation. *Cancer* 2001;92:629–633. [11505408]

35. Jatoi A, Yamashita J, Sloan JA, et al. NCCTG 95-92-55: does megestrol acetate down-regulate interleukin-6 patients with cancer-associated anorexia and weight loss? a North Central Cancer Treatment Group investigation. *Support Care Cancer* 2002;10:71–75. [11777191]

36. Jatoi A, Kumar S, Sloan JA, Nguyen PL. On appetite and its loss. *J Clin Oncol* 2000;18:2930–2932. [10920143]

37. Goldberg RM, Loprinzi CL, O'Fallon JR, et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *J Clin Oncol* 1994;12:155–158. [8270972]

38. Loprinzi CL, Michalak JC, Quella SK, et al. Megestrol acetate for the prevention of hot flashes. *N Engl J Med* 1994;331:347–352. [8028614]

39. Barton DL, Loprinzi CL, Quella SK, et al. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol* 1998;16:495–500. [9469333]

40. Pockaj BA, Loprinzi CL, Sloan JA, et al. Pilot evaluation of black cohosh for the treatment of hot flashes in women. *Cancer Invest* 2004;22:515–521. [15565808]

41. Loprinzi CL, Sloan JA, Perez EA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Oncol* 2002;20:1578–1583. [11896107]

42. Loprinzi CL, Kugler JW, Sloan JA, et al. Randomized phase III controlled trial of venlafaxine in the management of hot flashes. *Lancet* 2000;356:2059–2063. [11145492]

43. Loprinzi CL, Levitt R, Barton D, et al. Phase III comparison of depomedroxyprogesterone acetate to venlafaxine for managing hot flashes: North Central Cancer Treatment Group Trial N99C7. *J Clin Oncol* 2006;24:1409–1414. [16505409]

44. Pockaj BA, Gallagher J, Loprinzi CL, et al. A phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG trial N01CC1. *J Clin Oncol* 2006;24:2836–2841. [16782922]

45. Loprinzi CL, Pisansky TM, Fonseca R, et al. Pilot evaluation of venlafaxine hydrochloride for the therapy of hot flashes. *J Clin Oncol* 1998;16:2377–2381. [9667254]

46. Quella SK, Loprinzi CL, Sloan J, et al. Pilot evalu-

ation of venlafaxine for the treatment of hot flashes in men undergoing androgen ablation therapy for prostate cancer. *J Urol* 1999;162:98–102. [10379749]

47. Perez DG, Loprinzi CL, Sloan J, et al. Pilot evaluation of bupropion for the treatment of hot flashes. *J Palliat Med* 2006;9:631–637. [16752968]

48. Perez DG, Loprinzi CL, Barton DL, et al. Pilot evaluation of mirtazapine for the treatment of hot flashes. *J Support Oncol* 2004;2:50–56. [15330372]

49. Loprinzi L, Barton DL, Sloan JA, et al. Pilot evaluation of gabapentin for treating hot flashes. *Mayo Clin Proc* 2002;77:1159–1163. [12440550]

50. Barton DL, Loprinzi CL, Novotny P, et al. Pilot evaluation of citalopram for the relief of hot flashes. *J Support Oncol* 2003;1:47–51. [15352642]

51. Loprinzi CL, Barton DL, Carpenter LA, et al. Pilot evaluation of paroxetine for treating hot flashes in men. *Mayo Clin Proc* 2004;79:1247–1251. [15473404]

52. Barton DL, Loprinzi C, Atherton PJ, et al. Dehydroepiandrosterone for the treatment of hot flashes: a pilot study. *Support Cancer Ther* 2006;3:91–97.

53. Loprinzi CL, Flynn PJ, Carpenter LA, et al. Pilot evaluation of citalopram for the treatment of hot flashes in women with inadequate benefit from venlafaxine. *J Palliat Med* 2005;8:924–930. [16238505]

54. Quella SK, Loprinzi CL, Barton DL, et al. Evaluation of soy phytoestrogen for the treatment of hot flashes in breast cancer survivors: an NCCTG trial. *J Clin Oncol* 2000;18:1068–1074. [10694559]

55. Pandya KJ, Raubertas RF, Flynn PJ, et al. Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. *Ann Intern Med* 2000;132:788–793. [10819701]

56. Hammack JE, Michalak JC, Loprinzi CL, et al. Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum-induced peripheral neuropathy. *Pain* 2002;98:195–203. [12098632]

57. Wong GY, Michalak JC, Sloan JA, et al. A phase III double blinded, placebo controlled, randomized trial of gabapentin in patients with chemotherapy-induced peripheral neuropathy—a North Central Cancer Treatment Group study. *J Clin Oncol* 2005;23(16S):8001.

58. Renno SI, Rao RD, Sloan JA, et al. The efficacy of lamotrigine in the management of chemotherapy-induced peripheral neuropathy: a phase III randomized, double blind, placebo-controlled NCCTG trial, N01C3. *J Clin Oncol* 2006;24(18S):8530.

59. Jacobson SD, Loprinzi CL, Sloan JA, et al. Glutamine does not prevent paclitaxel-associated myalgias and arthralgias. *J Support Oncol* 2003;1:274–278. [15334869]

60. Witzig TE, Silberstein PT, Loprinzi CL, et al. A phase III randomized double-blind study of epoetin alfa versus placebo in anemic patients with cancer undergoing chemotherapy. *J Clin Oncol* 2005;23:2606–2617. [15452187]

61. Steensma DP, Molina R, Sloan JA, et al. Phase III study of two different dosing schedules of erythropoietin in anemic patients with cancer. *J Clin Oncol* 2006;24:1079–1089.

62. Williams MS, Burk M, Loprinzi CL, et al. Phase III double-blind evaluation of an aloe vera gel as a prophylactic agent for radiation-induced skin toxicity. *Int J Radiat Oncol Biol Phys* 1996;36:345–349. [8892458]

63. Loprinzi CL, Abu-Ghazaleh S, Sloan JA, et al.

References continued on page 128

Phase III randomized double-blind study to evaluate the efficacy of polycarbophil-based vaginal moisturizer in women with breast cancer. *J Clin Oncol* 1997;15:969-973. [9060535]

64. Vivino FB, Al-Hashimi I, Khan Z, et al. Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial. P92-01 Study Group. *Arch Intern Med* 1999;159:174-181. [9927101]

65. Barton DL, Loprinzi CL, Wender DB, et al. Transdermal testosterone in female cancer survivors with decreased libido. *J Clin Oncol* 2006;24(18S):8507.

66. Davis T, Miser AW, Loprinzi CL, et al. Comparative

morphine pharmacokinetics following sublingual, intramuscular and oral administration in patients with cancer. *Hosp J* 1993;9:85-90. [8406404]

67. Wilwerding MB, Loprinzi CL, Mailliard J, et al. A randomized crossover evaluation of methylphenidate in cancer patients receiving strong narcotics. *Support Care Cancer* 1995;3:135-138. [7539701]

68. Chong SF, Bretscher ME, Mailliard JA, et al. Pilot study evaluating local anesthetics administered systemically for treatment of pain in patients with advanced cancer. *J Pain Symptom Manage* 1997;13:112-117. [9095569]

69. Hammack JE, Mailliard JA, Loprinzi CL, et al. Transdermal fentanyl in the management of cancer pain in ambulatory patients: an open-label pilot

study. *J Pain Symptom Manage* 1996;12:234-240. [8898507]

70. Ellison N, Loprinzi CL, Kugler J, et al. Phase III placebo-controlled trial of capsaicin cream in the management of surgical neuropathic pain in cancer patients. *J Clin Oncol* 1997;15:2974-2980. [9256142]

71. Miser AW, Goh TS, Dose AM, et al. Trial of a topically administered local anesthetic (EMLA cream 5%) for pain relief during central venous port accesses in children with cancer. *J Pain Symptom Manage* 1994;9:259-264. [8089542]

72. Loprinzi CL, Kugler JW, Sloan JA, et al. Lack of effect of coumarin in women with lymphedema after treatment for breast cancer. *N Engl J Med* 1999;340:346-350. [9929524]