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SYMPTOM CLUSTERS IN SUPPORTIVE & PALLIATIVE CARE: MOVING TOWARD THE NEW FRONTIER IN MANAGING CANCER PATIENTS

A continuing education monograph
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Jointly sponsored by the University of Kentucky College of Medicine and Continuing Edge

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Program Overview

Cancer patients may experience multiple concurrent symptoms—symptom clusters—caused by their disease, their treatment, or a combination of both. The complex relationships between and among symptoms, as well as their clinical antecedents and consequences, have not been well described. Studying the complex symptoms of oncology patients will yield increased understanding of the patterns of association, interaction, and synergy among symptoms that produce specific clinical outcomes. It will also provide a scientific basis and new directions for clinical assessment and intervention.

The majority of clinical studies on symptoms associated with cancer are focused on a single symptom rather than on clusters. Although this approach has led to advances in our understanding of a particular symptom, patients rarely present with a single symptom. Therefore, even though research focused on single symptoms needs to continue, it is imperative that symptom management research begins to focus on evaluating multiple concurrent symptoms, using cross-sectional and longitudinal study designs. In addition, research needs to focus on evaluating the relationships between symptoms, as well as specific interventions and patient outcomes.

Recognition of symptom clusters should help the understanding of symptom pathophysiology and the targeting of therapies that perhaps can be used to relieve multiple symptoms in that cluster. This could result in improved quality of life for patients with advanced cancer and perhaps reduce polypharmacy, lessen drug side effects, and have pharmacoeconomic benefits. Symptom clustering in cancer patients is clearly both an emerging field of investigation and also a timely topic for continuing education regarding patient management. This monograph discusses symptom clustering involving fatigue, pain, thrombosis, nausea, and vomiting in the context of disease effects and chemotherapy-associated effects.

Educational Objectives

At the conclusion of this activity, participants should be better able to:

- Assess recent advances in defining and managing symptom clusters in cancer patients
- Discuss the management of early and delayed-onset chemotherapy-induced nausea and vomiting (CINV) and identify key elements of the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines
- Define breakthrough cancer pain, its causes, and options for managing breakthrough pain (BTP) in cancer patients
- Identify fatigue as an expected outcome of cancer itself in addition to cancer treatments and discuss its management
- Discuss the importance of recognizing and managing cancer-related thrombosis and identify key components of the recent NCCN guidelines

Intended Audience

This program has been designed for medical oncologists and oncology nurses.

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Faculty Member	*Disclosure*
Stuart M. Lichtman, MD, FACP	Speaker's bureau for Amgen, sanofi-aventis
Sonia Ancoli-Israel, PhD	Discusses off-label treatments that are commonly used for insomnia Speaker's bureau for Cephalon, Inc, King Pharmaceuticals, Inc., Neurocrine Biosciences, Inc., sanofi-aventis, and Sepracor, Inc. Consultation fees from Acadia, Cephalon, Inc., Ferring Pharmaceuticals, GlaxoSmithKline, King Pharmaceuticals, Inc., Merck, Neurocrine Biosciences, Inc., Neurogen, Inc., sanofi-aventis, Sepracor, Inc., and Takeda Pharmaceuticals North America, Inc.
Richard J. Gralla, MD	Discusses Abstract #9111 from the ASCO 2007 meeting which describes an investigational use of the antiemetic aprepitant; identifies that this is an investigational use of this approved agent. Consultation fees from Merck, Helsinn, MGI Pharma
Neal E. Slatkin, MD	Discusses unlabeled/investigational use of morphine, oxycodone, hydromorphone for cancer BTP Speaker's bureau for Pfizer, Ortho-Biotech, Cephalon, Valeant; grant/research support from Bioscience Delivery, Cephalon, Sucampo, Pfizer, Wyeth; consultation fees from Valeant, Cephalon, Wyeth
Michael B. Streiff, MD	Speaker's bureau for sanofi-aventis, GlaxoSmithKline; consultation fees from sanofi-aventis, Eisai

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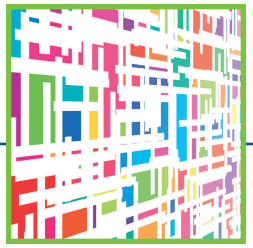


What Do We Currently Know About Symptom Clusters in Cancer Patients?

Stuart M. Lichtman, MD, FACP

Abstract

Much progress has been made in the treatment of cancer yet this disease and its management are widely known to be associated with a constellation of adverse effects. Attempts to ameliorate these adverse effects have largely relied on approaching and treating symptoms individually. It is possible that treatment may be optimized if related symptoms — symptom clusters — can be identified and dealt with simultaneously. For example, the symptoms of fatigue, pain, sleep deprivation, and depression are often seen together in cancer patients. Together, these may be considered as the "pain cluster." Other proposed clusters include the fatigue/anorexia-cachexia cluster, the neuropsychological cluster, the upper gastrointestinal cluster, the nausea and vomiting cluster, the aerodigestive cluster, and the debility cluster. Symptoms need not necessarily share a common etiology to be grouped together in a cluster (although some may have a common etiology), but a common pathophysiology may be implied. More research is needed to determine the relationships between baseline factors and the development of symptom clusters and to determine the precise role of clusters in treatment.

Introduction

A key aspect of the overall management of patients with cancer is controlling symptoms that interfere with patients' quality of life.[1] Cancer patients may present with any of a very large number of symptoms that may negatively impact patient well-being.[2,3] In one study of 1000 cancer patients, 38 different symptoms were reported, and each was reported by at least 3% of patients with known symptom status.[3] Pain, easy fatigue, nausea, and vomiting were reported by 84%, 69%, 36%, and 23% of patients with known symptom status, respectively, and these were each among the most commonly reported symptoms. Recent studies of patients with cancer have shown that patients with advanced cancer are likely to have multiple chronic symptoms that are moderate or severe in intensity. These symptom clusters are closely related to age and performance status as well as the patient's prognosis.[1]

Symptom Clusters

Symptom clusters in cancer patients have been defined as three or more concurrent symptoms that are related to each other. The suggested strength of those relationships has not been specified and the symptoms within a cluster are not required to have the same etiology. In addition, the amount of time that all of the symptoms within the clusters need to be present to be considered a "cluster" has not been specified. Nevertheless, it has been suggested that symptom clusters have an adverse effect on patient outcomes and may have a synergistic effect as a predictor of patient morbidity.[4]

While operational criteria for the definition of a symptom cluster in cancer patients remain to be fully described, results from one recent study of 25 symptoms in a cohort of 922 patients employed cluster analysis in conjunction with hierarchical analysis to define symptom clusters. In this analysis, a correlation ≥ 0.68 between pairs of symptoms was the threshold for grouping symptoms into a cluster. This approach identified seven clusters, as listed in Table 1.[1] The investigators who carried out this analysis suggested that understanding these clusters and their underlying pathophysiology has the potential to guide targeting of therapies that may benefit several symptoms within the cluster. Such an approach has the potential to decrease polypharmacy and improve quality of life for cancer patients.[1]

Pain-Depression-Fatigue: A Common and Well-Described Symptom Cluster in Cancer Patients

Pain, depression, and fatigue often occur together in patients with cancer. Results from a recent analysis of data from the Health and Retirement Study provided strong evidence for the comorbidity of these three symptoms in individuals with and without cancer.[5] Analysis of results for 2161 subjects with a history of cancer and 15049 without cancer history indicated that the prevalences of pain (33% versus 29%), depression (21% versus 18%), and fatigue (25% versus 18%) were all significantly higher in patients with cancer.[5] Further analysis of information from these two groups indicated that 7.8% of subjects

Table 1. Symptom Clusters in Cancer Patients Demonstrated by Correlational Analysis

1. The fatigue–anorexia–cachexia cluster: easy fatigue, weakness, anorexia, lack of energy, dry mouth, early satiety, weight loss, taste changes
2. The neuropsychological cluster: sleep problems, depression, anxiety
3. The upper gastrointestinal cluster: dizzy spells, dyspepsia, belching, bloating
4. The nausea and vomiting cluster: nausea, vomiting
5. The aerodigestive cluster: dysphagia, dyspnea, cough, hoarseness
6. The debility cluster: edema, confusion
7. The pain cluster: pain, constipation

Data from Walsh and Rybicki.[1]

with a history of cancer had the cluster of pain, fatigue, and depression versus 5.7% of those without a history of cancer.[5] Further analysis from this study indicated that the risk for at least 2 of the symptoms from the triad of pain, fatigue, and depression was increased by several other factors in addition to cancer history, including older age, female sex, and increasing number of comorbid medical conditions.[5]

Results from another study of cancer patients with bone metastases referred to a palliative radiotherapy clinic also identified symptoms that occur together. This study evaluated information collected from 518 patients with bone metastases using the Edmonton Symptom Assessment Scale (ESAS) with a symptom cluster defined as at least 2 symptoms that occur together, are stable, and are relatively independent of other clusters. Patients were assessed at 1, 2, 4, 8, and 12 weeks post-radiation treatment and analyses included both responders and nonresponders to radiation, with response defined by the International Bone Metastases Consensus Working Party. The four most common symptoms in this group of patients were poor sense of well-being (93.5%), fatigue (92.3%), pain (84.1%), and drowsiness (81.8%). A principal components factor analysis of study data identified three symptom clusters: 1) fatigue, pain, drowsiness, and poor sense of well-being; 2) anxiety and depression; and 3) shortness of breath, nausea, and poor appetite. Symptom clusters in these patients were not static and they changed following radiation therapy. Pain clustered with different symptoms or remained a separate symptom among patients who responded to radiotherapy. In contrast, symptom clusters remained largely consistent among those who did not respond to treatment.[6]

Why Do Symptoms Cluster in Cancer Patients?

The results summarized in the preceding sections provide strong support for the view that specific symptoms are likely to occur together in cancer patients. The reason for this grouping has not been elucidated, but several investigators have put forward hypotheses to explain symptom clustering in cancer patients.

Cleeland and colleagues have suggested that clustering of symptoms may be related to a phenomenon referred to as cytokine sickness.[7] Studies in animals and human patients have indicated that injection of pro-inflammatory cytokines, most notably interleukin (IL)-1, produce sickness-related behavior[8,9]; and Cleeland and coworkers have suggested that elevated levels of pro-inflammatory cytokines may underlie clustering of specific symptoms that occur commonly in patients with cancer. They noted that treatment of patients with chronic hepatitis C infection, chronic myelogenous leukemia, melanoma, or renal cell carcinoma with pro-inflammatory cytokines, including interferon and IL-2, may produce symptoms that include pain, fatigue, cognitive impairment, depression, and even psychosis.[7]

A recent animal study has provided clear support for the links between treatment with conventional chemotherapeutic agents, activation of cytokine-related pathways, and sickness symptoms. Wood and colleagues showed that injection of etoposide into mice induced production of IL-6 in macrophages and induced changes in behavior indicative of sickness in these animals, including decreased food intake, weight loss, reduced hemoglobin, and less voluntary wheel running.[10] Study results also indicated significant correlations between IL-6 concentration and fatigue, cachexia, and hemoglobin levels.[10] These findings from animal experiments are closely paralleled by results from a study that assessed the effects of chemotherapy in 90 breast cancer patients (70 treated with paclitaxel and 20 who received 5-fluorouracil, doxorubicin, and cyclophosphamide). Study results indicated that chemotherapy increased levels of IL-6, IL-8, and IL-10. The rise in IL-10 levels was correlated with development of joint pain and IL-8 concentrations were correlated with the emergence of flu-like symptoms.[11]

It is important to note that inflammatory pathways are also abnormally activated in untreated cancer patients. Evaluation of tissue from 56 patients with gastroesophageal cancer and 12 healthy controls indicated that pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, and tumor necrosis factor-∝ were significantly over-expressed in tissues from the cancer patients versus controls at both the mRNA and protein levels.[12]

Thus, a growing body of evidence provides support for the view that clustering of symptoms in cancer patients may have a clear biologic basis related to the impact to cancer therapy, and perhaps the disease itself, on inflammatory pathways.

Treatment of Symptom Clusters in Cancer Patients

Guiding principles for the treatment of cancer patients are listed in Table 2 and should provide the basis for management throughout the course of disease. These basic principles include active symptom evaluation and management at each patient

encounter and at every stage of the disease from diagnosis to end of life; a primary role for symptom management after surgery, chemotherapy, radiation, or hormonal or biologic therapies; the fact that clustering of symptoms with potentially overlapping etiology (eg, pain, depression, and fatigue) makes "pure" diagnoses for patients' symptoms relatively unimportant; and that management of symptoms can be accomplished with a combination of accepted and less accepted treatment modalities, particularly when the latter have favorable side effect profiles.[13]

Table 2. Basic Principles of Symptom Management in Cancer

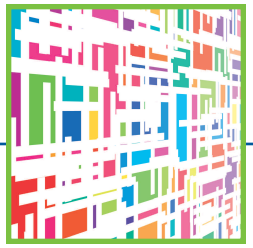
1. Active symptom evaluation and management (treatment) are integral to each patient encounter in the cancer setting
2. Active symptom management has a role in every stage of cancer treatment from the day of diagnosis on. Symptom management becomes the primary cancer therapy after surgery, chemotherapy, radiation, hormonal or biological therapies, either as transition back to follow-up by primary care provider or oncologist for survivors, or serves as a bridge to end-of-life care
3. Overlap in treatments for pain, depression, and fatigue make it less important to sort out pure diagnoses
4. Each syndrome has "accepted" treatment modalities, and others that are less accepted, which may or are even likely to minimize symptom burden
5. Use of less accepted modalities can be more easily recommended if they have favorable side-effect profiles or minimal toxicities

Reproduced with permission from Fleishman.[13]

The fact that symptoms cluster in cancer patients has the potential to simplify management and it is important to seek treatments that are accepted for one symptom, but also may have efficacy in the treatment of others. For example, cognitive-behavioral therapy (CBT) may be useful for pain management and fatigue reduction. Administration of erythropoietic agents can correct anemia and decrease fatigue.[13] Similarly, overlapping pain and fatigue in cancer patients have been shown to respond to a movement and exercise program. Results from one study of women undergoing radiotherapy for breast cancer showed that participation in an exercise program (an individualized, self-paced walking program carried out at home) significantly improved physical functioning and decreased symptom intensity, particularly fatigue, anxiety, and difficulty sleeping.[14]

Conclusions

We are just beginning to recognize symptom clusters in cancer patients and many questions remain to be answered. For example, we do not know whether they are disease- or problem-specific (ie, are specific symptom clusters more likely to be associated with specific cancers or therapies?), or whether they vary as a function of other patient characteristics (eg, patient age, sex, receiving curative versus palliative care). Longitudinal studies are also needed to determine whether clustering of symptoms changes over time; and it is particularly important to determine which therapies are most likely to have beneficial effects on multiple symptoms within a cluster.



Chemotherapy-Induced Symptom Clusters: Focus on Nausea and Vomiting

Richard J. Gralla, MD

Abstract

The control of emesis remains a key issue in supportive care in cancer. As both a side effect of treatment and a symptom in some malignancies, emesis is a persistent problem in all aspects of cancer care. Marked progress has occurred in the basic understanding of the mechanisms underlying emesis, the control of emesis, and in the documentation of the impact of nausea and vomiting on patients receiving anticancer treatment. Studies have shown that failure to control emesis causes an immediate major fall in patient-expressed quality of life. Patients rate their quality of life as unchanged 3 days after receiving chemotherapy if complete control of emesis is maintained. In contrast, those without complete control indicate a one-third decline in quality of life over the same time interval. Emesis affects many of the dimensions of quality of life. Patients experiencing emesis are unable to function normally. This affects social, psychological and spiritual factors beyond the physical and functional domains. The strategy for maintaining quality of life during treatment requires prevention of emesis and the assurance of complete control whenever possible. Adherence to the guidelines published in the last 2-3 years by major organizations, such as the American Society of Clinical Oncology (ASCO), the Multinational Association of Supportive Care in Cancer (MASCC), the European Society for Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN) leads to improved emetic control. All of these guidelines support the use of corticosteroids plus serotonin-receptor antagonists and neurokinin-receptor antagonists in appropriate risk groups to prevent acute and delayed emesis. Controlling emesis mitigates a variety of problems at the center of maintaining good quality of life during chemotherapy and in the whole spectrum of cancer care.

Introduction

Two of the most frequent adverse effects associated with cancer chemotherapy are nausea and vomiting. The effects of these problems are so broad that quality of life is negatively influenced if control of emesis is poor. This has been well demonstrated in a number of trials, including a major study using the validated Functional Living Index-Emesis (FLIE) and Functional Living Index-Cancer (FLIC). The study demonstrated that patients who experienced chemotherapy-induced emesis had a significant reduction in quality of life while no decline in quality of life was demonstrated for those who did not report emesis. Scores from the FLIE indicated that patients with cancer-induced emesis felt that vomiting, and to a slightly lesser extent nausea, negatively affected their ability to complete household tasks, enjoy meals, spend time with family and friends, and maintain daily function and recreation.[15]

The high impact of emesis in patients results from the fact that it affects all dimensions of quality of life. This is illustrated in Table 3, which lists the 5 major dimensions or domains incorporated in the concept of quality of life and the corresponding detrimental outcomes that may occur if emesis is poorly controlled. Whatever one's degree of acceptance of the concept of symptom clustering, it is clear that controlling emesis in patients receiving cancer chemotherapy is vital if one is to avoid many symptoms and maintain a good level of quality of life.

Table 3. The 5 Major Dimensions or Domains Incorporated in the Concept of "Quality of Life" and Corresponding Detrimental Outcomes That May Occur if Emesis is Poorly Controlled

Dimension	Examples
Physical	Emesis, fluid-electrolytes, fatigue, etc
Functional	Activities of daily living
Psychological	Anxiety (conditioned emesis), depression
Social	Work, role in family, sexuality
Spiritual	Dispiriting

Emesis associated with chemotherapy may be either acute (occurring within 24 hours after treatment) or delayed (occurring more than 24 hours after treatment). Delayed emesis occurs frequently after treatment with chemotherapeutic agents of moderate or high emetogenic risk, and occurs more frequently than estimated by many oncology nurses or physicians.[16] In one study, the observed rates of delayed emesis with highly and moderately emetogenic chemotherapy were 50% and 28%, respectively. The respective estimates by oncologists and nurses were 22% and 15%.[17] This underestimation can be associated with undertreatment of delayed emesis and with quality of life decreases that could have been prevented.

Antiemetic Therapy: Current Treatment Guidelines

Current guidelines from MASCC, ASCO, and NCCN indicate that there are three major classes of antiemetic drugs for first-line prevention in most settings: corticosteroids, serotonin-receptor antagonists (5-HT_3), and neurokinin type 1 (NK_1)-receptor antagonists; the guidelines note that different agents or combinations are suited for different clinical situations.[18-20] For example, for acute emesis, the most recent update of the ASCO guidelines (Table 4) recommends the combination of a serotonin-receptor antagonist, dexamethasone, and an NK_1-receptor antagonist, in patients receiving agents with high (>90%) emetic risk. Treatment with a serotonin-receptor antagonist plus a corticosteroid is recommended in patients receiving agents with moderate (30%-90%) emetic risk, unless the chemotherapy is a regimen based on anthracycline-cyclophosphamide ("AC" chemotherapy). In that instance, an NK_1-receptor antagonist is added. A single agent (dexamethasone alone or a serotonin-receptor antagonist) can be used for prevention in patients receiving agents with low (10%-30%) emetic risk.[18]

Table 4. Treatment Recommendations for Antiemetic Prophylaxis

Emetic Risk Categories	
High (> 90%) emetic risk	The three-drug combination of 5-HT_3 serotonin receptor antagonist, dexamethasone, and aprepitant is recommended. The Update Committee recommends a 5-HT_3 serotonin receptor antagonist only before chemotherapy.
Moderate (30%-90%) emetic risk	The three-drug combination of a 5-HT_3 receptor serotonin antagonist, dexamethasone, and aprepitant is recommended for patients receiving AC. For patients receiving other chemotherapy of moderate emetic risk, we continue to recommend the two-drug combination of a 5-HT_3 receptor serotonin antagonist and dexamethasone.
Low (10%-30%) emetic risk	Dexamethasone 8 mg is suggested for patients treated with agents of low emetic risk. No regular preventive use of antiemetics for delayed emesis is suggested.
Minimal (< 10%) emetic risk	It is suggested that for patients treated with agents of minimal emetic risk, no antiemetic be routinely administered before chemotherapy. No regular preventive use of antiemetics for delayed emesis is suggested.

The update committee suggests that, when combination chemotherapy is given, the patient should be given antiemetics for the chemotherapeutic agent of greater emetic risk. 5-HT_3 = serotonin type 3 receptor; AC = anthracycline plus cyclophosphamide. Adapted with permission from the updated 2006 ASCO Recommendations for Antiemetics in Oncology.[18]

Efficacy of Specific Treatments

Serotonin-receptor antagonists

Serotonin-receptor antagonists have been used for prevention of chemotherapy-induced emesis for nearly two decades. Agents in this class include ondansetron, granisetron, tropisetron, dolasetron, and palonosetron. While all of these drugs have demonstrated efficacy, there are some studies suggesting that the newest member of this class, palonosetron, may be more efficacious. Palonosetron has preclinical advantages in that it has markedly greater binding affinity for the 5-HT_3 receptor, and a longer half-life in the blood than the older serotonin-receptor antagonists. Single doses of palonosetron have been compared with ondansetron in one phase 3 trial and with dolasetron in a second phase 3 trial. A total of 1132 patients receiving moderately emetic chemotherapy were included in these trials.

Superior results in acute and delayed emesis were observed with palonosetron over the comparative agents in each study.[21] Both these studies used single doses of single agents. Comparative studies with combinations of antiemetics or with continued dosing have not been reported.

NK_1-receptor antagonists

Substance P is a tachykininan, an 11-amino-acid regulatory peptide that is found in many parts of the central, peripheral, and enteric nervous systems. Substance P is the natural ligand for the NK_1 receptor, and in animals, substance P administration can cause emesis.[22] In the laboratory, NK_1-receptor antagonists have a broad spectrum of antiemetic activity. This activity has been shown to inhibit emesis induced by centrally acting agents (eg, apomorphine and loperimidine) and peripherally acting drugs (eg, copper sulfate and cisplatin).[22]

Currently, the only NK_1-receptor antagonist commercially available (or with reported results of phase 3 trials at the time of this writing) is aprepitant. Phase 3 studies demonstrated that aprepitant provides significant added efficacy when combined with a standard treatment using a serotonin-receptor antagonist and a corticosteroid for preventing both acute and delayed emesis in patients receiving high-risk chemotherapy (cisplatin) and moderately emetic chemotherapy ("AC"). As an example, a multicenter, randomized, double-blind, placebo-controlled parallel-group study included 568 patients treated with cisplatin chemotherapy. These patients were randomized to receive either ondansetron plus dexamethasone or aprepitant plus ondansetron plus dexamethasone. The triple-drug combination was significantly superior to standard treatment; over the entire 5-day observation period after chemotherapy, 62.7% of patients in the aprepitant 3-agent group and 43.3% who received the 2-agent standard treatment had complete responses (no emesis and no rescue therapy). For acute emesis, the complete response rates were 82.8% and 68.4%, respectively. For days 2–5, the respective complete response rates were 67.7% and 46.8%.[23] A second similar comparison of aprepitant plus ondansetron and dexamethasone versus ondansetron and dexamethasone in 530 patients receiving ≥ 70 mg/m^2 cisplatin indicated that the addition of aprepitant to standard treatment resulted in significantly lower risk for emesis on days 1-5, day 1, and days 2-5.[24]

Additional analyses of these results have demonstrated that men and women have the same degree of control of both acute and delayed emesis when aprepitant is added to the standard regimen. This is particularly important in that it has

Table 5. Efficacy of Aprepitant plus Ondansetron and Dexamethasone Versus Ondansetron and Dexamethasone Only in Preventing Acute and Delayed Emesis in Men and Women Receiving Cisplatin (≥ 70 mg/m²)

	Aprepitant regimen	Control regimen
Acute		
All patients	86%	73%
Women	86%	66%
Men	87%	80%
Delayed		
All patients	72%	51%
Women	70%	45%
Men	73%	56%

Data from Hesketh et al.[25]

previously been more difficult to control emesis in women. However, when aprepitant is added to therapy, this difference disappears, and equivalent complete response rates are seen for both men and women (Table 5).[25]

Clinical trial results have also shown that the aprepitant-containing three-drug combination provides sustained efficacy over multiple chemotherapy cycles. In a recent study, 866 women with breast carcinoma who were previously untreated with chemotherapy were treated with cyclophosphamide alone or in combination of with doxorubicin or epirubicin. As in the studies described above, patients were randomly assigned to receive either aprepitant plus ondansetron and dexamethasone or only the serotonin-receptor antagonist and the corticosteroid. Data on nausea, emesis, and use of rescue medication were collected over four cycles of chemotherapy and a complete response to treatment was defined as no emesis or use of rescue therapy. Complete response rates declined over cycles of chemotherapy, but remained significantly higher with the aprepitant-containing regimen versus two-drug treatment over the duration of follow-up.[26] As an example, the rates for the complete control of vomiting (the most accurately measured endpoint) were 63% for those on the 3-drug regimen and 39% for those receiving only the 2-agent standard regimen (Figure 1). The rate of discontinuation of chemotherapy before completion of all four cycles was lower in the patients who had aprepitant added to ondansetron and dexamethasone.[26]

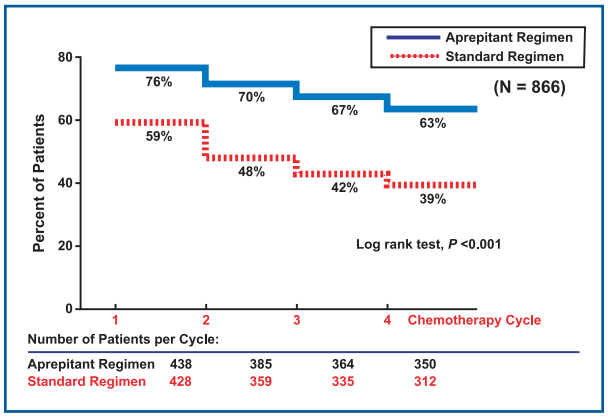
Aprepitant has been studied as a second-line or "salvage" therapy in patients receiving AC chemotherapy not effectively controlled by the combination of a serotonin-receptor antagonist and dexamethasone in their first treatment cycle. Forty-two women were enrolled in the trial. Of these, 34 women did not have complete emetic control with their first cycle of treatment. In cycle 2, all treatments remained the same except that aprepitant was added to therapy. During cycle 1, only 38% of patients had no emesis; the 34 patients who had emesis during the first cycle had a much higher complete control rate of emesis in the second cycle—79%—with the addition of aprepitant.[27]

Aprepitant, palonosetron, and dexamethasone have recently been combined in an investigational single-dose regimen which is being studied to determine whether it would maintain or improve upon efficacy while providing maximum convenience in that all agents were given only prior to chemotherapy. In this interesting study, the typical 3-day aprepitant dose was given as 1 oral administration (a total of 285 mg) plus palonosetron at the usual 0.25 mg IV dose, plus dexamethasone at 20 mg orally. The 41 previously untreated patients were evaluated for protection from vomiting and nausea over the ensuing 5 days following AC chemotherapy. The percentages of patients with no emesis were 100% for acute emesis and 95% for all 5 post-treatment days. The compelling results seen with higher-dose aprepitant as part of a 3-drug single-day treatment indicate that this strategy deserves further study in large randomized trials.[28]

Conclusions

Antiemetics continue to be crucial in the treatment of patients with most malignancies. These agents decrease chemotherapy-induced emesis and help preserve quality of life in patients receiving chemotherapy. They also permit safe delivery of chemotherapy on an outpatient basis. Newer antiemetic agents and the employment of combination therapy significantly improve control in both acute and delayed emesis. Effective management of emesis and related symptoms (eg, nausea, decreased appetite, symptoms associated with fluid and electrolyte loss) is increasingly important as new anticancer agents are introduced and as chemotherapy is used in a broader range of patients.

Figure 1. Sustained No Vomiting Rate ("AC" Chemotherapy) over Four Cycles of Chemotherapy in Patients Receiving Aprepitant plus Ondansetron and Dexamethasone Versus Ondansetron and Dexamethasone Only



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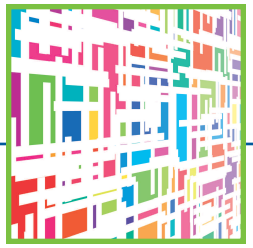


The Pain Cluster and Managing Breakthrough Pain

Neal E. Slatkin, MD

Abstract

Though cancer pain is often considered as a unified concept, there are at least two distinct core components of its clinical presentation. The first is the tendency for cancer pain to influence, and in turn be influenced by, other common symptoms of cancer such as fatigue and depression. The recognition that these symptoms often occur together in cancer patients has provided much of the impetus for development of the concept of symptom clusters. The second is the tendency for cancer pain to be both persistent (ie, to cause discomfort and distress throughout most of the day) and to also be marked by flares and exacerbations which occur independently or in relationship to activity. These latter occurrences have been termed "breakthrough" pain (BTP). This brief review relates the phenomenon of BTP to the construct of symptom clusters, emphasizing how the former may interfere with patient mood, function, and overall quality of life. The potential impact of the patient's emotional state on the appearance of pain flares is also considered. Potential strategies for controlling BTP, particularly those designed to more closely match the temporal profiles of this episodic pain are reviewed.

Introduction

Pain is one of the most prevalent and feared complications of cancer and its treatment.[29] It has been estimated that 50% of cancer patients will experience pain at some point during the course of their disease and that pain is present in 75% of patients with advanced or terminal illness.[30] Cancer-related pain, which may arise from either the cancer or its treatment, is often heterogeneous in its etiology and consequent to the different types of pain that may exist simultaneously in a single patient. Pain may be multifocal in patients with widespread metastases, and is not uncommonly severe, requiring high drug doses and rational polypharmacy to achieve optimal pain control. Additionally, pain arising directly from malignancies may remit in response to chemotherapy only to relapse as the benefits of such therapy begin to wane.

While there are many agents available for the management of cancer-related pain, selection of therapy may be limited by a number of factors, including clotting problems that may contraindicate specific medications; dysphagia and partial gastrointestinal obstruction that may interfere with absorption of orally administered agents; renal or hepatic insufficiency; and drug interactions associated with medications used to treat other acute or chronic conditions in these patients.

"Total pain" in the cancer patient has multiple dimensions that go beyond the pain that results from nociceptive stimuli.[31] Other physical conditions, such as fatigue, sleepiness, nausea, and constipation may impact the perception of pain or become independent causes of distress. Likewise, psychosocial and cognitive factors such as anxiety; depression; interpersonal distress arising from family, social, and financial problems; and normative distress due to alienation, existential, spiritual problems and the meaning of the pain in the context of the patient's illness, often contribute greatly to the patient's overall level of distress and their report of pain.[32]

Apart from occasional fluctuations in the level of persistent pain, the majority of cancer patients additionally experience periodic exacerbations of moderate-to-severe pain that occurs against a background of well-controlled persistent pain. Commonly referred to as breakthrough pain (BTP),[33] such flares of pain have been shown to negatively impact quality of life and levels of function. The remainder of this section of the monograph focuses on the characteristics, impact and management of BTP in cancer patients.

Characteristics and Prevalence of Breakthrough Pain

The consensus panel on the assessment and management of BTP has identified three types of BTP. The first of these is incident pain that results from activity or movement. Some causes of incident pain are predictable—such as those regularly associated with a particular movement—while others are unpredictable. Examples of the latter might be rib metastasis pain occasionally induced by cough, or abdominal pain following certain meals but not others. Incident pain that is predictable is often relatively responsive to anticipatory treatment with pharmacologic agents or to interventions aimed at the underlying cause of the pain. The second type of BTP is idiopathic or spontaneous pain. Examples include colicky abdominal cramping in a patient with peritoneal carcinomatosis, or paroxysmal

neuralgia superimposed upon background neuropathic pain. Since these types of pain cannot be anticipated, the thrust of treatment is often preventive; breakthrough episodes are treated with rapid-acting abortive medications. The third recognized type of BTP occurs when pain escalates just prior to the next scheduled dose of the around-the-clock (ATC) analgesic; this is sometimes referred to as end-of-dose failure. Although short-acting BTP medications may be used to bridge the gap in analgesia, treatment modifications in the face of BTP are usually focused on adjusting the drug regimen, such as by increasing the ATC dose or decreasing its dosing interval.[34]

Studies in diverse settings of cancer pain have shown a high prevalence of breakthrough pain. A survey of 164 cancer inpatients with controlled background pain indicated that 51.2% had experienced one or more episodes of BTP during the previous day.[33] Seventy percent of cancer outpatients being treated at a Veterans Administration Medical Center were found to have BTP, which was unpredictable in 58%. For most patients the increase in pain was very rapid, with a median time from onset to worst pain severity of 3 minutes.[35] Finally, a survey of 245 cancer patients admitted to a hospice indicated that 89% had BTP. More than one-third of the episodes of BTP experienced by patients in this study were described as severe or excruciating. Episodes of BTP occurred often (median number of episodes per day = 7) and most (59%) were unpredictable.[36]

The majority of BTP appears to arise from the same origin as persistent background pain[33] and shares the same characteristics. Results from one survey indicated that the background pain had both nociceptive and neuropathic features in 52% of patients, nociceptive characteristics alone in 38%, and was solely neuropathic in 10%. In another survey, the BTP itself was classified as somatic in 46% of patients, visceral in 30%, neuropathic in 10%, and having mixed etiology in 16%.[36]

Portenoy and others have identified a number of factors that increase the likelihood that a cancer patient will experience BTP.[33] These include worse Karnofsky Performance Status (KPS), the presence of metastatic or locally advanced disease, more persistent background pain, and more frequent prn dosing. An international survey of 1095 patients (64.8% with BTP) identified additional patient, disease, pain, and treatment characteristics significantly associated with increased risk for the development of BTP, including a multiplicity of pain locations; vertebral, pelvic, or long bone metastasis; metastatic plexopathy and radiculopathy; and the use of adjuvant treatments and nonopioid analgesics.[37]

Impact of Breakthrough Pain

BTP has a profoundly negative impact on quality of life for cancer patients. Results from the above-described study of 1095 patients with cancer-related pain indicated that the presence of BTP was a significant predictor of overall higher pain intensity.[38] Portenoy and colleagues assessed quality of life in 80 cancer patients with controlled background pain and no reported BTP the previous day and 84 similar patients who had controlled background pain but did report having BTP the previous day. Scores for the patients with BTP were significantly higher (ie, worse) for all components of the Brief Pain Inventory (BPI). Measurements of mood, depression, and anxiety were also worse in the patients with BTP versus those without these episodes.[33] Taylor and others found similar results in patients with non-cancer BTP, and additionally showed an improvement in these quality-of-life measures following medication treatment.[39]

For many patients, their worst pain is their BTP. Using a multivariate analysis, Hwang found that a patient's worst pain severity most highly predicted interference of their pain with function and this in turn was most highly predictive of declines in quality of life.[35] The occurrence of BTP also greatly increases healthcare utilization and the costs of care. Results from a survey of 1000 cancer patients indicated that the annual cost of pain-related hospitalizations, emergency department visits, and physician visits was $12 000 per year for patients with BTP versus $2400 per year for those without BTP.[40] Finally, patients with BTP are likely to report dissatisfaction with their pain treatment and control.[36]

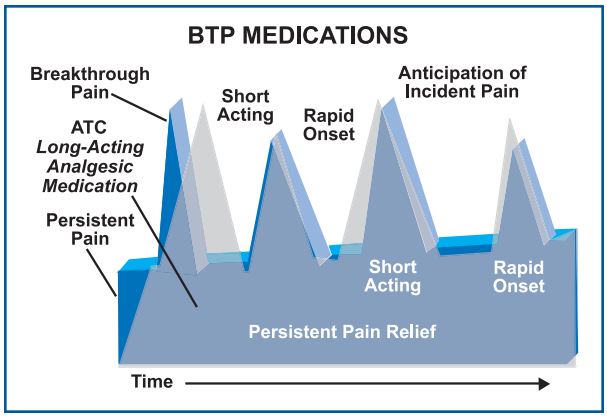
Treatment of Breakthrough Pain

A variety of approaches can be employed in managing the patient with BTP. Education is useful for many patients, particularly those with predictable incident BTP who often respond best to taking breakthrough medication in anticipation of planned activity. When this approach fails, patients can be instructed in modifying activities that result in BTP or, if necessary, in avoiding them completely. Management of end-of-dose BTP typically requires alteration of the ATC treatment regimen with increased doses or shorter dosing intervals. Other potential approaches to the management of BTP include radiation therapy, orthotic devices, surgical stabilization including vertebroplasty, and possibly radiofrequency lesioning.[41]

The pharmacologic management of idiopathic or unpredictable incident BTP is particularly challenging. The treatment selected should have pharmacokinetic and pharmacodynamic characteristics that match the temporal properties of these episodes. The peak intensity of these subtypes of BTP is reached rapidly after onset (typically within 3–5 minutes) and episodes are relatively brief, lasting about 30 to 60 minutes (Figure 2). An analgesic with a rapid onset of action and short duration of effect is therefore best suited for unpredictable episodes of BTP.[41]

Fentanyl is a potent, highly lipophilic synthetic opioid with an established safety profile, and is currently available in parenteral, transdermal and transmucosal formulations, with sublingual, intranasal, and inhaled delivery systems undergoing investigation. Due to its rapid parenteral/transmucosal distribution into the central nervous system, it is suited for novel, rapid-onset formulations that can be employed for the treatment of BTP.[41]

Figure 2. Temporal Characteristics of Persistent and Breakthrough Pain



Dark blue area indicates persistent or breakthrough pain. Shading indicates analgesic activity (note that this does not always match the intensity of pain).

Only two fentanyl-based formulations have been rigorously tested for the treatment of BTP in cancer patients and have FDA approval for this indication. The first approved rapid-onset preparation was oral transbuccal fentanyl citrate (OTFC). This formulation consists of a fentanyl citrate in a sugar matrix lozenge attached to a stick; the medication is administered by actively rubbing the lozenge inside the buccal mucosa. The high lipophilicity of the fentanyl and high vascularity of the buccal mucosa allows rapid absorption of medication into the bloodstream with maximum plasma drug concentrations reached in about 20 minutes. This preparation has been shown effective for the treatment of BTP and also has a favorable safety profile.

In a double-blind, double-dummy randomized trial, OTFC produced superior pain relief to immediate-release morphine at all time points from 15 to 60 minutes, and with a higher percentage of patients enjoying > 33% relief at 15 minutes.[42] In a retrospective review of chronic non-cancer BTP, patients reported significantly shorter times to meaningful and maximum pain relief with OTFC than their usual short-acting BTP medication.[39] A recent meta-analysis of clinical trials has demonstrated significant efficacy of OTFC over control treatment in providing pain relief at 15 minutes after administration (Table 6).[43] Most recently, both OTFC and intravenous morphine decreased BTP in cancer patients by > 33% at 15 minutes, with a greater degree of analgesia achieved with parenteral morphine at 15 but not 30 minutes.[44] The most common adverse events reported for OTFC in clinical trials include nausea, headache, somnolence, and dizziness.[45]

While OTFC has a good efficacy and safety record for the treatment of BTP, the formulation does have potentially important limitations, including a transbuccal bioavailability of only 22%,[46] potential child safety issues due its sugar base and resemblance to a "lollipop," the dependence of its efficacy on active administration, the attendant need for education on proper medication administration, and risk for dental caries.

Table 6. Oral Transbuccal Fentanyl Citrate Shows Superiority over Placebo, Normal Release Morphine, and Previous Rescue Medication for Relief of Cancer-Related BTP at 15 Minutes in a Review of Four Comparative Studies (N = 393)[a]

	OTFC Group		Control Group		
	N	Mean pain relief score (SD)[b]	N	Mean pain relief score (SD)[b]	*P* value for comparison
Christie 1998[c]	41	1.88 (1.06)	47	0.85 (0.63)	.0001
Coluzzi 2001[d]	75	1.36 (0.89)	75	1.11 (0.74)	≤ .009
Farrar 1998[e]	86	1.42 (0.76)	86	0.93 (0.81)	< .0001
Portenoy 1999[c]	31	2.01 (0.87)	48	1.23 (0.76)	< .003

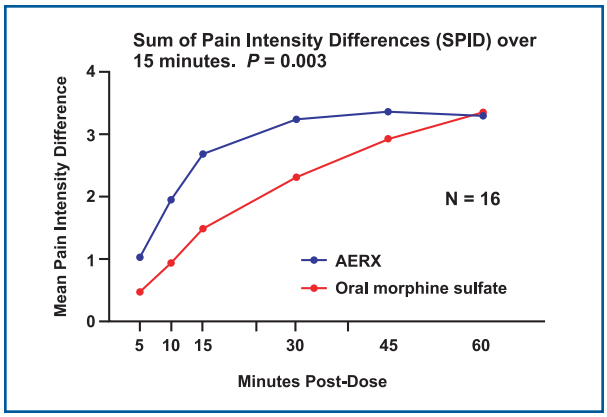
[a]Data from Zeppetella and Ribiero,[43] Coluzzi et al,[42] Portenoy et al.[47]
[b]Pain relief score based on 5-point scale (0 = no pain; 1 = slight pain; 2 = moderate pain; 3 = lots of pain; 4 = complete pain).
[c]Comparison between OTFC and participants' usual rescue medication.
[d]Comparison between OTFC and normal release morphine.
[e]Comparison between OTFC and placebo.
SD = Standard deviation.

The fentanyl buccal tablet (FBT) is a second-generation rapid-onset opioid developed to improve upon the pharmacokinetics of transbuccal delivery and the ease and predictability of administration. The FBT is formulated using technology that produces an effervescent reaction facilitating fentanyl absorption across the buccal mucosa. This formulation demonstrates higher fentanyl bioavailability and a shorter time to maximum concentration than OTFC.[46] The FBT has been shown to be effective for the treatment of BTP in cancer patients,[47] with statistically significant pain relief demonstrated in some patients at 10 minutes following use, and clinically significant relief in more than 50% of patients by 30 minutes. A number of potential advantages of FBT over OTFC can be identified including a lower requirement for patient education on route of administration and proper placement of the tablet, a much less conspicuous method of dosing, and a lower risk for dental caries.

Other novel routes of opioid delivery in the treatment of BTP include intranasal, sublingual, and pulmonary administration. For example, the AERx® PainManagement System (PMS) (Aradigm Corporation, Hayward, CA) employs 1-micron sized nozzles to allow fine particles of medications, such as morphine or fentanyl, to be delivered to the pulmonary alveolar bed. This leads to rapid absorption into systemic circulation,[48] providing fast relief from pain. This approach to morphine delivery has been demonstrated to provide more rapid reduction in pain intensity than oral morphine sulfate in cancer patients with BTP (Figure 3).[49]

Patient-controlled analgesia (PCA) can also be employed for the management of BTP. This approach provides flexible dosing and permits delivery of drug boluses for episodes of BTP. It also allows consistent medication delivery and it is very useful in patients with unstable pain. Disadvan-

Figure 3. Efficacy of Inhaled Versus Oral Morphine in Cancer Patients with BTP



Data from Slatkin.[49]

tages of PCA include the high cost of the pump, inconvenience associated with refilling the device, and safety concerns about bolus dosing in cognitively impaired patients.[50]

Conclusions

Breakthrough pain is a common and often poorly addressed symptom in many cancer patients, even in those with well-controlled persistent pain. Results from a large number of studies have shown that BTP is associated with increased functional impairment and decreased quality of life. These effects may alter patient perception of persistent pain. The presence of BTP is also associated with lower overall satisfaction with the pain control regimen.

Pharmacologic treatment for BTP should have pharmacokinetic and pharmacodynamic properties that match the temporal characteristics of BTP. Oral transmucosal fentanyl formulations, particularly FBT, are well suited for the treatment of BTP, and other approaches to rapid analgesic administration, such as inhaled morphine, are also worthy of additional study.

Managing Fatigue and Cluster Overlap

Sonia Ancoli-Israel, PhD

Abstract

Fatigue affects three-fourths of patients undergoing chemotherapy or radiation therapy and is a source of great concern to these individuals. Cancer-related fatigue is generally characterized by a subjective sense of persistent tiredness not commensurate with recent activity and not relieved by rest. Disruption of chronobiological functions, such as sleep patterns, contributes to fatigue in cancer patients; cancer patients have significantly more difficulty sleeping than healthy individuals. Although some studies have suggested that this may be a result of psychological distress and physical pain associated with cancer, other data suggest that difficulty in sleeping may be independent of these factors. Insomnia affects >50% of cancer patients, most of whom indicate that cancer exacerbated or caused their sleep difficulties.

Interventions for cancer-related fatigue include exercise, cognitive behavioral therapy (CBT), and pharmacologic interventions. Hematopoietic support that elevates hemoglobin levels has also been shown to relieve fatigue and improve quality of life in cancer patients. Other investigational interventions for fatigue include antidepressants, corticosteroids, and psychostimulants. Antidepressants have not improved fatigue in limited clinical trials; corticosteroids have been shown to temporarily decrease fatigue in short-term studies of metastatic cancer patients, but potential side-effect issues warrant longer-term evaluations. There have been very few well-controlled studies of traditional psychostimulant therapy in cancer patients with fatigue; however, two studies—one open-label and one double-blind—have shown improvements in fatigue and randomized controlled trials are currently ongoing.

Introduction

Fatigue is one of the most frequent complaints of cancer patients. It has been reported that over 75% of patients undergoing chemotherapy or radiation therapy report feeling tired and weak.[51,52] Cancer-related fatigue encompasses multiple domains, including physical, emotional, mental, and general/motivational[53,54]; and it is a condition about which cancer patients express great concern.[51] Cancer-related fatigue does not end when treatment is completed; it can persist for months or years after the end of therapy.[51]

Fatigue is generally defined as a state of weariness after a period of exertion—mental or physical—characterized by a decreased capacity for work and reduced efficiency to respond to stimuli. However, this definition does not fully describe the experience of cancer patients, who have a decreased capacity to carry out normal daily activities and an abnormally slow physical recovery from routine tasks. Fatigue in cancer patients is more severe than that experienced by healthy individuals; it is also more distressing and not relieved by rest.[55] The NCCN defines cancer-related fatigue as a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.[51]

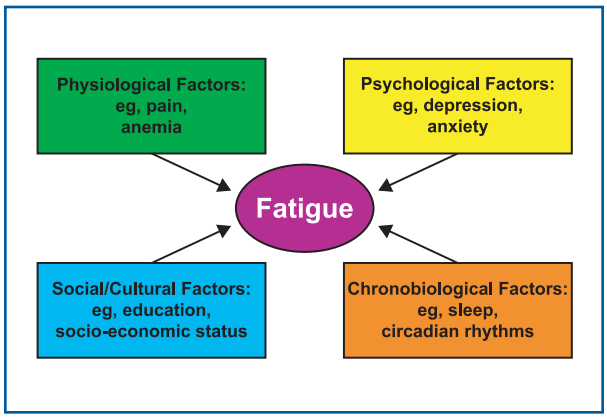
The impact of fatigue in patients with cancer is exacerbated due to the fact that it is underdiagnosed and undertreated.[51] Many patients do not discuss fatigue with their healthcare providers. Reasons for this lack of communication include the assumptions that fatigue is an expected outcome of their cancer treatment, that it will not persist, and that nothing could be done to improve their condition.[56]

Etiology of Fatigue in Cancer Patients

Physical, psychological, and social factors may all contribute to the development of fatigue in cancer patients (Figure 4). Physical factors that may lead to fatigue in cancer patients include cachexia, weight loss, and biochemical, hematological and endocrine abnormalities.[57] Development of cancer- or treatment-related anemia may be an important physical cause of fatigue in cancer patients.[58] Depression is a major psychological component of fatigue. It is common in both cancer patients and in others reporting fatigue. However, the cause and effect relationship between fatigue and depression in cancer patients has not been well established.[57]

Chronobiologic factors (eg, sleep disturbance, altered circadian rhythms) and social/cultural factors (eg, education and socioeconomic status) may also contribute to the development of fatigue in cancer patients.[57] The guidelines established by the NCCN suggest that pain, emotional distress, sleep disturbance, anemia, poor nutrition, altered activity levels, and comorbid diseases unrelated to cancer may all contribute to the development of fatigue in cancer patients.[51]

Figure 4. Factors that May Contribute to the Development of Fatigue in Cancer Patients



Reprinted with permission from Ancoli-Israel and Moore. The relationship between fatigue and sleep in cancer patients: a review. *Eur J Cancer Care.* Published by Wiley-Blackwell.[57]

Sleep Disruption in Cancer Patients

Sleep disruption is common in cancer patients.[59,60] Savard and colleagues have estimated the prevalence of insomnia in a cohort of 300 consecutive women who had been treated with radiotherapy for non-metastatic breast cancer. Study results indicated that 19% of the subjects met diagnostic criteria for an insomnia syndrome, and that insomnia was chronic in all but one of these individuals. Thirty-three percent of the patients began experiencing insomnia after the diagnosis of breast cancer and 58% reported that cancer either caused or aggravated their sleep difficulties. A number of factors were associated with increased risk for the development of insomnia. These included sick leave, unemployment, widowhood, lumpectomy, chemotherapy, and a less-severe cancer stage at diagnosis.[61]

It has been suggested that sleep problems in patients with cancer may result from the disease itself, or may be a part of a stress reaction to having cancer, be secondary to other cancer symptoms (eg, pain), or be an adverse reaction to cancer treatment.[62] However, sleep disturbances have been reported by cancer patients even when pain and anxiety were low, suggesting that the sleep problem may be independent of these psychological/physiological factors.[63]

A recent study by Ancoli-Israel and colleagues has demonstrated that many women with breast cancer are likely to experience disturbed sleep and fatigue prior to the initiation of chemotherapy. This study included 85 women with Stage I-III breast cancer who were scheduled to begin adjuvant or neoadjuvant anthracycline-based chemotherapy. Each subject had sleep/wake activity recorded with actigraphy for 72 consecutive hours and filled out questionnaires on sleep, fatigue, depression, and functional outcome. Study results indicated that the women slept for an average of 6.0 hours per night and napped for 1.1 hours during the day. Results obtained with the Pittsburgh Sleep Quality Index indicated disturbed sleep and poor sleep quality. The total score for this measure was 7.0 (any score > 5 is indicative of poor sleep). Women in this study also reported significant fatigue and there was a correlation between disturbed sleep and fatigue. Women with disturbed sleep were also more likely than those with normal sleep to report that cancer affected their ability to function. While none of the women in this study were clinically depressed, higher scores on the Center for Epidemiologic Studies Depression Scale (CES-D) were significantly correlated with poorer sleep, greater fatigue, and decreased ability to function. These results indicate that breast cancer patients with disturbed sleep experience significant daily dysfunction secondary to fatigue. They also suggest that strategies to improve disturbed sleep prior to initiation of chemotherapy may be beneficial in improving function in breast cancer patients.[64]

Evaluation and Treatment of Fatigue in Cancer Patients

Patient evaluation

The NCCN recommends that fatigue be screened for, assessed, and managed according to clinical practice guidelines. All patients should be screened for fatigue at their initial visit, at regular intervals during and following cancer treatment, and as clinically indicated. Severity of fatigue should be measured on a 0-10 scale (0 = no fatigue and 10 = worst fatigue imaginable) or categorically (none, mild, moderate, severe). Patients with moderate-to-severe fatigue (4-10 on the 10-point scale) should have a focused history that includes collection of information about disease status and treatment to rule out recurrence or progression, current medications and medication changes, review of systems, and an in-depth fatigue assessment (onset, pattern, duration, change over time, associated or alleviating factors, and interference with function). Careful attention should be paid to potentially treatable contributing factors that may include pain, emotional distress, sleep disturbance, anemia, nutritional abnormalities, activity level, and comorbid disease (Table 7).[51]

Treatment

Cancer patients with fatigue should receive adequate information about the causes and significance of fatigue and education regarding daily self-monitoring of fatigue levels and approaches to its management. They should also be reassured that treatment-related fatigue is not necessarily an indicator of disease progression.[51] A wide range of pharmacologic and non-pharmacologic interventions have been employed to manage fatigue in patients with cancer.

Pharmacotherapy

Pharmacologic interventions that have been employed in cancer patients with fatigue include hematopoietic growth factors to treat anemia, psychostimulants, antidepressant therapy, and corticosteroids.

Table 7. Recommended Evaluation for Cancer Patients With Moderate-to-Severe Fatigue

Focused History
- Disease status and treatment
  - ➤ Rule out recurrence or progression
  - ➤ Current medications/ medication changes
- Review of systems
- In-depth fatigue assessment
  - ➤ Onset, pattern, duration
  - ➤ Change over time
  - ➤ Associated or alleviating factors
  - ➤ Interference with function

Assessment of Treatable Contributing Factors
- Pain
- Emotional distress
  - ➤ Depression
  - ➤ Anxiety
- Sleep disturbance
- Anemia
- Nutrition assessment
  - ➤ Weight/caloric intake changes
  - ➤ Fluid electrolyte imbalance: sodium, potassium, calcium, magnesium
- Activity level
  - ➤ Decreased activity
  - ➤ Decreased physical fitness
- Comorbidities
  - ➤ Infection
  - ➤ Cardiac dysfunction
  - ➤ Pulmonary dysfunction
  - ➤ Renal dysfunction
  - ➤ Hepatic dysfunction
  - ➤ Neurologic dysfunction
  - ➤ Endocrine dysfunction (hypothyroidism, hypogonadism, adrenal insufficiency)

As noted above, anemia is common in cancer patients and low hemoglobin levels have been correlated with fatigue. A systematic review of results from clinical trials of erythropoiesis-stimulating agents (ESA), including epoetin or darbepoetin alfa, indicates that treatment with these growth factors can increase hemoglobin levels, decrease fatigue, increase activity levels, and improve quality of life in patients with cancer-related anemia.[65] (It should be noted that the FDA issued a label change for these agents in 2007 directing physicians to monitor hemoglobin levels so the patient takes the minimum ESA dosage needed to avoid a blood transfusion. The change was the result of recent clinical trials showing that patients with chronic kidney failure who take higher than the recommended dose of ESAs were at increased risk of death, strokes, heart attacks and blood clots; cancer patients not on chemotherapy taking recommended doses of ESAs also had an increased risk of death; and those taking ESAs at the recommended dose after orthopedic surgery experienced an increased risk of blood clots.[66])

Psychostimulants, most notably methylphenidate, have been employed to treat excessive daytime sleepiness secondary to insomnia in patients with cancer. Methylphenidate has been shown to be effective in relieving fatigue in cancer patients in several open-label studies and one double-blind trial. However, the potential benefits of this agent should be weighed against its common adverse events, including irritability, anorexia, insomnia, labile mood, nausea, and tachycardia.[65]

Studies of modafinil to treat fatigue as well as cognitive function in cancer patients have not yet been published, but preliminary findings from three studies presented at scientific conferences suggest that this treatment may provide benefit in reducing the severity of fatigue and improving some aspects of cognitive function.[67-69]

The antidepressant paroxetine has been evaluated in patients with cancer-related fatigue. In one study, 549 patients who reported fatigue during their second chemotherapy cycle were randomly assigned to 20 mg/day of paroxetine or placebo for 8 weeks. Assessments of fatigue and depression were performed at cycles 3 and 4 of chemotherapy. No difference was detected in fatigue between patient groups, but there was a significant between-group difference in severity of depression.[70] A second double-blind clinical trial of 94 breast cancer patients carried out by the same group indicated that treatment with paroxetine also relieved depression, but did not significantly improve fatigue in this group.[71]

Results from studies of corticosteroid administration indicated that these agents decreased fatigue, relieved pain, and improved quality of life in patients with metastatic cancers. It is important to note that these trials had short durations and that longer-term trials may be warranted because of the well-known side effects (eg, osteoporosis) of corticosteroids.[65]

Nonpharmacologic interventions

Results from a large number of studies have demonstrated that a wide range of nonpharmacologic interventions, including exercise and CBT, are effective in decreasing fatigue in cancer patients.

A large number of studies have demonstrated a significant benefit from exercise in patients with cancer-related fatigue. Results from these trials have demonstrated that both hospital- and home-based exercise programs can significantly decrease fatigue and psychological distress, and improve quality of life.[72-74]

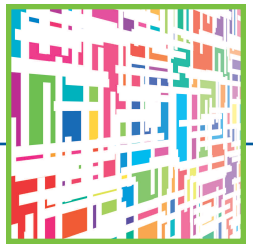
Cognitive-behavioral therapy (CBT) for insomnia has also been shown to have significant benefit in reducing the severity of insomnia and fatigue in cancer patients in controlled clinical trials. Results from a small study that included 10 patients with metastatic breast cancer and insomnia indicated that CBT resulted in improvements in sleep efficiency and total wake time. Treatment also decreased fatigue and improved mood and global and cognitive dimensions of quality of life.[75] A larger study that included 57 women with insomnia caused or aggravated by breast cancer indicated that 8 weekly sessions of CBT administered in a group setting resulted in significantly better subjective sleep indices, decreased use of medication, lower levels of depression and anxiety, and better quality of life than a control condition. These benefits were maintained up to 12 months after the intervention.[76]

The results summarized in this section provide clear support for the use of nonpharmacologic interventions in the

treatment of insomnia and fatigue in cancer patients. Such approaches may be particularly suited for this population because they have minimal risk for interacting with cancer treatment, do not add to the pharmacologic burden for the patient, and can target specific symptoms, (such as insomnia and fatigue) that are common in this group.[77]

Conclusions

Fatigue and sleep disturbance are both very common in cancer patients. These symptoms decrease patients' ability to carry out daily activities and decrease quality of life. Despite the availability of pharmacologic and nonpharmacologic treatments with proven benefit, fatigue is underdiagnosed and undertreated in this population. All cancer patients should be evaluated for fatigue and therapy should be initiated when appropriate. Aggressive intervention to decrease poor sleep, depression, and fatigue in cancer patients prior to the initiation of therapy may decrease the severity of these symptoms after the initiation of treatment. This suggestion is strongly supported by recent study results indicating all of these symptoms are exacerbated by cancer treatment regardless of their severity prior to intervention.[78]



Cancer-Related Thrombosis: Can It Be Related to a Symptom Cluster?

Michael B. Streiff, MD

Abstract

Venous thromboembolism (VTE) is a serious threat to the general population but is of particular concern in cancer patients. As a result of their disease and its treatment, cancer patients have a 4-7–fold increased risk of VTE compared to the general population. Despite widespread recognition of the association between VTE and cancer, prophylaxis remains underutilized. Consequently, health care quality organizations have made the use of risk-stratified VTE prophylaxis a priority for patient safety. Numerous clinical studies confirm the benefit of VTE prophylaxis. The first oncology-specific guidelines for the management of VTE—developed by the NCCN—recommend that all medical and surgical oncology patients receive risk-stratified VTE prophylaxis upon hospital admission. Pharmacologic prophylaxis with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH—eg, enoxaparin, dalteparin), or a pentasaccharide anticoagulant that selectively inhibits factor Xa (ie, fondaparinux) is preferred in the absence of contraindications. Since the risk of VTE in surgical oncology patients extends beyond the period of acute hospitalization, extended prophylaxis should be considered for high-risk patients following discharge. In contrast, routine use of anticoagulant-based central venous catheter prophylaxis is not supported by the literature. For cancer patients who develop VTE, more convenient treatment options such as fondaparinux or an LMWH that can be administered at home are replacing UFH as the standard of care for acute therapy. Since vitamin K antagonists such as warfarin are associated with inferior outcomes in cancer patients with VTE, NCCN guidelines recommend that physicians strongly consider employing monotherapy with a LMWH for the first 3-6 months of therapy.

Introduction

Venous thromboembolism is a common complication of cancer and its treatment, and is a significant source of morbidity and mortality in patients with malignancies.[79] Cancer has been shown to be a significant independent risk factor for the development of VTE and increases the risk of thrombotic events by 4-7–fold.[80,81] Venous thromboembolism has been demonstrated to occur in about 15% of cancer patients, and these events result in a 2-3–fold increase in mortality risk in this population.[82,83] Morbidity associated with VTE includes post-thrombotic syndrome (occurring in 37% of patients over 2 years of follow-up),[84] and recurrent thrombosis and bleeding (occurring in 21% and 12%, respectively, over 1 year).[85]

Despite the availability of a wide range of agents for VTE prophylaxis, the occurrence of VTE events is increasing in cancer patients. Over the period from 1979 to 1999, the incidence of venous thromboembolism in cancer patients increased from approximately 1.5 to 3.5 per 100 hospital discharges.[86]

Etiology of VTE in Cancer Patients

The pathophysiologic mechanisms that give rise to the increased risk for VTE in cancer patients are not fully understood. It has been noted that cancer patients have evidence of activation of the coagulation cascade, even in the absence of symptomatic thrombosis. Investigators have documented that cancer patients have elevated levels of several markers of activated coagulation including elevated levels of thrombin-antithrombin complexes, prothrombin fragment 1 + 2, and D-dimer.[87] The process by which cancer cells trigger activation of the coagulation cascade is multifactorial. A wide variety of cancer cells have been demonstrated to express tissue factor, a key cofactor in the initiation of coagulation, and cancer procoagulant, a cysteine protease that can activate coagulation factor X.[79] These factors directly activate the coagulation cascade. Tumor cells can also indirectly activate coagulation through the production of proinflammatory/procoagulant cytokines (such as IL-1, IL-8, and tumor necrosis factor-$\propto$) that trigger tissue factor expression by monocytes and endothelial cells, upregulate expression of anti-fibrinolytic proteins such as plasminogen activator inhibitor (PAI-1) and downregulate endogenous anticoagulants such as the protein C anticoagulant pathway. Interleukin-8 also acts as a chemoattractant for neutrophils, which may adhere to the vascular endothelium and promote thrombus formation.[88] Extrinsic compression of vessels by lymph node or tumor masses can lead to venous stasis and vessel wall injury that may also contribute to the development of VTE in cancer patients.[79,87]

Risk Factors for VTE in Cancer Patients

A number of factors are associated with an increased risk for thromboembolism in cancer patients. These risk factors include advanced age, the type (the risk is highest in patients with pancreatic and brain tumors) and extent (patients with metastatic cancer are at greater risk than those with localized disease) of cancer, major surgery, immobility, chemotherapy, hormonal therapy, radiotherapy, treatment with anti-angiogenic agents, central venous catheters, acute medical illness, a previous history of VTE, thrombophilia, and obesity.[88,89]

Failure to prescribe adequate prophylaxis also contributes to the increased burden of thrombotic disease experienced by cancer patients. Results from the FRONTLINE survey of 3891 respondents indicated that only 52% of surgeons and less than 5% medical oncologists routinely prescribed thromboprophylaxis in their cancer patients. In addition, 24% of medical oncologists and 11% of cancer surgeons reported using aspirin for VTE prophylaxis, despite the absence of good evidence supporting the effectiveness of this agent in the prevention of VTE in cancer patients.[90] These results highlight the need for continued educational programs that increase awareness among providers regarding the risk of VTE in cancer patients and optimal approaches to prophylaxis.

VTE Prophylaxis in Cancer Patients: Current Guidelines

The NCCN recommends that all cancer patients at risk receive prophylaxis against VTE. Patient characteristics placing them at high risk for thromboembolism are summarized in Table 8. Patients without contraindications to pharmacotherapy (ie, recent central nervous system bleeding, intracranial or spinal lesion at high risk for bleeding, significant active or chronic bleeding, thrombocytopenia, severe platelet dysfunction, underlying bleeding disorder, epidural anesthesia/lumbar puncture, or high risk for falls) should be treated with a LMWH (enoxaparin, tinzaparin, or dalteparin), the pentasaccharide fondaparinux, or UFH. Agents demonstrated to be effective for extended outpatient VTE prophylaxis include LMWH, fondaparinux, and warfarin adjusted to an International Normalized Ratio of 2 to 3. Those with a contraindication to anticoagulant prophylaxis should receive mechanical prophylaxis with graduated compression stockings and sequential compression devices until this contraindication is no longer present.[89]

Table 8. Risk Factors for VTE in Cancer Patients

- **Age**
- **Prior VTE**
- **Familial and/or acquired thrombophilia**
- **Active cancer**
- **Trauma**
- **Major surgical procedures**
- **Acute or chronic medical illness requiring hospitalization or prolonged bed rest**
- **Central venous catheter/IV catheter**
- **Congestive heart failure (CHF)**
- **Pregnancy**
- **Regional bulky lymphadenopathy with extrinsic vascular compression**
- **Modifiable risk factors:**
  - ➤ **Smoking, tobacco**
  - ➤ **Obesity**
  - ➤ **Activity level/exercise**
- **Therapeutic agents associated with increased risk:**
  - ➤ **Chemotherapy**
  - ➤ **Exogenous estrogen compounds**
    - ◆ **Hormone replacement therapy (HRT)**
    - ◆ **Oral contraceptives**
    - ◆ **Tamoxifen/Raloxifene**
    - ◆ **Diethylstilbestrol**
  - ➤ **Thalidomide/lenalidomide**

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Benefits of VTE Prophylaxis

Prophylaxis in medical patients

Two recent meta-analyses of results from clinical trials have demonstrated significant benefit of VTE prophylaxis in medical patients.[91,92] Dentali et al examined nine randomized trials, including 19958 patients, that compared anticoagulant prophylaxis versus no treatment in hospitalized medical patients. The investigators found that prophylaxis was associated with a statistically significant 60% reduction in the risk of pulmonary embolism (PE) and fatal PE and with a trend toward fewer symptomatic deep venous thromboses (DVT) and an increase in major bleeding. Anticoagulant prophylaxis had no effect on all-cause mortality.[91] Similar results were obtained by a second meta-analysis performed by Wein et al. These investigators analyzed 36 studies comparing UFH, LMWH/heparinoid, and fondaparinux to control/placebo as well as twice-daily (BID) and thrice-daily (TID) UFH compared to each other and LMWH/heparinoid. They found that anticoagulant prophylaxis with either UFH, LMWH/heparinoid, or fondaparinux reduced the risk of DVT by 55% (relative risk [RR] 0.45; 95% confidence interval [CI], 0.39-0.53) and PE by 43% (RR 0.57; 95% CI, 0.45-0.72) compared with no prophylaxis. Thrice-daily UFH was associated with a greater risk reduction in DVT (RR, 0.27; 95% CI, 0.20-0.36) than twice-daily UFH (RR, 0.52; 95% CI, 0.28-0.96). LMWH was associated with a lower risk of DVT than UFH (RR, 0.68; 95% CI, 0.52-0.88) with no significant difference in PE, major bleeding, or mortality.[92]

Prophylaxis with LMWH versus no treatment or unfractionated heparin in surgical patients

VTE prophylaxis also has significant benefits in surgical patients. Mismetti and colleagues analyzed 59 randomized studies of 54144 general surgical patients that received LMWH,

UFH, or placebo/control for VTE prophylaxis. Eight studies including 5520 patients compared LMWH with placebo/no treatment. In these, LMWH significantly decreased the risk of asymptomatic DVT, clinical PE, and clinical VTE compared with no treatment or placebo. LMWH was compared with UFH in 51 studies that enrolled 48 624 patients. LMWH was associated with a significant reduction in clinical VTE compared with UFH while asymptomatic DVT, clinical PE, mortality and bleeding were similar in both treatment groups.[93]

LMWH versus factor Xa inhibition

Direct inhibition of factor Xa with fondaparinux has been shown to be at least as effective as administration of the LMWH dalteparin for prophylaxis against VTE in patients undergoing high-risk abdominal surgery. In a double-blind, double-dummy randomized study, patients scheduled for major abdominal surgery under general anesthesia received once-daily subcutaneous injections of fondaparinux or dalteparin for 5-9 days. Among 2048 patients evaluable for efficacy, 4.6% of those who received fondaparinux had VTE, versus 6.1% of those administered dalteparin; this difference represented a relative risk reduction of 24.6% (95% CI, -9.5% to 47.9%) indicating that fondaparinux was at least as effective as dalteparin in prevention of VTE in patients undergoing major abdominal surgery. Among these cancer surgery patients, 4.7% of those who received fondaparinux and 7.7% of those administered dalteparin had VTE; a 39% relative risk reduction (95% CI, 6.7 to 59.7) for VTE with fondaparinux compared to dalteparin. Overall, major bleeding was observed in 3.4% of patients who received fondaparinux versus 2.4% of those administered dalteparin.[94]

Importance of long-term prophylaxis in patients undergoing cancer surgery

The clinical impact of VTE on patient outcomes is underscored by the results of the @RISTOS Project, a prospective observational study of 2373 cancer patients undergoing general, urologic, or gynecologic surgery. Overall, 81.6% of patients received inpatient VTE prophylaxis, but only 30.7% continued to receive prophylaxis after discharge. Symptomatic VTE developed in 2.1% of patients with 40% of events occurring more than 21 days after surgery. VTE was responsible for 46% of patient deaths during the 30-day follow-up period. In comparison, only 7% of deaths were due to bleeding. Risk factors for VTE included a previous history of VTE (odds ratio [OR] 6.0; 95% CI, 2.1-16.8), operative times of 2 hours or more (OR 4.5; 95% CI, 1.1-19.0), bed rest for more than 3 days (OR 4.4; 95% CI, 2.5-7.8), advanced stage disease (OR 2.7; 95% CI, 1.4-5.2) and age 60 years or more (OR 2.6; 95% CI, 1.2-5.7). These data indicate the importance of optimizing VTE prophylaxis in cancer surgery patients and considering extended prophylaxis in high-risk subjects.[95]

Results from two large-scale clinical trials have demonstrated the effectiveness of prolonged prophylaxis with LMWH (dalteparin or enoxaparin) in patients undergoing major surgery. The ENOXACAN II study included 332 patients undergoing planned curative open surgery for abdominal or pelvic cancer who received enoxaparin daily for 6-10 days and were then randomly assigned to enoxaparin or placebo for an additional 21 days. The rates of VTE at the end of double-blind treatment were 4.8% for enoxaparin versus 12.0% for placebo. At 3 months after surgery, the respective values were 5.5% and 13.8%. There were no between-group differences in bleeding or other complications.[96]

More recently, Rasmussen and colleagues carried out a multicenter, prospective, assessor-blinded, open-label, randomized trial that compared 7 versus 28 days of prophylaxis against VTE with dalteparin in 427 patients undergoing major abdominal surgery. The primary efficacy endpoint was objectively verified VTE occurring between 7 and 28 days after surgery. The rates of VTE with short- and long-term prophylaxis were 16.3% and 7.3%, respectively; the risk for bleeding events was not increased with long- versus with short-term prophylaxis.[97]

Catheter prophylaxis

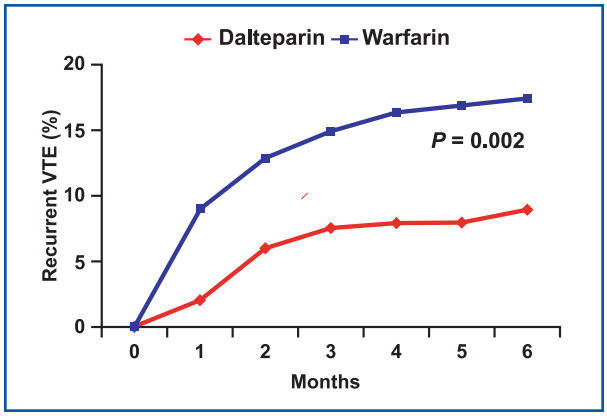
While results from individual clinical trials and meta-analyses provide strong support for VTE prophylaxis in medical and surgical cancer patients, the case for prophylaxis to prevent central venous catheter thrombosis is less clear. Two early open-label studies that evaluated VTE in patients with long-term catheter placement using venography indicated that low-dose warfarin (1 mg daily) and dalteparin (2500 IU daily) were each significantly more effective than no treatment.[98,99] Results from the study of low-dose warfarin found that 9.5% of patients receiving warfarin developed symptomatic VTE versus 25% of those who did not receive treatment.[98] More recent studies that have evaluated both LMWH and warfarin in patients with long-term catheters have failed to demonstrate significant benefit of prophylaxis in decreasing clinical or venographic VTE.[100-102] Consequently, at this time, available data do not support routine use of VTE prophylaxis to prevent central venous catheter thrombosis.

Alternatives for long-term VTE treatment in cancer patients

With conventional treatment of VTE using warfarin, cancer patients are 3-fold more likely to suffer recurrent thromboembolism and 2-6–fold more likely to suffer major bleeding than patients without cancer.[85,103] This disparity in clinical outcomes has prompted investigation of the efficacy and safety of LMWH in the long-term treatment of VTE in cancer patients. In the CANCENOX study, Meyer and colleagues compared enoxaparin (1.5 mg/kg daily) to warfarin for 3 months in an open-label multicenter trial of 146 cancer patients undergoing treatment of VTE. The primary endpoint was a composite of major bleeding and recurrent VTE. At the end of 3 months of follow-up, 21.1% of patients treated with warfarin experienced events compared with 10.5% of those receiving enoxaparin ($P = 0.09$). There was also a trend toward greater mortality in the warfarin arm (22.7% vs 11.3%, respectively, $P = 0.07$). There were 6 deaths resulting from hemorrhage among the patients who received warfarin versus none in the enoxaparin group.[104]

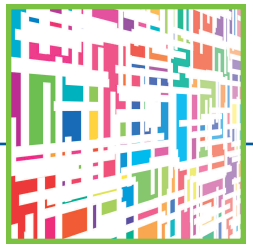
The LITE (Long-term Innovations in TreatmEnt) study randomized 200 cancer patients with VTE to tinzaparin (175 IU/kg daily) for the entire 3-month treatment course versus initial therapy with UFH (at least 5 days) followed by long-term (84 days) warfarin therapy.[105] At 3 months, 6 patients on tinzaparin and 10 on warfarin had suffered recurrent thromboembolism. By 12 months 7 patients taking tinzaparin and 16 patients taking warfarin experienced a recurrent VTE (P = .044). Major bleeding (7% versus 7%) was identical in both treatment groups. The largest randomized study of LMWH in the treatment of VTE in cancer patients is the Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) study. Lee et al compared 6 months of treatment with dalteparin versus a coumarin derivative in 672 patients with acute, symptomatic proximal DVT, PE, or both. Over the 6-month follow-up period, 8.0% of the patients who received dalteparin had recurrent VTE versus 15.8% of those in the coumarin group (Figure 5). The respective rates for major bleeding were 6% and 4%.[106] As a consequence of these studies, LMWH is recommended as the preferred treatment for patients with advanced cancer for the first 3-6 months of therapy.[89]

Figure 5. Kaplan-Meier Estimates of the Probability of Symptomatic Recurrence of VTE in Patients with Cancer who Received Dalteparin or a Coumarin Derivative as Secondary Prophylaxis



Conclusions

The results reviewed in this paper indicate that VTE occurs often in cancer patients and is a major cause of morbidity and mortality. A major reason for the high risk of VTE among cancer patients is underutilization of prophylaxis. All cancer patients should be assessed for VTE risk factors on admission to the hospital and receive appropriate prophylaxis. Unfractionated heparin, LMWH, and fondaparinux are appropriate pharmacologic options for VTE prophylaxis in cancer patients, and extended prophylaxis should be considered for cancer surgery patients. Low-molecular-weight heparin should be strongly considered for chronic therapy of VTE in cancer patients.



References

1. Walsh D, Rybicki L. Symptom clustering in advanced cancer. *Support Care Cancer.* 2006;14(8):831-836.
2. Miaskowski C, Dodd M, Lee K. Symptom clusters: the new frontier in symptom management research. *J Natl Cancer Inst Monogr.* 2004(32):17-21.
3. Walsh D, Donnelly S, Rybicki L. The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. *Support Care Cancer.* 2000;8(3):175-179.
4. Dodd MJ, Miaskowski C, Paul SM. Symptom clusters and their effect on the functional status of patients with cancer. *Oncol Nurs Forum.* 2001;28(3):465-470.
5. Reyes-Gibby CC, Aday LA, Anderson KO, Mendoza TR, Cleeland CS. Pain, depression, and fatigue in community-dwelling adults with and without a history of cancer. *J Pain Symptom Manage.* 2006;32(2):118-128.
6. Chow E, Fan G, Hadi S, Filipczak L. Symptom clusters in cancer patients with bone metastases. *Support Care Cancer.* 2007.
7. Cleeland CS, Bennett GJ, Dantzer R, et al. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. *Cancer.* 2003;97(11):2919-2925.
8. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. *Brain Behav Immun.* 2007;21(2):153-160.
9. Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behaviour: mechanisms and implications. *Trends Neurosci.* 2002;25(3):154-159.
10. Wood LJ, Nail LM, Perrin NA, Elsea CR, Fischer A, Druker BJ. The cancer chemotherapy drug etoposide (VP-16) induces proinflammatory cytokine production and sickness behavior-like symptoms in a mouse model of cancer chemotherapy-related symptoms. *Biol Res Nurs.* 2006;8(2):157-169.
11. Pusztai L, Mendoza TR, Reuben JM, et al. Changes in plasma levels of inflammatory cytokines in response to paclitaxel chemotherapy. *Cytokine.* 2004;25(3):94-102.
12. Deans DA, Wigmore SJ, Gilmour H, Paterson-Brown S, Ross JA, Fearon KC. Elevated tumour interleukin-1beta is associated with systemic inflammation: A marker of reduced survival in gastro-oesophageal cancer. *Br J Cancer.* 2006;95(11):1568-1575.
13. Fleishman SB. Treatment of symptom clusters: pain, depression, and fatigue. *J Natl Cancer Inst Monogr.* 2004(32):119-123.
14. Mock V, Dow KH, Meares CJ, et al. Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. *Oncol Nurs Forum.* 1997;24(6):991-1000.
15. Lindley CM, Hirsch JD, O'Neill CV, Transau MC, Gilbert CS, Osterhaus JT. Quality of life consequences of chemotherapy-induced emesis. *Qual Life Res.* 1992;1(5):331-340.
16. Kris MG, Hesketh PJ, Herrstedt J, et al. Consensus proposals for the prevention of acute and delayed vomiting and nausea following high-emetic-risk chemotherapy. *Support Care Cancer.* 2005;13(2):85-96.
17. Grunberg SM, Deuson RR, Mavros P, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. *Cancer.* 2004;100(10):2261-2268.
18. Kris MG, Hesketh PJ, Somerfield MR, et al. 2006 Update of the ASCO recommendations for antiemetics in oncology: guideline summary. jop.stateaffiliates-asco.org/July06 Issue/193.pdf. Accessed June 30, 2007.
19. NCCN. Antiemesis. http://www.nccn.org/professionals/physician gls/PDF/ antiemesis.pdf. Accessed July 1, 2007.
20. Roila F, Hesketh PJ, Herrstedt J. Prevention of chemotherapy-and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. *Ann Oncol.* 2006;17(1):20-28.
21. Rubenstein EB, Gralla RJ, Eisenberg P, et al. Palonosetron (PALO) compared with ondansetron (OND) or dolasetron (DOL) for Prevention of Acute & Delayed Chemotherapy-Induced Nausea and Vomiting (CINV): Combined Results of Two Phase III Trials. *Proc Am Soc Clin Oncol.* 2003;22:2932.
22. Saria A. The tachykinin NK1 receptor in the brain: pharmacology and putative functions. *Eur J Pharmacol.* 1999;375(1-3):51-60.
23. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer.* 2003;97(12):3090-3098.

24. Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin--the Aprepitant Protocol 052 Study Group. *J Clin Oncol.* 2003;21(22):4112-4119.
25. Hesketh PJ, Grunberg SM, Herrstedt J, et al. Combined data from two phase III trials of the NK1 antagonist aprepitant plus a 5HT 3 antagonist and a corticosteroid for prevention of chemotherapy-induced nausea and vomiting: effect of gender on treatment response. *Support Care Cancer.* 2006;14(4):354-360.
26. Herrstedt J, Muss HB, Warr DG, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. *Cancer.* 2005;104(7):1548-1555.
27. Hesketh PJ, Younger J, Sanjay R, et al. Aprepitant as salvage antiemetic therapy in breast cancer patients receiving doxorubicin and cyclophosphamide (AC). *J Clin Oncol.* 2006;24(18S):8618.
28. Grunberg SM, Dugan M, Muss HB, Wood M, Burdette-Radoux S, Weisberg T. Efficacy of a 1-day 3-drug antiemetic regimen for prevention of acute and delayed nausea and vomiting induced by moderately emetogenic chemotherapy. *J Clin Oncol.* 2007;25(18S):9111.
29. Carr DB, Goudas LC, Balk EM, Bloch R, Ioannidis JP, Lau J. Evidence report on the treatment of pain in cancer patients. *J Natl Cancer Inst Monogr.* 2004(32):23-31.
30. Ripamonti C, Dickerson ED. Strategies for the treatment of cancer pain in the new millennium. *Drugs.* 2001;61(7):955-977.
31. Saunders C. The symptomatic treatment of incurable malignant disease. *Prescribers J.* 1964;4:68-73.
32. Slatkin N. Cancer-related pain and its pharmacologic management in the patient with bone metastasis. *J Support Oncol.* 2006;4(2 Suppl 1):15-21.
33. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain.* 1999;81(1-2):129-134.
34. Bennet D, Burton AW, Fishman AE. Consensus panel recommendations for the assessment and management of breakthrough pain: part 1. Treatment. *Pharmacol Ther.* 2005;30:296-301.
35. Hwang SS, Chang VT, Kasimis B. Cancer breakthrough pain characteristics and responses to treatment at a VA medical center. *Pain.* 2003;101(1-2):55-64.
36. Zeppetella G, O'Doherty CA, Collins S. Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice. *J Pain Symptom Manage.* 2000;20(2):87-92.
37. Caraceni A, Martini C, Zecca E, et al. Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey. *Palliat Med.* 2004;18(3):177-183.
38. Caraceni A, Portenoy RK. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. *Pain.* 1999;82(3):263-274.
39. Taylor DR, Webster LR, Chun SY, et al. Impact of break through pain on quality of life in patients with chronic, noncancer pain: patient perceptions and effect of treatment with oral transmucosal fentanyl citrate (OTFC, ACTIQ). *Pain Med.* 2007;8(3):281-288.
40. Fortner BV, Okon TA, Portenoy RK. A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. *J Pain.* 2002;3(1):38-44.
41. McCarberg BH. The treatment of breakthrough pain. *Pain Med.* 2007;8 Suppl 1:S8-13.
42. Coluzzi PH, Schwartzberg L, Conroy JD, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Pain.* 2001;91(1-2):123-130.
43. Zeppetella G, Ribeiro MD. Opioids for the management of breakthrough (episodic) pain in cancer patients. *Cochrane Database Syst Rev.* 2006(1):CD004311.
44. Mercadante S, Villari P, Ferrera P, Casuccio A, Mangione S, Intravaia G. Transmucosal fentanyl vs intravenous morphine in doses proportional to basal opioid regimen for episodic-breakthrough pain. *Br J Cancer.* 2007;96(12):1828-1833.
45. Aronoff GM, Brennan MJ, Pritchard DD, Ginsberg B. Evidence-based oral transmucosal fentanyl citrate (OTFC) dosing guidelines. *Pain Med.* 2005;6(4):305-314.
46. Darwish M, Kirby M, Robertson P, Jr., Tracewell W, Jiang JG. Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate. *J Clin Pharmacol.* 2007;47(3):343-350.
47. Portenoy RK, Taylor D, Messina J, Tremmel L. A random ized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. *Clin J Pain.* 2006;22(9):805-811.
48. Farr SJ, Otulana BA. Pulmonary delivery of opioids as pain therapeutics. *Adv Drug Deliv Rev.* 2006;58(9-10):1076-1088.
49. Slatkin N. Analgesic efficacy of morphine delivered with the AERx mPMS for breakthrough cancer pain (open-label cross-over). 21st Annual Meeting of the American Pain Society; Baltimore, 2002.
50. Mercadante S, Radbruch L, Caraceni A, et al. Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care. *Cancer.* 2002;94(3):832-839.
51. NCCN. Cancer-related fatigue. http://www.nccn.org/professionals/physician_gls/PDF/fatigue.pdf. Accessed July 6, 2007.

52. Prue G, Rankin J, Allen J, Gracey J, Cramp F. Cancer-related fatigue: A critical appraisal. *Eur J Cancer.* 2006;42(7):846-863.

53. Hjermstad MJ, Oldervoll L, Fossa SD, Holte H, Jacobsen AB, Loge JH. Quality of life in long-term Hodgkin's disease survivors with chronic fatigue. *Eur J Cancer.* 2006;42(3):327-333.

54. Osoba D, Aaronson NK, Muller M, et al. Effect of neurological dysfunction on health-related quality of life in patients with high-grade glioma. *J Neurooncol.* 1997;34(3): 263-278.

55. Stasi R, Abriani L, Beccaglia P, Terzoli E, Amadori S. Cancer-related fatigue: evolving concepts in evaluation and treatment. *Cancer.* 2003;98(9):1786-1801.

56. Curt GA, Breitbart W, Cella D, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *Oncologist.* 2000;5(5):353-360.

57. Ancoli-Israel S, Moore PJ, Jones V. The relationship between fatigue and sleep in cancer patients: a review. *Eur J Cancer Care (Engl).* 2001;10(4):245-255.

58. Rao A, Cohen HJ. Symptom management in the elderly cancer patient: fatigue, pain, and depression. *J Natl Cancer Inst Monogr.* 2004(32):150-157.

59. Kaye J, Kaye K, Madow L. Sleep patterns in patients with cancer and patients with cardiac disease. *J Psychol.* 1983;114(1st Half):107-113.

60. Silberfarb PM, Hauri PJ, Oxman TE, Schnurr P. Assessment of sleep in patients with lung cancer and breast cancer. *J Clin Oncol.* 1993;11(5):997-1004.

61. Savard J, Simard S, Blanchet J, Ivers H, Morin CM. Prevalence, clinical characteristics, and risk factors for insomnia in the context of breast cancer. *Sleep.* 2001;24(5):583-590.

62. Hu DS, Silberfarb PM. Management of sleep problems in cancer patients. *Oncology (Williston Park).* 1991;5(9): 23-27; discussion 28.

63. Cimprich B. Pretreatment symptom distress in women newly diagnosed with breast cancer. *Cancer Nurs.* 1999;22(3):185-194; quiz 195.

64. Ancoli-Israel S, Liu L, Marler MR, et al. Fatigue, sleep, and circadian rhythms prior to chemotherapy for breast cancer. *Support Care Cancer.* 2006;14(3):201-209.

65. Carroll JK, Kohli S, Mustian KM, Roscoe JA, Morrow GR. Pharmacologic treatment of cancer-related fatigue. *Oncologist.* 2007;12(suppl 1):43-51.

66. US Food and Drug Administration. *FDA Strengthens Safety Information for Erythropoiesis-Stimulating Agents (ESAs).* Washington, DC: Department of Health and Human Services; 2007.

67. Kaleita T, Wellisch D, Graham C, et al. Pilot study of modafinil for treatment of neurobehavioral dysfunction and fatigue in adult patients with brain tumors. *J Clin Oncol.* 2006;24(18S):1503.

68. Morrow G, Gillies L, Hickok J, Roscoe J, Padmanaban D, Griggs J. The positive effect of the psychostimulant modafinil on fatigue from cancer that persists after treatment is completed. *J Clin Oncol.* 2005;23 (16S):8012.

69. Kohli S, Fisher SG, Tra Y, Wesnes K, Morrow GR. The cognitive effects of modafinil in breast cancer survivors: a randomized clinical trial. *J Clin Oncol.* 2007;25(18S): 9004.

70. Morrow GR, Hickok JT, Roscoe JA, et al. Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. *J Clin Oncol.* 2003;21(24):4635-4641.

71. Roscoe JA, Morrow GR, Hickok JT, et al. Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. *Breast Cancer Res Treat.* 2005;89(3):243-249.

72. Dimeo FC, Stieglitz RD, Novelli-Fischer U, Fetscher S, Keul J. Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. *Cancer.* 1999;85(10):2273-2277.

73. Mock V, Pickett M, Ropka ME, et al. Fatigue and quality of life outcomes of exercise during cancer treatment. *Cancer Pract.* 2001;9(3):119-127.

74. Schwartz AL. Daily fatigue patterns and effect of exercise in women with breast cancer. *Cancer Pract.* 2000;8(1): 16-24.

75. Quesnel C, Savard J, Simard S, Ivers H, Morin CM. Efficacy of cognitive-behavioral therapy for insomnia in women treated for nonmetastatic breast cancer. *J Consult Clin Psychol.* 2003;71(1):189-200.

76. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part I: Sleep and psychological effects. *J Clin Oncol.* 2005;23(25):6083-6096.

77. Fiorentino L, Ancoli-Israel S. Insomnia and its treatment in women with breast cancer. *Sleep Med Rev.* 2006;10(6):419-429.

78. Ancoli-Israel S. *Breast Cancer Res Treat.* 2006;100 (Suppl 1):S239.

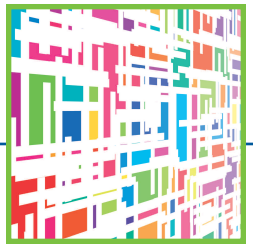
79. Heit JA. Cancer and venous thromboembolism: scope of the problem. *Cancer Control.* 2005;12 Suppl 1:5-10.

80. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA.* 2005;293(6):715-722.

81. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med.* 2000;160(6):809-815.

82. Hillen HF. Thrombosis in cancer patients. *Ann Oncol.* 2000;11 Suppl 3:273-276.

83. Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med.* 2000;343(25):1846-1850.
84. Kahn SR, Kearon C, Julian JA, et al. Predictors of the post-thrombotic syndrome during long-term treatment of proximal deep vein thrombosis. *J Thromb Haemost.* 2005;3(4):718-723.
85. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood.* 2002;100(10):3484-3488.
86. Stein PD, Beemath A, Meyers FA, Skaf E, Sanchez J, Olson RE. Incidence of venous thromboembolism in patients hospitalized with cancer. *Am J Med.* 2006;119(1):60-68.
87. Piccioli A, Falanga A, Baccaglini U, Marchetti M, Prandoni P. Cancer and venous thromboembolism. *Semin Thromb Hemost.* 2006;32(7):694-699.
88. Adess M, Eisner R, Nand S, Godwin J, Messmore HL, Jr., Wehrmacher WH. Thromboembolism in cancer patients: pathogenesis and treatment. *Clin Appl Thromb Hemost.* 2006;12(3):254-266.
89. NCCN. Venous thromboembolic disease. http://www.nccn.org/professionals/physician_gls/PDF/vte.pdf. Accessed July 3, 2007.
90. Kakkar AK, Levine M, Pinedo HM, Wolff R, Wong J. Venous thrombosis in cancer patients: insights from the FRONTLINE survey. *Oncologist.* 2003;8(4):381-388.
91. Dentali F, Douketis JD, Gianni M, Lim W, Crowther MA. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. *Ann Intern Med.* 2007;146(4):278-288.
92. Wein L, Wein S, Haas SJ, Shaw J, Krum H. Pharmacological venous thromboembolism prophylaxis in hospitalized medical patients: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007;167(14):1476-1486.
93. Mismetti P, Laporte S, Darmon JY, Buchmuller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *Br J Surg.* 2001;88(7):913-930.
94. Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. *Br J Surg.* 2005;92(10):1212-1220.
95. Agnelli G, Bolis G, Capussotti L, et al. A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS project. *Ann Surg.* 2006;243(1):89-95.
96. Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med.* 2002;346(13):975-980.
97. Rasmussen MS, Jorgensen LN, Wille-Jorgensen P, et al. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. *J Thromb Haemost.* 2006;4(11):2384-2390.
98. Bern MM, Lokich JJ, Wallach SR, et al. Very low doses of warfarin can prevent thrombosis in central venous catheters. A randomized prospective trial. *Ann Intern Med.* 1990;112(6):423-428.
99. Monreal M, Alastrue A, Rull M, et al. Upper extremity deep venous thrombosis in cancer patients with venous access devices--prophylaxis with a low molecular weight heparin (Fragmin). *Thromb Haemost.* 1996;75(2):251-253.
100. Couban S, Goodyear M, Burnell M, et al. Randomized placebo-controlled study of low-dose warfarin for the prevention of central venous catheter-associated thrombosis in patients with cancer. *J Clin Oncol.* 2005;23(18):4063-4069.
101. Karthaus M, Kretzschmar A, Kroning H, et al. Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. *Ann Oncol.* 2006;17(2):289-296.
102. Verso M, Agnelli G, Bertoglio S, et al. Enoxaparin for the prevention of venous thromboembolism associated with central vein catheter: a double-blind, placebo-controlled, randomized study in cancer patients. *J Clin Oncol.* 2005;23(18):4057-4062.
103. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Buller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. *J Clin Oncol.* 2000;18(17):3078-3083.
104. Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med.* 2002;162(15):1729-1735.
105. Hull RD, Pineo GF, Brant RF, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med.* 2006;119(12):1062-1072.
106. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med.* 2003;349(2):146-153.



Posttest

To receive continuing education credit, complete the posttest answer form and evaluation on page 27 and follow the instructions.

1. Which of the following has not been identified as a symptom cluster in cancer patients?

    a. Fatigue-anorexia-cachexia
    b. Neuropsychological
    c. Upper gastrointestinal
    d. Urological

2. Which of the following cytokines/chemokines has been implicated in symptom clustering in cancer patients?

    a. IL-2
    b. IL-12
    c. ICAM-1
    d. IL-6

3. True or false: Oncology physicians and nurses accurately estimate the risk for acute, but not delayed, emesis in their patients.

    True False

4. Which of the following statements regarding the ASCO guidelines for managing emesis in cancer patients is correct?

    a. The combination of a serotonin-receptor antagonist, dexamethasone, and aprepitant is recommended for patients receiving agents with low emetic risk.

    b. Treatment with a serotonin-receptor antagonist alone is recommended in patients receiving agents with high emetic risk.

    c. Dexamethasone is not recommended as monotherapy for any patients.

    d. The combination of a serotonin-receptor antagonist, dexamethasone, and aprepitant is recommended for patients receiving agents with high emetic risk.

5. True or false: End-of-dose pain occurs because of inadequate analgesic dosing or an overly long dosing interval and should prompt re-evaluation and modification of the treatment regimen.

    True False

6. A survey of 1095 patients indicated that which of the following was associated with increased risk for the development of breakthrough pain?

    a. Localized disease
    b. Metastatic disease
    c. Pulmonary involvement
    d. Treatment with opioids

7. The guidelines set forth by the NCCN indicate that which of the following contributes to the development of fatigue in cancer patients?

    a. Anemia
    b. Obesity
    c. Advanced age
    d. Low Karnofsky Performance Score

8. Which of the following statements about the effects of paroxetine in patients with cancer-related fatigue is true?

    a. Paroxetine relieved pain
    b. Paroxetine increased sleep efficiency
    c. Paroxetine decreased symptoms of depression
    d. Paroxetine decreased fatigue

9. Which of the following has not been associated with increased risk for VTE in cancer patients?

    a. Advanced age
    b. Type and extent of cancer
    c. Sex
    d. Treatment with anti-angiogenic agents

10. Agents recommended for long-term management of cancer patients at risk for VTE include which of the following?

    a. LMWH
    b. UFH
    c. Fondaparinux
    d. Antithrombin-III

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Posttest Answers *(circle the correct answer)*

1.	a b c d	6.	a b c d
2.	a b c d	7.	a b c d
3.	True False	8.	a b c d
4.	a b c d	9.	a b c d
5.	True False	10.	a b c d

Evaluation	**Poor**				**Satisfactory**	**Excellent**
1. Extent to which the objectives were achieved:	1	2	3	4	5	
2. Potential impact on your practice:	1	2	3	4	5	
3. Detail of information presented:	1	2	3	4	5	
4. Extent to which commercial bias appeared:	1	2	3	4	5	

5. Suggestions for future CE topics: _____

_____

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