Essential Drugs in Supportive Care

Bassam Estfan

Progress in cancer treatment has brought with it challenges that go beyond cure. Toxicities and morbidity are among the biggest hurdles for a cancer patient to face while hoping for the end of chemotherapy or radiation therapy. Important advances have been made in the science of supportive care to address cancer treatment toxicities and complications. Nausea and vomiting, bone complications, hot flashes, and bone marrow failure are some areas where a huge impact has been made on quality of life and treatment experience. Complications that remain without good remedies await a better understanding of new targets and drugs.

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The science of oncology has exponentially advanced over the past few decades. As our experience with new therapies increases so does our understanding of their complications and side effects (Table 1). Newer targeted therapies are associated with different side effects and have expanded the list of supportive drugs. Examples are antihypertensive drugs with anti-angiogenesis agents, and antibiotics for acneiform rash with agents targeting epidermal growth factor receptor pathways.1,2 Newer approaches incorporate more aggressive regimens and extensive combinations, and focus on dose-intensity to improve outcomes and cure rates. These approaches are usually associated with higher morbidity and side effects and reduce quality of life. Interest in supportive care emerged and improved management of some side effects of chemotherapy and radiotherapy like nausea and vomiting, febrile neutropenia, therapy-associated anemia, and hot flashes. We have yet to find more potent and effective therapies for other common side effects. A common example is peripheral neuropathy, sometimes irreversible, with agents like platinum, taxanes, thalidomide, or bortezomib. Other examples include chemotherapy- and radiation therapy-related mucositis and fatigue.

This article discusses the most common drugs in supportive cancer care. Some drugs have established roles (Table 2). Others have failed in prospective trials but continue to be used, like methylphenidate. The management of treatment-related toxicities is an art. It will at some point require a multidisciplinary approach.

BISPHOSPHONATES

This class of medication has been around for more than a century. Bisphosphonates (BPs) inhibit osteoclast activity and bone resorption and have potential antitumor effects through promoting apoptosis, inhibiting cancer cell growth, and attachment to bone.3 Zoledronic acid (ZA) is more potent than other BPs.4 The indications for BPs in supportive care (and perhaps in therapeutic oncology) are increasing.

Lytic bone metastases are common in lung, breast, and kidney cancer, afflicting 30% to 70% of patients during the disease course. They are a hallmark in multiple myeloma with an incidence greater than 90%.5 A systematic review of skeletal events in 30 trials that compared BPs to each other or placebo showed a significant advantage to BP therapy in reducing the odds ratio for vertebral (0.69) and nonvertebral skeletal events (0.65), as well as the use of radiation therapy (0.67) when study length was at least 6 months.6 When BPs were used for more than 1 year, there was a significant reduction in surgical interventions needed.

Hypercalcemia of malignancy is another indication for BP administration. While the decision for maintenance therapy in hypercalcemia should be individualized, initial treatment is more effective and durable compared to other interventions. Hypercalcemia is frequently a marker of disease recurrence, progression, new bony metastases, or treatment failure. In malignant hypercalcemia ZA was superior to pamidronate in response at 10 days (88% v 70%). At 4 days, corrected calcium levels were normalized in half of those treated with ZA compared to a third treated with pamidronate.7 A significant prophylactic effect against hypercalcemia with BPs was also noted.6 A similar effect was not seen in multiple myeloma, perhaps related to a different mechanism of this complication.8

Hormonal deprivation in breast and prostate cancer
is associated with increased osteopenia and osteoporosis.\textsuperscript{9,10} BPs have been used successfully at 6- to 12-month intervals to treat and prevent mineral bone loss.\textsuperscript{11–16} This effect was even more pronounced when early versus delayed application was studied in breast cancer.\textsuperscript{16}

There is increasing evidence linking BPs (especially ZA) to improved disease-free survival and overall survival. Patients with breast cancer randomized to receive ZA had a relative reduction of 36% in disease progression.\textsuperscript{17} In another retrospective analysis, hormone receptor-negative breast cancer patients with bony metastases who were on BPs had a better overall survival (hazard ratio of 0.56).\textsuperscript{18} Several prospective trials are trying to address the question of adjuvant BPs (B-34, Adjuvant Treatment with Zoledronic Acid in Stage II/III Breast Cancer [AZURE] trial, and Southwest Oncology Group [SWOG] 0307).

Nonetheless, the use of BPs has potential risks and side effects. The true incidence of osteonecrosis of the jaw (ONJ) is not well established. A recent systematic review indicated that the mean weighted prevalence is 6%.\textsuperscript{19} Treatment is supportive in early stages but may require aggressive surgical debridement where advanced. The risk increases with BP potency, extended BP exposure, number of treatments, and underlying dental health.\textsuperscript{20,21} Nephrotoxicity is another side effect in about 4% of cancer patients, especially with other nephrotoxic drugs like nonsteroidal anti-inflammatory drugs (NSAIDs).\textsuperscript{22}

### Table 1. Common Treatment Complications in Cancer

<table>
<thead>
<tr>
<th>Complication</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>Platinum agents, radiation</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Radiation, antimetabolites</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Radiation, anthracyclines, taxanes</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Platinum agents, taxanes, thalidomide, bortezomib</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Hormonal therapy</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Radiation, most chemotherapy agents</td>
</tr>
<tr>
<td>Anorexia and cachexia</td>
<td>Variable</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5-Fluorouracil, gemcitabine, irinotecan, bowel irradiation</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>Highly active chemotherapy in sensitive high-burden tumors</td>
</tr>
<tr>
<td>Bone marrow failure/febrile neutropenia</td>
<td>Platinum agents, antimetabolites, anthracyclines, alkylating agents, taxanes</td>
</tr>
<tr>
<td>Mineral bone loss (osteopenia/osteoporosis)</td>
<td>Hormonal therapy</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Trastuzumab, anthracyclines</td>
</tr>
</tbody>
</table>

### Table 2. List of Other Agents in Supportive Care

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>Prevention of tumor lysis syndrome</td>
</tr>
<tr>
<td>Amphotamin*</td>
<td>Radiation-induced mucositis</td>
</tr>
<tr>
<td>Benzodiamine†</td>
<td>Mucositis</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>CINV</td>
</tr>
<tr>
<td>Denosumab†</td>
<td>Bone metastases</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>CINV</td>
</tr>
<tr>
<td>Dexrazoxane</td>
<td>Cardioprotective agent with anthracyclines</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Potential use in CINV, neuropathy(?), hot flashes</td>
</tr>
<tr>
<td>Mesna</td>
<td>Hemorrhagic cystitis prevention</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Intractable diarrhea</td>
</tr>
<tr>
<td>Palifermin</td>
<td>Mucositis in bone marrow transplant</td>
</tr>
<tr>
<td>Rasburikase</td>
<td>Prevention and treatment of tumor lysis syndrome</td>
</tr>
</tbody>
</table>

Abbreviation: CINV, chemotherapy-induced mucositis.  
*Benzydamine is not available in the United States.  
†Denosumab was approved in cancer after this article was done.

### 5-HT\textsubscript{3} RECEPTOR ANTAGONISTS

Without antiemetic therapy, highly emetogenic chemotherapy (HEC) is associated with acute vomiting in more than 90% of patients.\textsuperscript{23} Serotonin receptors (5-HT\textsubscript{3}) are important in the pathophysiology of chemotherapy-induced nausea and vomiting (CINV).\textsuperscript{24} 5-HT\textsubscript{3} receptors have both a central and a peripheral distribution. Receptors in the gut make them a plausible target for drug therapy. Current antiemetics guidelines incorporate 5-HT\textsubscript{3} receptor antagonists for acute nausea and vomiting in HEC and moderately emetogenic.
chemotherapy (MEC). They are not routinely recommended for low emetogenic chemotherapy (whereas dexamethasone is recommended as a single treatment) unless unresponsive to single-agent dexamethasone.25–27

Meta-analyses concluded that there are no major differences between the old 5-HT\textsubscript{3} receptor antagonists (ondansetron, granisetron and tropisetron).28,29 The addition of dexamethasone is associated with a higher response when compared to single-agent 5-HT\textsubscript{3} antagonists. While most 5-HT\textsubscript{3} receptor antagonists are similar, palonosetron has a favorable impact on delayed CINV and acute CINV. A recent meta-analysis assessed five large trials comparing palonosetron to other 5-HT\textsubscript{3} receptor antagonists. It concluded that it was more effective in prevention of acute and delayed CINV. The newly updated Multinational Association of Supportive Care in Cancer (MASCC) guidelines specifically recommend palonosetron as the agent of choice for MEC.25

**NK\textsubscript{1} RECEPTOR ANTAGONISTS**

Aprepitant is an oral antagonist of the neurokinin-1 (NK\textsubscript{1}) receptor and blocks the binding of substance P. It acts centrally in the prevention of acute and delayed nausea and vomiting, especially in highly emetogenic single-agent or combination chemotherapy.30 The introduction of NK\textsubscript{1} receptor antagonists improved the experience of cancer patients suffering from CINV in addition to 5HT\textsubscript{3} receptor antagonists and dexamethasone. The effective dose of aprepitant is 125 mg on day 1 followed by 80 mg on days 2–5 during cisplatin.31 The protocol was later reduced to a 3-day regimen with 80 mg administered on days 2–3. Randomized trials showed a complete response rate of 72% to 83% in the acute phase in HEC using cisplatin and 55% to 73% in the delayed phase (Table 3).31–34 The success in MEC is less pronounced but has been demonstrated in cancer patient receiving doxorubicin and cyclophosphamide (AC) for breast cancer.35,36 A small, uncontrolled study showed the feasibility of aprepitant as a single dose of 285 mg on day 1 with palonosetron and dexamethasone in MEC. There was a complete response rate of 76% and 66% in acute and delayed CINV, respectively. Guidelines include aprepitant as a recommendation for HEC and AC, and a consideration for MEC refractory to treatment standards with 5HT\textsubscript{3} receptor antagonists and dexamethasone.25–27

Aprepitant moderately inhibits CYP3A4, for which reason dexamethasone (metabolized by the same cytochrome) doses are usually reduced in half. Fosaprepitant is an intravenous form and a pro-drug of aprepitant, and can be used on day 1 at a dose of 115 mg.38 Results from a newer oral NK\textsubscript{1} receptor antagonist, casopitant, in CINV have shown overall response rates of 73% to 75% in both HEC and MEC.39,40 Casopitant was recently withdrawn from further development.

**ERYTHROPOIESIS-STIMULATING AGENTS**

Anemia is a common manifestation of solid and hematologic malignancies.41 It is also a common side effect of chemotherapy and radiotherapy. Anemia is associated with reduced quality of life and other symptoms like fatigue and dyspnea.

Since their introduction in 1989 erythropoiesis-stimulating agents (ESAs: epoetin alpha and then the longer-acting darbepoetin alpha) have been used extensively in cancer patients with anemia to reduce transfusion requirement, and to improve quality of life and symptomatology. ESAs are the mainstay of treatment in some hematologic disorders like low-risk myelodysplastic syndrome (MDS) and they are associated with improved survival especially in responders.42,43

In the first randomized trial in patients with solid tumors and non-myeloid hematologic malignancies,

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy</th>
<th>Comparison</th>
<th>Acute Response</th>
<th>Delayed Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chawla, 2003*</td>
<td>Cisplatin</td>
<td>Placebo</td>
<td>83%</td>
<td>71%</td>
</tr>
<tr>
<td>Poli-Bigelli, 2003</td>
<td>Cisplatin</td>
<td>Placebo</td>
<td>83%</td>
<td>68%</td>
</tr>
<tr>
<td>Hesketh, 2003</td>
<td>Cisplatin</td>
<td>Placebo</td>
<td>89%</td>
<td>78%</td>
</tr>
<tr>
<td>Warr, 2005</td>
<td>AC/EC</td>
<td>Placebo</td>
<td>76%</td>
<td>69%</td>
</tr>
<tr>
<td>Schmoll, 2006*</td>
<td>Cisplatin</td>
<td>Control</td>
<td>72%</td>
<td>61%</td>
</tr>
<tr>
<td>Yeo, 2009</td>
<td>AC</td>
<td>Control</td>
<td>72%</td>
<td>73% (NS)</td>
</tr>
<tr>
<td>Rapoport, 2010</td>
<td>MEC- AC</td>
<td>Placebo</td>
<td>84%</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>MEC- not AC</td>
<td></td>
<td>93%</td>
<td>88% (NS)</td>
</tr>
</tbody>
</table>

Abbreviations: A, aprepitant; AC, doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; MEC, moderately emetogenic chemotherapy; NS, not significant; P, placebo
*Results were for the overall phase.
Epoetin alpha significantly improved quality of life and reduced transfusions. A recent meta-analysis of 52 trials using ESAs in cancer confirmed related improvement in quality of life and reduction in transfusion requirement (relative risk [RR] for both = 0.64).45 Thrombotic events were higher with ESAs (RR = 1.69), and highlighted the potential detrimental survival effect previously suggested (RR=1.15), although tumor responses were no different. Another analysis reached the same conclusion about the adverse effects of ESAs on survival and thrombotic events.46 A European analysis of 12 randomized controlled trials showed that if ESAs were initiated at hemoglobin levels <10–11 g/dL, survival was unaffected regardless of target hemoglobin. A favorable impact on disease progression with a hazard ratio of 0.73 was noted.47 Increased mortality was observed only if ESAs were initiated at a hemoglobin >11 g/dL. Another report evaluated the use of ESAs in a Medicare population with lung, breast, or colorectal cancer, or diffuse large B-cell lymphoma (results from Surveillance, Epidemiology and End Results [SEER]-Medicare database) between 1991 and 2002.48 ESAs use with chemotherapy increased 10-fold during this period to 46%. Interestingly, the rate of blood transfusion remained constant with ESAs use. More patient receiving ESAs developed a thromboembolic event (hazard ratio = 1.93), but survival was similar compared to those who did not receive them.

Although evidence-based guidelines exist, the controversy continues and the US Food and Drug Administration (FDA) issued a black box warning for ESAs regarding mortality and thrombotic events.

**GRANULOCYTE COLONY-STIMULATING FACTORS**

Neutropenia is common with many chemotherapy regimens. The risk of febrile neutropenia (FN) increases with the severity and duration of neutropenia. Incidence of FN increases with an absolute neutrophil count (ANC) <500/μL, and reaches 40% with an ANC <100/μL or when neutropenia persists for more than 3 days.50,51 FN leads to high-cost hospitalization and has about 7% mortality and reduced chemotherapy relative dose-intensity (RDI) and density.52-54 Reduction of RDI negatively affects outcomes in early-stage breast cancer and non-Hodgkin lymphoma.55,56 Colony-stimulating factors like filgrastim and timed-release pegfilgrastim may reduce the duration of neutropenia and subsequently FN, allowing a higher chance of adhering to the planned chemotherapy dosage and interval. In trials comparing filgrastim to pegfilgrastim, both were comparable regarding the rate of grade 4 neutropenia, but pegfilgrastim was superior in reducing the rate of neutropenic fevers.57 A recent systematic review pooled results from 17 granulocyte colony-stimulating factor (G-CSF) trials before chemotherapy.58 G-CSF use was associated with higher RDI and a 40% to 45% reduction in all-cause and infection-related mortality. FN occurred in 22% of those receiving G-CSF compared to 40% in controls; the reduction was more significant with pegfilgrastim.

Different oncological societies recommend G-CSF with chemotherapy regimens with a greater than 20% risk of FN, or a risk of less than 20% with risk factors like age ≥65 years, sepsis, prior FN, poor performance status, hypotension, cardiopulmonary comorbidities, fungal infections, and end organ dysfunction (Table 4). Chemotherapy regimens associated with a high risk for FN are available in these guidelines.59–61 Administration of G-CSF once FN is established is not usually recommended except in individual cases associated with high-risk factors. In these situations only filgrastim should be used if no other G-CSF agents were administered for prophylaxis. Secondary treatment with G-CSF in FN does not improve outcomes but is associated with a slightly shorter length of hospitalization.62 A common side effect with G-CSF is bony pain in up to 20% of patients. There is debate whether the risk of myeloid leukemia is increased with its use.

**OLANZAPINE**

Olanzapine is an atypical antipsychotic of the thienobenzodiazepine class of drugs used for schizophrenia in the acute phase.63 The spectrum of receptors targeted by olanzapine includes dopamine, serotonin, histamine, and adrenergic and muscarinic receptors.64 This has trig-

### Table 4. Societal Recommendations for Granulocyte Colony-Stimulating Factor Use

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High (≥20%)</td>
<td>Use G-CSF</td>
<td>Use G-CSF</td>
<td>Use G-CSF</td>
</tr>
<tr>
<td>Intermediate (10%–20%) (FN risk &lt;20%)</td>
<td>Consider with risk factors*</td>
<td>Consider with risk factors*</td>
<td>Consider with risk factors*</td>
</tr>
<tr>
<td>Low (&lt;10%)</td>
<td>Not discussed</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

Abbreviations: FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network; EORTC, European Organization for Research and Treatment of Cancer.

*Risk factors include: age ≥65 years, poor performance status, prior FN, concurrent chemoradiation, bone marrow failure due to metastases, active infections (fungal, sepsis), serious comorbidities, and end organ dysfunction.
Olanzapine was most recently tested for the prevention of CINV in two phase II trials. In the first trial, olanzapine was given with dexamethasone and granisetron. In the second, olanzapine 10 mg was given on days 1–4 with palonosetron and dexamethasone. No NK1 receptor antagonists were used. Both trials showed a remarkable improvement of acute CINV with a 100% complete response rate in HEC and 97% to 100% in MEC. Delayed CINV also was associated with complete response rates of 75% to 80% in HEC and 75% to 85% in MEC. The combination was well tolerated with no grade 3 or 4 toxicity. Randomized studies are warranted.

In addition to its antiemetic effect, olanzapine is associated with increased appetite and weight gain as a side effect. This was exploited recently in a trial randomizing 76 patients suffering from anorexia and cachexia to megestrol acetate (MA) or MA plus olanzapine. Results were in favor of the olanzapine combination, with 85% achieving weight gain >5%, and improved appetite in 65% (compared to 40% and 5%, respectively, in those on MA alone). The study also showed improvement of nausea.

**METHYLPHENIDATE**

Methylphenidate is a psychostimulant used with some success in fatigue and cognitive deficit in advanced cancer and brain tumors. The evidence has been largely from case series. Unfortunately, at least four recent studies failed to show an improvement in fatigue in different settings. In the most recent trial, 148 patients with cancer-related fatigue were randomized to long-acting methylphenidate at a target maximum dose of 54 mg/d or placebo over 28 days. Sixty-four percent were receiving chemotherapy. The study found no difference in quality of life or fatigue scores compared to baseline between both arms. More nervousness and decreased appetite were noted in the methylphenidate arm. A randomized study of methylphenidate versus placebo evaluated its efficacy in 57 women undergoing chemotherapy for breast cancer with a maximum dose of 20 mg daily. Quality of life, fatigue, and cognitive function were assessed. There was no statistical difference between study arms in all three aspects of evaluation. Similar results were noted in 68 patients undergoing radiotherapy to brain tumors randomized to placebo or methylphenidate at a maximum dose of 30 mg daily. The only randomized trial in advanced cancer examined “as needed” use of methylphenidate compared to placebo. There was an improvement in fatigue scores in both arms, but the difference was not statistically significant between placebo and active drug. These studies present a disappointing result from a potential agent to target one of the most common side effects afflicting cancer patients in active treatment and entice us to look for other agents with potentially different mechanisms of action.

**MEGESTROL ACETATE**

Megestrol acetate (MA) has been used for hormonal manipulation of metastatic breast and prostate cancer but its antitumor use has gone out of favor. Nevertheless, it has potential uses for some of the symptoms associated with cancer treatment or complications like hot flashes and cancer-related anorexia and cachexia syndrome (ACS). Several studies evaluated the efficacy of MA on appetite and weight gain compared to placebo and other agents. A Cochrane database meta-analysis reviewed 32 trials of MA in cancer and AIDS patients suffering from ACS. The review concluded with a demonstration of the efficacy of MA in improving appetite and weight gain in cancer patients. The most remarkable effect on ACS is in combination with olanzapine. Evaluation of the added value of MA to olanzapine should be studied.

Randomized clinical trials in breast cancer and prostate cancer patients on hormonal therapy proved that MA probably has the highest efficacy for suppression of hot flashes. Earlier studies in this population documented reduction of hot flashes in 85% of patients receiving 40 mg daily of MA compared to 20% in the placebo group. Seventy-one percent reported reduction of greater than 50%. A follow-up assessment 3 years later noted that 45% were still using MA (Table 5) with good results and tolerance. Some of the concerns regarding the use of progesterin date back to reports from the Woman’s Health Initiative (WHI) where a combined estrogen/progesterone therapy compared to estrogen alone was associated with an increased risk for breast cancer, suggesting a possible role for the combination. The role of progesterone agents alone was not addressed in the WHI. Others have concerns regarding MA and possible prostate cancer progression. MA or medroxyprogesterone acetate (MPA) is highly effective and unlikely to be detrimental with short-term use if the efficacy of other “safer” agents like venlafaxine or gabapentin is lacking.

**SELECTIVE SEROTONIN REUPTAKE INHIBITORS**

Hot flashes are associated with serotonin levels in menopausal women. Anecdotal reports of the efficacy of the antidepressant paroxetine and other selective serotonin reuptake inhibitors (SSRIs) led to the investigation of paroxetine in treatment-related hot flashes in phase I trials with promising results. SSRIs studied in randomized trials include paroxetine, sertraline, fluoxetine, and citalopram. The results for most studies were summarized in a pooled analysis (Table 6). Among these antidepressants, paroxetine offers the best results in reducing hot flashes.
by greater than 50%. Sertraline and fluoxetine were not associated with a significant reduction in hot flashes. Some studies were conducted in menopausal women (as opposed to hormonal treatment for breast cancer), but efficacy is suggested in breast cancer patients.83,90 SSRIs use is faced with recent concerns due to their suppression of CYP2D6 in the liver, which converts tamoxifen to its active metabolite, endoxifen.91 SSRIs vary in the inhibitory effect to CYP2D6, but paroxetine (inhibition constant $K_i = 0.15 \mu M/L$) represents the most potent inhibitor, followed by fluoxetine (0.6 $\mu M/L$) and sertraline (0.7 $\mu M/L$). Citalopram, although still associated with some inhibitory activity, is a weak inhibitor (5.1 $\mu M/L$).92 A recent study retrospectively evaluated breast cancer patients receiving tamoxifen and concurrent SSRIs.93 A striking association between the concurrent use of paroxetine and tamoxifen was associated with a significant increase in the rate of deaths from breast cancer and all-cause mortality, which increased with longer duration of co-treatment. This effect was not noted with other antidepressants, including venlafaxine (see below), which was even associated with a trend towards better survival.

This has translated into a departure from using SSRIs for hot flashes in breast cancer survivors taking tamoxifen, with a trend toward using other agents like gabapentin or venlafaxine.

### VENLAFAXINE

Venlafaxine is a serotonin and noradrenaline re-uptake inhibitor (SNRI). The mechanism is likely serotonin-related and may mirror SSRIs.94,95 Multiple randomized trials assessing efficacy in hot flashes have been conducted (Table 7) and established venlafaxine as a reasonable option for hot flashes with a reduction of hot flashes score by greater than 50% in

<table>
<thead>
<tr>
<th>Study</th>
<th>Condition</th>
<th>Drug</th>
<th>Daily dose</th>
<th>50% Reduction in HF Score</th>
<th>Median Reduction in HF Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loprinzi, 199476</td>
<td>BC, PC</td>
<td>Fluoxetine 20 mg</td>
<td>42%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Barton, 201088</td>
<td>Menopause</td>
<td>Citalopram 10 mg</td>
<td>39%</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Menopause</td>
<td>Paroxetine 12.5 mg</td>
<td>58%</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>Stearns, 200382</td>
<td>Menopause</td>
<td>Paroxetine 10 mg</td>
<td>NR</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>Stearns, 200583</td>
<td>BC</td>
<td>Sertraline 50 mg</td>
<td>36%</td>
<td>Reported NS</td>
<td></td>
</tr>
<tr>
<td>Kimmick, 200686</td>
<td>BC</td>
<td>Sertraline 50 mg</td>
<td>30% (&gt;33% reduction)</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Gordon, 200684</td>
<td>Menopause</td>
<td>Sertraline 50 mg</td>
<td>NR</td>
<td>41% (NS)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BC, breast cancer; HF, hot flashes; NR, not reported; NS, not significant.
Another interesting aspect of venlafaxine is its activity in neuropathic pain in non-cancer patients. One randomized trial in non-cancer patients compared venlafaxine 225 mg to imipramine and placebo in painful polyneuropathy. Both were associated with a 20% reduction in pain scores, but this effect was modest. An attempt to exploit the analgesic effect of venlafaxine was made in breast cancer for prevention of postmastectomy pain syndrome. A recent report attempted replication of these findings in comparing venlafaxine to gabapentin and placebo in women undergoing mastectomy and axillary dissection. The authors suggested that there was a reduction in burning and stabbing pain at 6 months.

Other reports have indicated possible role in cancer patients, including a study in 15 patients with breast cancer and treatment-related neuropathy who were randomly given venlafaxine or placebo. Average daily pain intensity did not differ between both interventions, but there was a significant improvement in average pain relief diary and maximum pain. Few published case reports note a possible role for venlafaxine in chemotherapy-induced neuropathy, including oxaliplatin and paclitaxel. Although these reports (from the same center) do not justify its regular use in the treatment or prevention of chemotherapy-induced neuropathy, they invite us to further evaluate the utility of venlafaxine.

### SUMMARY

Cancer treatment is associated with significant toxicity and morbidity. Over the last two decades, important steps were made in the field of supportive care to reduce the morbidity and suffering sometimes associated with cancer treatment. For example, NK1 receptor antagonists added value to an already established standard with 5-HT3 receptor antagonists in CINV. Bigger strides are needed in other areas of supportive care such as the treatment of mucositis, treatment-related fatigue, and prevention of neuropathy.

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