

FEATURE STORY

# Under New Management

BY PAUL ENGSTROM

*Newer and better supportive care drugs to control side effects are making treatments easier for patients.*

Two decades ago, treating the symptoms of cancer and side effects of therapy were almost an afterthought. Today, new drug combinations, targeted drugs, delivery of preventive medications, new delivery methods, and other innovations reflect a dramatic shift toward a greater focus on supportive care that is sparked by a wider recognition of the huge impact that symptoms and side effects have on patients' well-being.

Although many challenges remain, supportive care experts see substantial progress in treatments for some of the major problems that cancer patients undergoing treatment have long feared or struggled with, including nausea and vomiting, pain, and constipation. They also see promising advances on the horizon.

Thanks to preventive agents such as Emend (aprepitant), a minority rather than a majority of patients receiving chemotherapy that can cause severe nausea and vomiting now experience these side effects, says Paul Hesketh, MD, chief of the Division of Hematology and Oncology at Caritas St. Elizabeth's Medical Center in Boston. "If you look over the last 20 years," he says, "we've made enormous progress in preventing nausea and vomiting."

There have also been significant strides on the pain management front.

"When I started doing pain management a long time ago, we had a bunch of opioids and anti-inflammatory drugs, and we used two or three non-traditional analgesics for selected problems like nerve pain," says Russell Portenoy, MD, chairman of the Department of Pain Medicine and Palliative Care at Beth Israel Medical Center in New York.

"Now the list of nontraditional analgesics—drugs that are on the market for other reasons, but are used for various types of pain—has grown to probably 60 or 70.

We have so many more options for nerve pain, for bone pain, for bowel obstruction pain. I'm pretty optimistic that in the next 10 years research will bring a whole series of new chemical entities with the capacity to help some people with pain."

Supportive care has become more complex and refined in recent years for several reasons. One is the greater focus on patients and their quality of life, rather than just on the disease. Better recognition and treatment of symptoms and side effects has involved a cultural shift in the way oncologists, nurses, and other health professionals care for patients.

### [View Illustration: Cancer Pain at Its Source](#)

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A second reason is the mushrooming number of cancer treatments, each with its own potential side effects. Researchers are devoting much more attention than they did in the past to understanding the physiology of these myriad effects so that tailored management therapies, especially preventive agents, can be developed.

Finally, many patients are living longer, which means there are more opportunities for symptoms and side effects to arise. In earlier decades, lung cancer patients who were given a poor prognosis typically received only morphine to ease their pain, says Neal Slatkin, MD, director of the Department of Supportive Care, Pain and Palliative Medicine at City of Hope Medical Center in Duarte, California. These days, treatments that inhibit growth factors are improving outcomes for some lung cancer patients but are also causing side effects that require their own therapy.

"All the while, you're trying as best as possible to balance the side effects of treatment with quality of life," Slatkin says.

### [The Rise of NK-1s](#)

The newest class of combination drugs for chemotherapy-induced nausea and vomiting are the neurokinin-1 receptor antagonists, including Emend, which has been on the market since 2003, and Rezonc (casopitant), a similar compound still in clinical trials.

NK-1 receptor antagonists block cell receptors in the small intestine that are stimulated by chemotherapy. They follow a class of drugs—5-hydroxytryptamine (5-HT<sub>3</sub>) antagonists—that revolutionized management of nausea and vomiting in the early 1990s and now consist of five widely available agents, including Zofran (ondansetron), Kytril (granisetron), and Aloxi (palonosetron).

"NK-1 antagonists are clearly better than anything we've ever had," says Richard Gralla, MD, vice president for cancer services and chief of hematology and oncology at North Shore-Long Island Jewish Health System in Manhasset, New York. "There's some evidence, although it is speculative, that perhaps higher

doses of NK-1 are very safe and might further escalate the ability to prevent nausea and vomiting.”

## View Chart: Agents in the Pipeline

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Because some chemotherapy drugs rarely or never cause nausea and vomiting, while others nearly always do, oncologists decide which NK-1 agent to use preventively based on the type of cancer treatment, Gralla says. “The biggest barrier right now,” he adds, “is understanding the proper dosing and scheduling of these drugs.”

Despite the advent of 5-HT<sub>3</sub> and NK-1 antagonists, many patients still experience acute nausea and vomiting during chemotherapy. Two oral medications now available for these patients are Marinol (dronabinol) and Cesamet (nabilone). They contain synthetic cannabinoids, compounds found in marijuana. Research suggests that combining cannabinoids with dopamine receptor antagonists—drugs used for chemotherapy-related nausea and vomiting and as antipsychotics and antidepressants—is more effective against acute nausea and vomiting than either alone.

The American Society of Clinical Oncology updated its guidelines in 2006 to recommend use of a 5-HT<sub>3</sub> antagonist, dexamethasone (a steroid), and Emend to prevent acute chemotherapy-induced nausea and vomiting.

## Stopping the Pain

Drug mixes are also a current trend in pain management, according to Tom Smith, MD, chairman of the Division of Hematology/-Oncology and Palliative Care at Virginia Commonwealth University Massey Cancer Center in Richmond. Clinicians might administer morphine or another opioid plus the anti-seizure drug Neurontin (gabapentin) to control the burning, shooting, or stinging sensation caused by nerve damage—a kind of pain that is unlike the deep aching pain of cancer and that calls for more targeted management.

A number of cancer-related factors—a tumor and its effects, surgery, chemotherapy, and radiation—can damage nerves and lead to pain (see illustration). Extensive research has shown that fear of pain and depression may increase the perceived severity, such that patients may need medications to treat both its physical and psychological aspects. A number of antidepressants, among them Elavil (amitriptyline) and Cymbalta (duloxetine), have proven effective against neuropathic pain.

For relief of moderate to severe pain, most patients receive opioids such as morphine or a more potent narcotic such as fentanyl. But “there aren’t a whole lot of new opioids on the market for treating any cancer pain,” Smith says. “We’ve got a couple of long-acting ones and a couple of short-acting ones, but there haven’t been any great advances in terms of either.”

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—Russell Portenoy, MD

One modest advance is Fentora (fentanyl buccal tablet), a new opioid formulation that alleviates breakthrough, or sudden and short-lived, pain. A recent study involving 30 outpatient centers in the United States concluded that the tablet also seems to work well in patients with both breakthrough and chronic pain.

A pain-relieving mouth spray, Sativex, contains a marijuana extract that does not make users high. Canada has approved Sativex for moderate to severe cancer pain and for nerve pain caused by multiple sclerosis. Clinical trials are under way that could lead to approval in the United States.

### Byproduct of Relief

A frequent side effect of opioids themselves is constipation. An important step forward in preventing this type of constipation in patients with advanced disease was the Food and Drug Administration’s approval in April of Relistor (methylnaltrexone), which reverses the effect that opioids have on the bowel.

“We’ve had many, many patients over the years who curtailed their use of opioids due to constipation, which they found more distressing even than the pain they were experiencing,” says Slatkin. “Now we have a very targeted therapy that can relieve opiate-induced constipation without causing any worsening of pain and without causing opiate withdrawal.”

A third recent advance is administering opioids in ways that are fast-acting and also easier, more acceptable, or more convenient for patients than intravenous delivery. In addition to the tablet Fentora, similar products include Actiq (transmucosal fentanyl citrate), a lozenge rubbed on the inside of the cheek for sudden pain, enabling the drug to enter the bloodstream quickly, and a longer-acting fentanyl skin patch called Duragesic for chronic pain.

Smith cites “very exciting work” at Mayo Clinic in Rochester, Minnesota, where researchers have tested calcium and magnesium to prevent the nerve damage and pain caused by Eloxatin (oxaliplatin), a common chemotherapy for advanced colon cancer. In a small Mayo Clinic study of 102 patients, calcium-magnesium infusions before and after chemotherapy reduced the debilitating pain that often prompts patients to halt Eloxatin treatment.

The hope, Smith says, is that newer intravenous drugs on the horizon, including investigational compounds derived from snake and sea snail venoms, would go right to the site of damaged nerves and help repair them, thereby alleviating pain. “That’s still a few years away, but I think it’s going to be a potentially exciting time,” he says.

## Fatigue Still A Puzzle

A common side effect of chemotherapy and radiation that still poses great difficulty is fatigue, mostly because the mechanism remains unclear and fatigue can be related to one or more symptoms, among them depression, pain, sleeplessness, or sleepiness during the day as a result of insomnia. Moreover, chemotherapy often causes anemia, a reduction of oxygen-carrying red blood cells that makes patients feel tired.

Gary Morrow, PhD, a professor of radiation oncology and psychiatry at the University of Rochester Medical Center in New York, says researchers have investigated a variety of possible therapies, including the antidepressant Paxil (paroxetine) and Ritalin (methylphenidate), an amphetamine-based psycho-stimulant often used to treat attention deficit disorder. Results, however, have been disappointing. Morrow says a problem with these and other agents, such as steroids, is that they can cause significant side effects of their own. Psychostimulants, for example, carry a dependence risk, aren't well tolerated by elderly patients, and aren't useful over the long term.

"Nothing is either totally safe or totally without consequences," Morrow says. "So far, no one has come up with something that seems to offer a reasonable trade-off."

At this year's ASCO meeting, Morrow presented findings from his study on the effectiveness of Provigil (modafinil), an FDA-approved drug for narcolepsy, for fatigue in patients undergoing chemotherapy. Patients with severe fatigue reported a significant improvement after receiving Provigil, but there was no significant improvement among those with mild to moderate fatigue.

Why Provigil may be more effective in treating severe fatigue is unclear, but Morrow noted any amount of relief from a severe side effect will be more noticeable to patients.

Meanwhile, researchers are investigating whether Nuvigil (armodafinil), an approved medication for excessive sleepiness, is effective against fatigue associated with cancer treatment.

## Breaking the Fall

Some types of cancer therapies accelerate the natural demineralization of bone, causing osteoporosis and increasing the risk of fracture, especially in the hip, vertebra, and wrist. Bone loss occurs most often in breast and prostate cancer patients undergoing hormone-modifying treatments.

The goal in preventing this side effect is to halt the breakdown of bone caused by the withdrawal of estrogen or testosterone—hormones that feed cancer.

Bisphosphonates, including Zometa (zoledronic acid), Fosamax (alendronate), Aredia (pamidronate), Actonel (risedronate), and Boniva (ibandronate), are the most effective treatments for cancer-related bone loss. They increase bone

mineral density by attaching to the surface of bone and stopping the unhealthy resorption of bone tissue that can take place when hormones are withdrawn during cancer therapy. A recent addition to the class of bisphosphonates—Reclast (zoledronic acid) for postmenopausal osteoporosis—is administered just once a year by infusion. Other bis-phosphonates are administered in daily, weekly, and monthly oral and intravenous formulations.

The most promising investigational agents for preventing bone loss, and the ones furthest along in clinical testing, are receptor activator of NF- $\kappa$ B -ligand (RANKL) blockers, says Allan Lipton, MD, a researcher and oncology division chief at the Milton S. Hershey Medical Center of Penn State College of Medicine in Hershey. RANKL is part of a pathway that controls the activation, differentiation, proliferation, and survival of bone-eating cells called osteoclasts, so blocking that pathway reduces bone loss.

A recent study of more than 1,400 men undergoing androgen-deprivation therapy for prostate cancer found that denosumab, a human monoclonal antibody and RANKL blocker, improved bone density and reduced the risk of vertebral fracture. The RANKL approach “seems to be very well tolerated and very effective so far in shutting down osteoclast function,” Lipton says. “It doesn’t have any renal toxicity either,” a side effect possible with bisphosphonates.

Another encouraging agent in the research pipeline, says Lipton, is odanacatib, an oral cathepsin K inhibitor. Early studies suggest odanacatib, which inhibits the cathepsin K enzyme in osteoclasts that breaks down protein in bone, reduces bone turnover in women with breast cancer and bone metastases.

Much work remains to be done on managing cancer-related symptoms and side effects, but experts are generally optimistic that the years ahead will see further progress.