New Pain Drugs in Pipeline, but Challenges to Usage Remain

By Vicki Brower

Over the past two decades, pain control has become a front-burner issue among oncologists, but glaring problems in treating pain remain, a new survey shows.

Barriers limiting pain control include patients’ reluctance to report pain and to take opioids, coupled with physicians’ reluctance to prescribe them, as well as increasing regulatory barriers, according to a study in the Nov. 14 online issue of the Journal of Clinical Oncology.

“In the 1980s, pain control got a lot of attention, but in the past two decades, medical expertise has not progressed as well as treatment for cancer itself,” said Russell Portenoy, M.D., an author of the study and chairman of the department of pain medicine and palliative care at Beth Israel Medical Center in New York.

“The drugs we have are not good enough, and we are not using the drugs we do have effectively,” according to Judy Paice, R.N., Ph.D., director of the cancer pain program at the Feinberg School of Medicine at Northwestern University in Evanston, Ill.

Types of Pain

The JCO study emphasized that not all pain is equal. “Patients with multifocal pain, those who are medically frail, and patients with neuropathic pain are more difficult to treat,” said Portenoy. “Up to 50% of patients with cancer, and 75% with advanced disease, have pain not adequately controlled with opioids and other drugs,” said Paice.

According to Clifford Woolf, M.D., Ph.D., professor of neurology and neurobiology at Harvard University in Boston, about 10 individual neurological mechanisms are involved in initiating and sustaining pain. His lab has identified the variant of a gene that makes an essential cofactor for the enzymes that synthesize amines and nitric oxide; this variant gene protects against developing pain by reducing synthesis of the cofactor in response to stress. Woolf is now working on making pain-susceptible individuals pain-resistant by mimicking the effect of the pain-protective gene variant with an enzyme inhibitor. Ultimately, he expects that no one type of analgesic will treat cancer pain but that control will be tailored to each patient.

Inflammatory pain is hypersensitivity to a defined pathology, such as a tumor pressing on an organ or radiation damage of sensitive tissues. By contrast, neuropathic pain results from altered neural processing due to damage to the nervous system, such as a tumor invading a nerve. Neuropathy typically continues even when a tumor is removed. Cancer pain is often a complex mixture of these two types of pain. Pain also has a heritable component, so in the long term, defining who is at risk and identifying ways to pharmacologically reduce that risk will be important, Woolf said.

Much current research is focusing on peripheral neuropathy, a common side effect of many anticancer drugs, including bortezomib, thalidomide, vincristine, platinum-based compounds, and taxanes. Joint and muscle pain from tamoxifen or other antiestrogenic drugs, mucositis from high-dose chemotherapy for bone marrow transplantation, and bone pain from prostate and breast metastases are also a focus of current research.

Neuropathic pain is extremely difficult to treat, because a limited number of only partially effective drugs exists. Experts estimate that 40%–50% of cancer patients experience neuropathic pain, which affects peripheral nerves and is characterized by sensitivity to innocuous as well as noxious stimuli—and often persists after tissue damage has healed. Chemotherapy-induced neuropathic pain (CINP) is a dose-limiting toxic effect of many drugs, but several new drugs to address CINP are in the works.

In October, the Journal of Pain and Symptom Management published phase IIa results of a double-blind, placebo-controlled, randomized, dose-escalation trial with KRN-5500. A derivative of the Streptomyces bacterium, KRN-5500 met the primary endpoints of pain reduction and safety and was superior to placebo, with some gastrointestinal side effects. The U.S. Food and Drug Administration fast-tracked the drug in August. Dara BioSciences, its developer, is working on a new formulation to reduce or eliminate the gastrointestinal side effects and is investigating its mechanism of action, which does not affect inflammatory pain, said Linda Jett, M.S.N., clinical director of drug development at Dara BioSciences.

Another neuropathic pain drug from Wex Pharmaceuticals of Vancouver, Canada, is the tetrodotoxin-based drug TTX-CINP-201. The company is planning a multicenter, phase II double-blind, placebo-controlled, randomized trial to treat moderate-to-severe CINP. Derived from the puffer fish, TTX is a nonpeptide, nonopioid neurotoxin that selectively blocks voltage-gated sodium channels located on nerves that conduct pain impulses. Wex is also developing another drug, TEC-006, to treat moderate-to-severe cancer-related pain as an opioid alternative in phase III Canadian trials. Unlike opioids, TTX-related drugs are nonaddictive and have no neurological and gastrointestinal side effects.

Potential Benefits of Cannabis?

Research into cannabinoids derived from marijuana is yielding many drug candidates. Sativex, developed by GW Pharma of Wiltshire, UK, is a cannabis extract now in two phase III trials for cancer pain and neuropathic pain. The drug is approved in Canada for spasticity and neuropathic pain.
in multiple sclerosis and as an adjunctive analgesic in patients with advanced cancer pain unrelated by opioids. Sativex, an oral-mucosal mouth spray, contains the principal psychoactive component of marijuana, THC (tetrahydrocannabinol), and CBD (cannabidiol), which bind to the cannabinoid receptors, said Director of R&D Stephen Wright, M.D. Sativex will be launched in several European countries during 2012.

Other researchers are homing in on CBD to treat pain as well as cancer itself. In a new preclinical study published in the October Anesthesia and Analgesia, low doses of CBD prevented CINP in mice treated with paclitaxel. “When given first, CBD prevented CINP, and when given on day 11 of chemotherapy, the drug reversed CINP,” said Sara Jane Ward, Ph.D., study leader and research assistant professor at Temple University’s School of Pharmacy in Philadelphia. “The mechanism of action of CBD is thought to be only marginally connected to the cannabinoid receptors. Instead, it appears to inhibit adenosine uptake and is also involved in TRP [transient receptor potential] ion channel activity.” TRP ion channels mediate pain and other sensations.

Ward’s colleague, Sean McAllister, Ph.D., a researcher at the California Pacific Medical Center Research Institute in San Francisco, has found that CBD also affects cancer itself. Writing in the August 2011 Breast Cancer Research and Treatment, he says, “CBD appears to inhibit the ID-1 [DNA-binding protein inhibitor] gene, which is involved in primary tumor growth, and invasion and metastasis in breast cancer and glioma cells.” McAllister is working to develop CBD-derived ID-1 inhibitors for breast cancer and glioma.

“New data also indicate that by targeting ID-1, we can resensitize cancer cells immune to first-line chemotherapy,” McAllister said in an interview.

**New Approaches to Opioids**

Opioids remain the standard for pain control. A new targeted gene therapy, called NP2, blocks pain signals locally with an HSV (herpes simplex virus) vector to deliver the naturally occurring opioid peptide enkephalin to sensory nerves. By local targeting, this therapy bypasses the central nervous system and causes none of the typical opioid-related side effects such as nausea, drowsiness, and constipation.

David Fink, M.D., chair of neurology at the University of Michigan in Ann Arbor, created a noninfectious form of the virus to locally deliver analgesic genes. In the August Annals of Neurology, Fink published a phase I study showing that higher dose of the treatment produced substantial pain relief in 10 terminally ill patients with intractable pain. “Sensory nerves naturally take up HSV, which delivers a pain-relieving chemical in a controlled site in the pain pathway,” Fink said. Patients receiving a low dose of the treatment had little pain relief, but those getting higher doses had a greater than 80% reduction in pain over 4 weeks after one treatment. The technology, which Fink developed over two decades with partner and wife Marina Mata, M.D., and Joseph Glorioso, Ph.D., of the University of Pittsburgh, is licensed by Diamyd Medical of Stockholm, Sweden. In an ongoing phase II open-label extension study, 32 non-terminally ill patients will receive up to three doses of NP2.

Fink has modified the vector to deliver other analgesic genes as well, including GAD (glutamic acid decarboxylase), to treat neuropathic pain, he said. Fink is also researching nerve growth factor 3 with a grant from the National Institutes of Health to determine whether it might prevent CINP in patients who receive high-dose platinum-based chemotherapy.

Another opioid drug in development is Nektar Therapeutics’ NKTR-181, an oral mu-opioid agonist developed with polymer conjugate technology to reduce abuse potential and central nervous system side effects, including depressed respiration and sleepiness. Nektar presented interim results of its phase I trial in September at the American Academy of Pain Management’s annual meeting, showing that the drug enters the brain slowly and does not cause the euphoria that occurs when healthy subjects take conventional opioids. All but the highest dose was well tolerated. A phase II study begins in 2012, said Chief Medical Officer Robert Medve, M.D.

**Barriers to Pain Control**

Although new therapies are in process, recent federal and state legislative initiatives are sharply restricting patient access to certain opioids. SkYROcketing rates of prescription drug addiction and deaths from opioid overdoses are driving these changes, reflected in a Nov.1 report from the Centers for Disease Control and Prevention showing that the number of deaths annually from prescription drug overdoses has nearly quadrupled in the past decade.

In New York, legislative changes have already made the job of physicians treating cancer pain more difficult, said Kathleen Foley, M.D., attending neurologist in the pain and palliative care service at Memorial Sloan–Kettering Cancer Center. “Medicaid changed its formulary so that now, instead of being able to prescribe hydromorphone, we have to prescribe methadone—when that is not necessarily the best drug for a patient’s pain,” she said. “We are seeing a changing pattern of drugs being prescribed in hospitals here,” Foley added.

The New York State attorney general is proposing an online, real-time database for pharmacists and physicians to prevent what the Government Accountability Office referred to in an October 2011 report as “Medicare subsidization of drug abuse by thousands of its members who ‘doctor-shop’ to fill larger quantities of narcotics than any patient can use safely.”
But, as Foley argues, cancer patients may need large quantities of opioids for adequate pain control and may legitimately see several physicians from whom they receive prescriptions, without “doctor shopping.” She opposes guidelines to set a maximum dose or number of pills per patient. “This is just politics dictating science,” Foley said.

Paice is more concerned with the chilling effects on prescribing that FDA’s REMS (Risk Evaluation and Mitigation Strategy) program has had (see JNCI News 2009;101:1376–7). “A new short-acting fentanyl for breakthrough pain is not being used much by physicians because of the paperwork and procedures REMS requires from physicians,” she said. A recent study showed that at least half of patients experience serious, untreated breakthrough pain. She and others are concerned that REMS will eventually be extended to all opioids, which will mean that less-safe drugs containing acetaminophen, which are easier to prescribe, will be used instead of oxycodone and morphine.

According to Portenoy, one of the biggest problems is the dearth of pain education among oncologists. The study showed that the number of continuing medical education hours does not equate with better pain management skills, and only 14% of oncologists referred patients with complicated pain to pain specialists. And those experts often use drugs that the oncologist will not know how to use. For example, ketamine—an NMDA receptor often used in palliative care—is effective when patients are pretreated with benzodiazepines and somatostatin (or its analog, octreotide), used for pain for bowel obstruction. Other treatments, such as neuraxial analgesics, which are administered into the spine, can have dramatic effects on pain and few side effects.

“Education for oncologists has not kept up with technology, and oncologists rarely make patient referrals to pain specialists because oncologists are imbued with an ethic of treating the whole patient,” Portenoy said. “It is time to reinvigorate our education when it comes to pain control for cancer patients.”