

CLINICAL UPDATE

Translating Scientific Advances into Clinical Practice

Recent Advances in the Treatment of Cancer Pain

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H&O About how many oncology patients experience pain associated either with their cancer or with their cancer treatment?

RP Large, epidemiologic studies from the past 25 years suggest that about one-third of patients who are undergoing active treatment for cancer will have pain severe enough to warrant treatment with an opioid drug. This proportion increases to as high as 75–90% in the population with far-advanced illness.

The nature of the pain is very diverse. Approximately 75% of the pain comes from direct involvement of the tumor, and approximately 15% or 20% comes from the cancer treatments. In a small proportion of patients with chronic pain, the pain is not related to the tumor or the treatment.

H&O Is most cancer pain treated according to accepted guidelines?

RP A number of studies have looked at the current ability of healthcare systems in developed countries (mostly in Europe and North America) to address the pain problem. Although there is much diversity in these studies, what most of them suggest is that approximately 30% of patients with pain are still receiving therapy that would not be consistent with what is considered to be the standard of care. For more than 15 years, pain management has been considered to be a best practice in oncology. And as with any best practice, it has to be routinized, meaning that the assessment of pain should be part of every clinical encounter with a patient. Patients who say they have significant pain should undergo an assessment that would allow the physician to understand the nature of the pain and how best to develop a plan of care.

H&O What is the standard approach for cancer pain management?

RP Since the mid-1980s, there has been international acceptance of a very broad strategy for cancer pain management, which was developed by the World Health Organization (WHO). That strategy has been based on expert observation. There have not been many empirical tests of it, but it generally works. The strategy says that patients who have mild pain usually do all right with a non-opioid analgesic, such as acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). Patients who have moderate-to-severe chronic pain should receive an opioid, typically a combination agent that includes both an opioid and a non-opioid constituent, such as oxycodone and acetaminophen. They are short-acting. The group also includes drugs like tramadol and tapentadol, which are centrally acting, unique analgesics that have opioid characteristics but are not pure opioid drugs. These drugs are generally used for moderate pain in patients who are relatively opioid-naïve.

Patients who end up requiring a short-acting drug on a regular basis and still complain of pain, or patients who present with very severe pain, are typically treated with a pure mu agonist drug. However, I would reiterate that there is no strong empirical reason for a physician to not go directly to a pure mu agonist drug, even in patients who use the word *moderate* to describe the intensity of their pain. That approach will work just as well, as long as the doses are selected appropriately. But, conventionally, most clinicians feel comfortable with these combination products and will start with them and then transition the patient to a pure mu agonist if needed. In the United States and Europe, the usual course is to select a pure mu agonist that is long-acting for the convenience of the patient, in the hope that the patient's adherence to therapy will be facilitated. There are now multiple long-acting opioid drugs that are prescribed orally, including various formulations of morphine, a long-acting oxycodone, a long-acting oxymorphone, and a recently approved long-acting hydromorphone, as well as a transdermal fentanyl, which is a long-acting formulation administered through the skin. Historically, we have often included levorphanol and methadone under the long-acting drugs that might be used at this time when patients have persistent pain that is severe enough to warrant treatment with a pure mu agonist drug. Methadone is an inexpensive drug

with a unique pharmacology that can be extremely useful as an analgesic, but it can be used safely only if the prescriber knows about the specific characteristics of the drug that influence how it should be prescribed.

H&O What must physicians know about methadone?

RP There has been increasing concern in the United States about methadone-related toxicities. There has been an increase in the deaths associated with methadone use in pain patients (noncancer pain patients). It is now clear that physicians who want to safely prescribe methadone must know about 3 characteristics: The first is a variable half-life that ranges from 12 hours to 150 hours. Because the exact half-life is unknown, there is a need to monitor the patient longer until the physician can be assured that the patient is approaching a steady state. The second characteristic is the potential to increase the QTc interval, which has now been documented in several studies. Although the prolongation to critical levels appears to be uncommon, it is still a concern, particularly among patients with existing heart disease or who are taking other drugs that can increase the QTc interval. The third characteristic is that methadone has an uncertain potency when it is substituted for another pure mu agonist drug. What that means is that when methadone is administered after a patient has been receiving morphine, oxycodone, hydromorphone, or any other pure mu agonist drug, the dose of methadone that can be given safely is uncertain because of the characteristic called *incomplete cross tolerance*. The higher the dose of the drug the patient was taking initially, the greater the necessary reduction in the calculated equianalgesic dose of methadone. National guidelines say that the oncologist who wants to prescribe methadone after a patient has been taking another pure mu agonist drug must calculate the equianalgesic dose from the standard equianalgesic dose tables, and then reduce the calculated equianalgesic dose by 75–90% and start dosing the methadone from there.

H&O Are cancer patients who take opiates for pain at risk of developing an addiction?

RP Patients are very worried about addiction, and there has in fact been much evidence from studies showing that a fear of addiction will inhibit patients from taking the drugs they need. It is a clear obligation for the physician to reassure the patient that he or she need not worry about addiction. But having said that, it is also important for the oncologist to recognize that a cancer diagnosis does not protect against the problems of substance abuse or addiction. Oncologists should recognize that substance abuse and addiction are extremely common in the United States. Approximately 15% of individuals in the United

States are addicted to alcohol, 5–6% are addicted to cocaine or heroin, and as many as 25% are addicted to nicotine. Many people have a biologic predisposition to addiction, and the inappropriate use of drugs occurs frequently in clinical practice. Whenever an opioid is prescribed, the oncologist must assess the risk that the patient might engage in behaviors that are problematic. Now, obviously, this is all in context. If the drug is being given to a patient with far-advanced cancer who has a short life expectancy, it is less of a concern than if the drug is being given to a patient who has been cured of cancer or who has an indolent cancer. A drug prescribed to a patient who is older and who has never engaged in drug abuse is very unlikely to cause problems. But a drug prescribed to a young person who is actively abusing marijuana is much more likely to cause problems.

The take-home message is this: Oncologists who prescribe opioids need to reassure patients, but every time they prescribe an opioid, they need to perform a risk stratification to assess the likelihood that the patient will be a responsible drug user or not. There are 3 questions: Does the patient have a personal history of alcohol or drug abuse? Does the patient have a family history of alcohol or drug abuse? Does the patient have a major psychiatric disorder? If the answer to any of these questions is yes, then the oncologist should consider categorizing the patient as a “relatively high-risk patient.” The prescribing regimen should then include enough monitoring so that the oncologist can feel comfortable over time that the patient will remain responsible with the drug use.

H&O What is breakthrough pain?

RP In cancer patients, the term *breakthrough pain* typically refers to a transitory flare of pain in the setting of chronic pain that is managed with opioid drugs. It has received much attention during the past 10 years because the pharmaceutical industry has developed products that are now specifically indicated for cancer-related breakthrough pain. The development of these products followed some epidemiologic studies showing that episodic severe pain is very common in patients with cancer—somewhere between one-third and two-thirds of patients will have these severe episodic pains. Patients who have severe episodic pains are more likely to have a bad pain syndrome—one associated with functional disturbance, mood disturbance, and higher cost of care.

Recognizing that these severe, episodic pains do represent a significant problem, physicians have been prescribing a short-acting opioid in combination with a long-acting opioid for a long time. The short-acting opioid has traditionally been called the *rescue dose*. Rescue doses have been used in combination with a fixed-scheduled regimen for many years.

About 10 years ago, a fentanyl lozenge was released, the goal of which was to provide a more rapid onset of relief for breakthrough pain. The lozenge is sucked so that the fentanyl—a lipophilic opioid—is absorbed through the mucosal membranes of the mouth and goes directly into the blood, bypassing the gastrointestinal tract. This formulation proved to be helpful to some patients and led to the development of other products with the same intent. In the United States, we have 3 approved products, and around the world, there are 6 approved products, which are the so-called *rapid onset opioids* for breakthrough pain.

The bottom line is that breakthrough pain is now considered to be a significant phenomenon in cancer patients, with a high prevalence and a high likelihood of being associated with adverse consequences. The treatment of breakthrough pain using a rescue dose is now the standard of care. Most patients are still being treated with an oral short-acting drug that is co-administered with a long-acting drug for background pain, but if a patient has a very rapid onset of pain or does not benefit enough from the oral drug because the pain comes on too quickly, then he or she might be considered for a trial of one of the rapid onset agents.

H&O What are some of the newer treatment options or approaches in cancer pain management?

RP Cancer pain management can be accomplished through the use of several different therapeutic categories. Pharmacotherapy is the most common, and it usually works well. Pharmacotherapy includes non-opioids, opioids, and adjuvant analgesics. There have been recent developments in each of these categories. In the non-opioid group, it is now recognized that NSAIDs are associated with cardiovascular risk and a risk of increasing blood pressure. In the opioid class, there are some new delivery systems, including the rapid-onset formulation and a once-daily hydromorphone, which has recently been approved. Also recently approved are 2 so-called *abuse-deterrent formulations*, one for oxycodone and one for morphine. These abuse-deterrent formulations have been developed in an effort to reduce accidental overdose and, perhaps, diversion. It is hoped that they might benefit public health, although it is not yet known whether or not they will do so. Oncologists will soon begin to see these drugs advertised as alternatives to the usual oxycodone and morphine formulations. They are the same molecule, but they are in a pill that cannot be adulterated in the same way other pills can be, so they are much less likely to be crushed and injected or crushed and snorted. It is likely that we will see more of these abuse-deterrent formulations on the market for the treatment of chronic

pain of any type, and this represents a change that oncologists must address.

Adjuvant analgesics should be considered nontraditional analgesics that are used in specific circumstances. One of the most important happenings in the last 10 years is the development of more and more drugs for neuropathic pain. Between 30–40% of chronic cancer pain is neuropathic. This type of pain may not respond as well to opioids as other pains. If a patient has a neuropathic pain that is not responding adequately to an opioid, then oncologists should know that there are other effective drugs. The most common are the gabapentinoids—either gabapentin or pregabalin—and there are also a variety of analgesic antidepressants that are used as first-line treatment for neuropathic pain. Historically, corticosteroids have also been used effectively for neuropathic pain, and there are many other agents if the more conventional ones do not work. As research continues, oncologists will begin to learn more about the role of these supplemental agents that can be used in specific circumstances.

Beyond pharmacotherapy, patients with cancer pain may be candidates for some more sophisticated pain management approaches. For example, pain specialists are able to use neuraxial infusion, which is an infusion of medications into the spine on a continuous basis. These medications can be delivered by an implanted pump, or, in certain patients, through an external system. There is at least one randomized study that shows that the use of an intrathecal pump yields better pain control and fewer side effects than conventional pain management. Pain specialists can offer a trial of spinal cord stimulation or peripheral nerve stimulation to treat severe neuropathic pain, which is another common approach for noncancer pain that might be appropriate for some patients with cancer pain.

H&O What is the role of palliative medicine in cancer pain management?

RP In the United States, palliative care has developed a very dramatic momentum during the past decade. In 2006, hospice and palliative medicine was designated an official subspecialty of American medicine. The Accreditation Council on Graduate Medical Education has approved formal fellowship training programs in hospice and palliative medicine. We therefore have a growing number of palliative medicine physicians, all of whom are trained to perform pain management, and could act, perhaps, as a resource for the oncologist faced with a difficult case. The resurgence of interest in pain management—which is very important—can be linked to the growth and development of palliative care in the United States.