Opioid Crisis Spurs New Strategies for Cancer Pain

BY DARCY LEWIS

IT WASN'T TOO MANY years ago that the primary concerns related to pain management for patients with cancer revolved around whether they were getting adequate relief. Now, with the United States in the throes of an opioid epidemic, the use of these powerful and addictive pain relievers for patients with cancer is coming under unprecedented scrutiny.

Major cancer centers are examining their current protocols to develop new ways to manage pain with shorter courses of opioids—or, if appropriate, with nonopioid approaches. Oncologists are increasingly being advised to assess patients for their risk of developing opioid dependence and monitor them for signs of abuse.

As more patients achieve long-term survivorship, the need for better management of pain medication will become more pressing, Alison Wakoff Loren, MD, MSCE, noted recently in a perspective for the *New England Journal of Medicine.*[1]

"Oncologists are accustomed to giving opioids, but we must also be comfortable taking them away and sometimes giving them in limited doses or not at all," wrote Loren, an associate professor of medicine in the Division of Hematology/Oncology at the Hospital of the University of Pennsylvania in Philadelphia. "We need to be aware of risk factors for substance use disorders and tools for preventing and addressing them… Although many cancer survivors live with chronic health issues caused by their treatment, opioid addiction should not be one of them."

DIMENSIONS OF THE EPIDEMIC

The emphasis on opioid prescribing practices in cancer care comes amid a grim litany of statistics about the nation's drug abuse problems. Prescription opioids have been identified as significant contributors to the overdose epidemic. The Centers for Disease Control and Prevention (CDC) reports that more than 35% of all US opioid overdose deaths in 2017 involved a prescription.[2]

In 2018, *JAMA Network Open* published a serial cross-sectional study that found that the percentage of deaths in the United States attributed to opioids rose 292% between 2001 and 2016.[2] That increase, from 0.4% (1 in 255) to 1.5% (1 in 65), represents 1.68 million years of life lost. During the same period, the rate of US opioid-related deaths increased from 3.3 to 13.1 deaths per 100,000.[3]

The age group bearing the highest burden was adults aged 25 to 34 years; in this age group, 1 in 5 deaths in the United States is now opioid related. However, adults aged 55 to 64 years, the most likely age group to be coping with cancer, experienced the largest relative increase in the proportion of deaths attributable to opioods, with an increase of 754%, from 0.2% to 1.7%.[3]

But what about opioid-related deaths and addiction among patients with cancer? Several medicines commonly used to treat cancer pain, including fentanyl, hydrocodone, methadone, morphine, and oxycodone, were among the drugs most frequently involved in fatal overdoses in the United States from 2011 to 2016, according to the CDC's National Center for Health Statistics.[4]

However, there are few statistics on the incidence and impact of opioid abuse among patients with cancer. Findings from a study presented at the American Society of Clinical Oncology (ASCO) 2018 Quality Care Symposium showed that patients with cancer were less likely to die of an opioid overdose than the general population. Nevertheless, the incidence of these deaths rose over a 10-year period (**See story, page 24**).[5]

Meanwhile, results from other studies indicate that many patients with cancer face a high risk of misusing prescription opioids. Investigators at The University of Texas MD Anderson Cancer Center in Houston found that 29% of 522 patients whose charts they reviewed were at high risk for opioid misuse. Patients with scores ≥4 on the Screener and Opioid Assessment for Patients with Pain-Short Form were more likely to be younger than 55 years, have a higher morphine-equivalent daily dose, and report more feelings of

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pain, depression, and anxiety.[6]

At the University of Michigan in Ann Arbor, investigators examined patterns of persistent opioid use among patients with cancer who had undergone curative-intent surgery from 2010 to 2014. The review consisted of insurance claims from 68,463 patients who had surgery for melanoma, breast, colorectal, lung, esophageal, and hepato-pancreato-biliary/gastric cancer. The findings showed that the risk of new persistent opioid use among opioid-naïve patients was 10.4% (95% CI, 10.1%-10.7%). A year after their surgeries, these patients were filling prescriptions with daily doses equivalent to 6 tablets per day of 5-mg hydrocodone.[7]

THE CDC'S RESPONSE

In response to the broad public health crisis, the CDC sought to take control of the situation in 2016 by issuing the *CDC Guideline for Prescribing Opioids for Chronic Pain*.[8] These voluntary guidelines apply to the prescribing of opioid pain medication for patients 18 and older in primary care settings. Although they specifically exclude active cancer treatment, palliative care, and end-of-life care, the CDC guidelines have nonetheless had a significant effect on both oncologists and their patients.

Key features of the CDC guidelines include reduced dosage recommendations compared with previous versions. Additionally, earlier guidelines stratified risk, urging extra safety precautions for patients deemed to be at high risk of opioid-related difficulties. The new guidelines note that "opioids pose risk to all patients, and currently available tools cannot rule out risk for opioid use disorder or other serious harm" and are more specific with preferred strategies for both monitoring and discontinuing opioids.

The National Conference of State Legislatures reports that, in response to the CDC guidelines, 33 states had enacted legislation that imposed limits or requirements related to opioid prescribing by October 2018.[9] The most common legislative action is to limit new opioid prescriptions to a set number of days, most often 7 days. Some states also set dosage limits in morphine milligram equivalents or require compliance with state prescription drug monitoring programs. States generally exempt treatment for cancer and chronic pain and palliative care from prescription limits, although the increased administrative requirements apply to all prescribers.

TABLE. NCCN GUIDELINES FOR MANAGING CANCER PAIN ≥4 IN OPIOID-TOLERANT PATIENTS[11]

- NCCN opioid-tolerant definition: patients chronically receiving opioid analgesic on a daily basis.
- FDA definition: those receiving at least 25 mcg/h fentanyl patch, at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphine daily, or an equianalgesic dose of another opioid for a week or longer.

Pain ≥4 (moderate to severe)	
Initial dose	
Oral analgesic	IV bolus
• Oral opioid dose equivalent to 10%-20% of total opioid taken in previous 24 hours → Reassess efficacy and adverse effects at 60 minutes.	• IV opioid dose equivalent to 10%-20% of the total opioid taken in the previous 24 hours → Reassess efficacy and adverse effects at 15 minutes.
Subsequent dose	
• Pain unchanged or increased → Increase dose by 50%-100%; reassess.	
• Pain decreased but inadequately controlled → Repeat same dose; reassess.	
• Pain improved and adequately controlled → Continue at current effective dose as needed over initial 24 hours.	
Subsequent pain management	
Oral analgesic	IV bolus
After 2-3 cycles pain increased, unchanged, or inadequately controlled	
• Consider IV titration and/or consult NCCN subsequent pain management of moderate to severe pain ≥4 for opioid-tolerant patient.	• Consult NCCN subsequent pain management of moderate to severe pain ≥4 for opioid-tolerant patients.
Pain improved or adequately controlled	
• Consult NCCN management of mild pain 0-3 for opioid-tolerant patients.	

IV indicates intravenous; NCCN, National Comprensive Cancer Network.

Insurers have also responded to the CDC guidelines. For example, America's Health Insurance Plans launched its Safe, Transparent Opioid Prescribing Initiative in 2017. A centerpiece of the benchmarking project is collecting data from more than 40 health plans "with the hope that it will encourage widespread adoption of the Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain," as the trade association's president, Matt Eyles, wrote on the group's website.[10]

Many insurers now take an active role in directing physicians' opioid-prescribing practices, whether by increasing documentation requirements or by requiring trials of nonopioid medications before authorizing opioids. It's also become common for insurers and health systems to track institutional and individual prescriber compliance with the CDC guidelines.

GUIDELINES FOR THE ONCOLOGY COMMUNITY

Since these large-scale policy directives from governmental bodies, professional societies, payers, and health systems will undoubtedly continue, oncologists will have to think creatively to manage their patients' pain effectively within today's challenging atmosphere, experts say.

The National Comprehensive Cancer Network has incorporated recommendations for managing the pain of patients who have become tolerant to opioids into its supportive care pain guidelines for adult patients. The guidelines suggest dose reductions followed by additional assessment and specialist consultation for those who continue to report moderate to severe pain (**TABLE**).[11]

ASCO guidelines advise cancer care providers to screen patients for pain levels at every visit, and for those who report chronic pain (lasting ≥3 months), prescribe systemic nonopioid analgesics and adjuvant analgesics. Opioids may be considered for those who do not respond to more conservative choices. The guidelines also stress the need for clinicians to learn about precautions and strategies to help their patients avoid opioid abuse.[12]

Cancer centers also are experimenting with pain management practices in an effort to decrease opioid use. For example, gynecologic surgeons at Roswell Park Comprehensive

Cancer Center in Buffalo, New York, tested a protocol to restrict the prescribing of opioids. Patients who underwent minimally invasive/ambulatory procedures and had no history of chronic pain received a 7-day supply of prescription-strength ibuprofen or acetaminophen. Patients who required 5 or more pills/doses of opioids or who had a history of chronic pain requiring opioids received a 3-day prescription, as opposed to the state-allowed 7-day prescription.[13]

The protocol resulted in an 89% reduction in the number of opioid tablets dispensed at discharge and a high rate of patient satisfaction, according to study findings presented at the 2018 Society of Gynecologic Oncology Annual Meeting.[13]

A LARGER ROLE FOR PHARMACISTS

Collaborative approaches also are recommended. Pharmacists have always been valuable partners to oncologists in optimizing patients' medications for their pharmacological expertise; now, their strategic and supply-chain knowledge can add even more value.

William Dale, MD, PhD, the Arthur M. Coppola Family Chair in Supportive Care Medicine at City of Hope Cancer Center in Duarte, California increasingly relies on his pharmacy colleagues for strategic support in managing patients' access to opioids.

"When we first encountered the more restrictive policies here, we began weekly meetings with pharmacy about which opioids were available so that, at least on the inpatient side, we didn't suddenly run out of medicines," he said in an interview with *OncologyLive®*. "Now we seem to be hitting a new normal. Our meeting this week lasted only 15 minutes to touch on naloxone availability, the CURES database, and how to ensure we meet the new rules on both." [CURES is the Controlled Substance Utilization Review and Evaluation System that California maintains.]

WILLIAM DALE MD, PHD

Managing patients' pain on an outpatient basis has its own challenges, of course. "At City of Hope, because we know what our own pharmacy has, we will increasingly ask people to fill their opioid prescriptions in our pharmacy," Dale said.

When patients don't live nearby, Dale either calls the patient's pharmacy to learn the available drug options there or he will suggest that the patient obtain the preferred drug at a specific pharmacy. "I used to assume that if I came up with a medically appropriate regimen, then patients would be able to get those medicines," he said. "These days it's the reverse. I have to develop an appropriate, effective pain regimen based on what's available."

PALLIATIVE CARE COLLABORATIONS

The whole-patient perspective that palliative

Study Finds Patients With Cancer Are Less Likely to Die of Opioid Overdose

DESPITE CHANGES AFFECTING how oncologists prescribe and manage opioid use among their patients, there are few data analyzing the frequency and extent to which patients with cancer die of opioid overdoses.

FUMIKO CHINO, MD

Fumiko Chino, MD, a radiation oncologist at Duke University School of Medicine in Durham, North Carolina, set out to shed some light on this poorly understood aspect of the opioid epidemic. She and 2 colleagues at Duke used National Center for Health Statistics death certificate data to create a dataset that included all US deaths for which opioid overdose was listed as the primary cause of death during a 10-year period.

The investigators then analyzed death certificates for people who had fatal overdoses but also listed cancer as a contributing cause of death. They calculated the opioid death incidence from the estimated cancer survivor population and the US population as a whole.

Chino, who presented the data at the 2018 ASCO Quality Care Symposium, reported that there were 895 opioid-related deaths in patients with cancer between 2006 and 2016. This compares with 193,500 such deaths in the US population as a whole.

Notably, the incidence rates of opioid deaths increased during that time in both populations, but the increase was much lower among patients with cancer. In the general population, opioid deaths rose from 5.33 to 8.97 per 100,000 people (P <.001). In the cancer population, opioid deaths increased from 0.52 to 0.66 per 100,000 people (P <.001) during the same 10-year period.

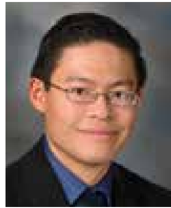
For Chino, these results provide reassurance that opioid-related deaths in the cancer population are much rarer than in the general population. At the same time, there is cause for concern, she said: "Even though our population's overdose risks were proportionately lower than the general public's, the numbers of fatal overdoses are still rising over time."

William Dale, MD, PhD, who helped organized the Quality Care Symposium, said that Chino's research was a strong addition to the symposium. "We know that studies based on death certificate data are limited by the subjectivity of the physician who fills out each death certificate, but Dr Chino took a methodologically appropriate approach to begin to get answers on whether our patients are more or less vulnerable to opioid overdose than the general population," he said. "We now have solid evidence to suggest that people with cancer are at a lower risk of death related to opioid use than the general population, which is important information for us as prescribers." ■

REFERENCE

Chino CL, Kamal AH, Chino JP. Opioid associated deaths in patients with cancer: a population study of the opioid epidemic over the past 10 years. Presented at: 2018 ASCO Quality Care Symposium; September 28-29, 2018; Phoenix, AZ. Abstract 230. meetinglibrary.asco.org/record/166352/abstract.

care specialists bring can also be invaluable to oncologists. As an oncologist whose primary appointment is in palliative care at MD Anderson, David Hui, MD, MSc, knows that each discipline has its strengths. "As palliative care physicians, opioids are our most-used drugs, so we become very comfortable using them to achieve optimal pain control while maximizing patient function, quality of life, and also minimizing adverse effects and abuse," he said in an interview. "Many oncologists do this very well, but the entire practice of palliative care has always been based on thorough assessment and monitoring. Knowing when to get help from a palliative care specialist is important."


DAVID HUI, MD, MSC

At Massachusetts General Hospital, medical oncologist Tara E. Soumerai, MD, has done just that. "With all of the prescribing challenges created by the opioid epidemic, we are leaning heavily on our team-based approach more than ever," she says. "As a hospitalist, I often have to manage pain crises in patients, yet opioid shortages and restrictions affect us as much as anyone. Some available opioids are not as familiar to me or I'm not as experienced in prescribing them, so I find I'm calling my palliative care colleagues more often and sooner in the admission."

TARA E. SOUMERAI, MD

It may also be helpful for oncologists to remember that the CDC guidelines, which specifically favor fast-acting opioids for short-term use, were not written to address the treatment and management of cancer-related pain, says Fumiko Chino, MD, a radiation oncologist at Duke University and lead author of the study into opioid overdoses.[5] "Our patients have long-term needs. Keeping patients on short-acting pain medications that wear off in a few hours, [as the guidelines suggest], is both less effective and less safe than transitioning them over time to a longer-acting agent so that pain levels don't yo-yo and patients can continue to function," she said. "Palliative care colleagues are experts at striking that balance."

Hui welcomes the increased referrals. "Early referral is a win-win situation for the patient, who gets better, more comprehensive management as a result," he said. "We enable the oncologist to focus on other aspects of cancer care while knowing their patients' symptoms will be well controlled. The palliative team will have the satisfaction of knowing they're able to optimize patients' care."

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>
> —Tara E. Soumerai, MD

NONOPIOID ALTERNATIVES

As the restrictions on opioids continue to tighten, one of the best ways to continue to provide good pain management regimens is to keep current on emerging nonopioid alternatives. For example, gabapentin and pregabalin have recently come to prominence as nonopioid therapies that can work either alone or in combination with opioids to treat neuropathic cancer pain.

But Dale, who was trained as a geriatrician, suggests caution. "Since the gabapentins affect the central nervous system, these drugs can have cognitive effects and increase fall risks for older patients," he says. "Their therapeutic window is pretty narrow and can be difficult to hit without overdosing. But even though I'm not a fan, I find myself using them more often."

Dale is also wary of using the so-called muscle relaxants, such as baclofen, to treat cancer pain. "These drugs work in a generalized manner and effectively make the entire body weaker, at least in older people," he says. "They're on the Beers list [of drugs that should not be given to older patients] because they affect alertness and balance."

Antidepressants have also entered the cancer pain management arsenal as effective nonopioid therapies effective against neuropathic pain. Duloxetine (Cymbalta) is used to combat chemotherapy-induced peripheral neuropathy, while venlafaxine (Effexor) can help reduce hot flashes in patients with breast cancer.

Older tricyclic antidepressants, such as amitriptyline, desipramine, and nortriptyline, can also be used to treat neuropathic pain. Dale suggests that colleagues consult the American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults before starting elderly patients on antidepressant therapy.[14]

Emphasizing appropriate nonmedical modalities like massage, meditation, physical therapy, or applied heat and cold as part of an effective pain management regimen can often allow for lower opioid dosing, as can topical formulations like lidocaine patches or rinses.

MANAGE PATIENT EXPECTATIONS

Patient education has always been a vital component of oncology practice, but the opioid crisis may be changing the nuances of what patients fear and the kinds of reassurance and information they need from their medical team.

Many oncologists report that the opioid epidemic has left some patients afraid or even unwilling to take opioids. "They have heard these rallying cries in the news, and it makes some of our most vulnerable patients with metastatic disease resistant to even trying some of these medications. They try to get by with just acetaminophen or ibuprofen," said Chino, adding that many patients have shared heartbreaking stories about opioid-related fatalities in their own families. "I often have to work hard to convince patients who are in tremendous pain to take a low-dose opioid to enable them to complete treatment." Seeing patients suffer needlessly is its own kind of heartbreak, she said.

For Dale, helping patients and families move beyond the old paradigm of 0 pain on a 0 to 10 pain scale has been critical. "That is no longer a realistic goal, if it ever was. I tell patients I want their pain to be as little as possible while still allowing them to be awake, interactive, and able to do the things that are important to them," he said. "If that means tolerating a little more pain, most people are happier with that trade-off, and it's safer for them." ■

For full list of references, see the article on *OncLive*.com.