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Opioids in Oncology Care

BY MICHELLE WALTER, DO, & AMY CASE, MD, FAAHPM

As the opioid epidemic continues across the U.S., it is important that physicians and health care providers possess basic pain management skills to avoid unnecessary risks for patients and themselves. This is particularly relevant for oncologists who often deal with cancer-related pain.

The first step in pain management is a thorough pain assessment. A cancer patient's pain may be related to the cancer itself, a side effect or sequelae of treatment, or a pre-existing condition. Through a careful history and physical, the oncologist can begin to distinguish the type of pain, which will guide the treatment plan.

CME Article

Different types of pain include nociceptive somatic, nociceptive visceral, and neuropathic, which all have specific sensations and etiologies. Nociceptive somatic pain is related to soft tissue and bone, such as bony metastases, and is often described

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Lung Cancer May Go Undiagnosed in Metastatic Kidney Cancer Patients

BY I. ALEX BOWMAN, MD

The incidence of a new lung cancer in patients with metastatic kidney cancer is not currently known. As both cancers are associated with tobacco smoking, it is likely that metastatic kidney cancer patients have an increased risk of developing lung cancer. However, literature on this subject is lacking. As patients with metastatic cancer are living longer thanks to new therapies, increased awareness and care for other competing causes of morbidity and mortality need to be considered, including new primary malignancies.

Since the introduction of anti-vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGF-TKIs), starting with sorafenib in 2005, the landscape of the management of kidney cancer has dramatically changed for the better. Before this, therapy was limited to immunotherapy with interferon or interleukin-2,

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Evolving Treatment Strategies for Mantle Cell Lymphoma

BY BITA FAKHRI, MD, & BRAD KAHL, MD

Mantle cell lymphoma (MCL) is a B-cell non-Hodgkin lymphoma, which has classically been considered an aggressive and incurable lymphoma. The median age at diagnosis is 68, with a 3:1 male predilection. The genetic hallmark is the chromosomal translocation t(11;14)(q13;q32) resulting in overexpression of cyclin D1. In terms of clinical presentation, one-third of MCL patients present with high levels of lactate dehydrogenase (LDH) and 25 percent of patients present with B symptoms. CNS involvement is extremely rare. In a work by the European MCL Network, it has been shown a combination of the Ki-67 index, independent of blastoid cytology and growth pattern, and MIPI score including four independent prognostic factors (i.e., age, performance status, LDH, and leukocyte count) provides strong prognostic value. The modified combined Ki-67 index and MIPI score has been increasingly utilized in clinical practice to further inform treatment decisions in patients with MCL.

Newly diagnosed MCL patients with low tumor burden and Ki-67 index ≤ 30 percent can be managed through a wait-and-watch strategy and defer therapy to the time of disease progression. Although MCL typically responds to frontline chemotherapy, it remains incurable with standard approaches. For patients in need of treatment, the critical decision is whether to proceed with an intensive treatment strategy

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PERIODICALS

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as sharp or aching. It is usually localized to a specific area. Nociceptive visceral pain is related to organ involvement, such as liver capsule pain from hepatomegaly or bladder pain from a tumor. It is often more diffuse and described as dull, crampy, aching, or sharp. Neuropathic pain results from damage to peripheral nerves or the central nervous system. An example of neuropathic pain is sciatica, which is often described as burning, shooting, radiating, tingling, or shock-like. Neuropathic pain may have a component of hyperalgesia or pain out of proportion to stimulus (*Palliative Care and Supportive Oncology* 2013).

It is important for the health care provider to ask themselves certain questions when evaluating pain:

- Is the pain acute in onset or chronically present?
- Is the pain constant or intermittent?
- Are there any temporizing or exacerbating factors?
- What has the patient done thus far to alleviate the pain and what was the effect?
- How does the pain impact activities of daily living and quality of life?
- Will the pain be expected to be relieved quickly (such as mucositis from chemotherapy) or become chronic (such as diffuse bony metastases)?
- Is the pain related to a side effect from chemotherapy, such as peripheral neuropathy, or was it present prior to the cancer diagnosis?

It may be necessary to investigate the pain complaint further to determine the etiology, such as evaluating for bony metastases or imaging the spine for possible spinal cord compression.

> After cancer treatment, many patients face chronic pain as a result of chemotherapy, surgery, or other procedures. Managing chronic pain in a cancer survivor should take into consideration the side effects and long-term effects of the treatment.

A complete pain assessment also includes a psychosocial assessment. A patient's experience with pain, including their ability to cope, may be affected by past pain experiences, as well psychological and behavioral factors (*Palliative Medicine* 2008). An assessment tool such as the Wisconsin Brief Pain Inventory can help clinicians complete a thorough pain assessment (*Pain* 1983;17:197-210).

When to Use Opioids

Once the provider completes a comprehensive pain assessment, a treatment plan can be made. Pain that is neuropathic in etiology may respond to opioids. Anti-neuropathic agents, however, may be better options, especially for long-term pain management. Prescribing anticonvulsants, such as gabapentin or pregabalin; selective norepinephrine reuptake inhibitors (SNRIs), such as duloxetine; or tricyclic antidepressants (TCAs) like nortriptyline avoid complications related to chronic opioid use.

Patients with acute, cancer-related pain can benefit from opioid therapy. It is important, however, to discuss with the patient the goals of treatment from the beginning. Complete resolution of pain may not be feasible or reasonable. A goal of minimizing pain and maximizing function is usually more appropriate and realistic.

When pain is chronic non-malignant pain, initiating therapies such as exercise, cognitive behavioral therapy, NSAIDS, acetaminophen, COX-2 inhibitors, and TCAs or SNRIs are preferred over opioid therapy (*Recommendations and Reports* 2016;65(1):1-49). The published NCCN guidelines for cancer pain support the above.

Opioids to Use

The World Health Organization (WHO) step ladder of analgesia has long been used as a reference for starting opioids. According to the WHO guidelines for cancer-related pain, mild pain should be treated with a non-opioid or an adjuvant as first-line. Mild or moderate pain should be treated with a moderate-potency opioid such as hydrocodone or oxycodone with or without an adjuvant. Moderate-to-severe pain can require a more potent opioid such as morphine or methadone with or without an adjuvant (WHO 2017; http://www.who.int/cancer/palliative/painladder/en/). Many cancer patients have pain that is constant and requires around-the-clock dosing. Pain control in these instances can best be achieved with long-acting opioids and short-acting opioids as needed for breakthrough. This regimen also can decrease risk of addiction, which will be discussed further below.

Opioid selection depends on the pain assessment and comorbidities of the patient. It is simplest to start with a short-acting opioid such as morphine or oxycodone, or a combination with acetaminophen such as hydrocodone/acetaminophen given orally every 4-6 hours, as needed. The optimal dose is the lowest effective dose or lowest dose without adverse effect (NCCN 2017; https://www.nccn.org/professionals/physician_gls/PDF/pain.pdf).

If the patient requires three or more doses of breakthrough medicine in a 24-hour period, transitioning to a long-acting opioid is appropriate and encouraged for more consistent analgesic coverage, with the goal of reducing breakthrough opioid use. Extended-release formulations exist for morphine, oxycodone, and oxymorphone, which is twice as potent as oxycodone. Using extended-release opioids may be more challenging as the tablets cannot be cut or crushed and do not come in liquid formulations. For patients who cannot swallow pills, methadone liquid or fentanyl patch are often better long-acting opioid options. Unlike extended-release formulations of short-acting opioids, methadone's long half-life makes it inherently long-acting and is usually dosed 2-3 times daily. We do not recommend using methadone on an as-needed basis due to the complex pharmacokinetics of this drug.

Providers should be mindful when their patients have liver or renal dysfunction. In the setting of renal failure, fentanyl or methadone are preferred agents as they do not have active metabolites that accumulate. Fentanyl patches can be used for those with absorption issues due to gastrointestinal tract dysfunction. Fentanyl patches also are useful if there is concern for opioid misuse. As a condition for treatment, a provider can request the patient return the used patches stuck on a notebook. This allows medical staff to monitor whether the patches are being used properly and whether anyone has tampered with them to extract the drug for illicit purposes. Anecdotally, fever could increase absorption of the fentanyl patch and cause toxicity, which could be a concern for a patient undergoing cancer treatment at higher risk for infection.

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Learning Objective for This Month's CME Activity: After participating in this CME activity, readers should be able to describe evidence-based recommendations for the management of cancer-related pain.

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Opioid Adverse Effects

Some adverse effects of opioids resolve quickly after initial use and others remain for the duration of treatment. The most common side effect of opioids is constipation, which should be managed concurrently with opioid use because it does not improve with time. A stool softener alone is usually not sufficient. Remedies such as fiber and water are also not effective. In patients with opioid-induced slowed colonic motility, fiber supplements cause a bloated feeling. In cancer patients, concurrent dehydration, poor oral intake, and decreased activity can exacerbate, or predate, the opioid-induced constipation. Common medications such as ondansetron and diuretics can also cause constipation. The NCCN recommends addition of a stimulant laxative such as sennosides, with or without a stool softener, taken regularly to treat opioid-induced constipation with the goal of a soft bowel movement daily to every other day. In refractory cases, methylnaltrexone or naloxegol may be used (NCCN 2017; https://www.nccn.org/professionals/physician_gls/PDF/pain.pdf). If a patient reports leaking stool in the setting of chronic opioid use, consider impaction and encopresis before stopping or limiting the bowel regimen (Assessing the patient in pain. In: *A Physician's Guide to Pain and Symptom Management in Cancer Patients* 2014).

Nausea is a common side effect that should resolve within a few days of starting an opioid. This can occur when rotating opioids from one agent to another. It is important to educate the patient to continue taking the opioid and take concurrent anti-emetics along with the opioid until they develop a tolerance to the nausea in a few days. Anti-emetics such as olanzapine, prochlorperazine, metoclopramide, or haloperidol may be initiated at the time opioids are started to be used prophylactically, or as needed. If nausea symptoms persist beyond a week, evaluate for other causes of nausea, including poor bowel motility and constipation, central nervous system (CNS) disease, or other medications prior to considering opioid rotation (Pharmacologic management of cancer pain. In: *A Physician's Guide to Pain and Symptom Management in Cancer Patients* 2014).

> When a cancer patient has pain, it is important to complete a comprehensive pain assessment and use interdisciplinary, multimodality approaches to treat and address all aspects of pain.

Providers may have difficulty determining the etiology of a cancer patient's fatigue. Fatigue can be caused by the cancer itself, chemotherapy, or dehydration, among other things. If fatigue occurs related to the initiation or increase of an opioid, it should improve after a few days. In patients with fatigue or sedation caused by opioids, transition to long-acting formulations with lower peak-opioid levels should decrease the sedative side effects. Sedation will precede respiratory depression when opioids are dosed and administered properly.

Prolonged QTc is a known side effect of methadone, as well as many other medications. Multiple studies have shown prolongation of the QT with relatively low doses of methadone (*Korean J Anesthesiol* 2010;58(4):338-343, *Arch Intern Med* 2006;166:1280-1287). Providers should take care when using methadone in conjunction with other QTc prolonging medications. If the oncology provider does not feel comfortable starting or titrating methadone, contact your palliative or pain management colleagues. It is recommended to evaluate QTc prior to initiating methadone therapy and then periodically thereafter.

Neurotoxicity with opioids may manifest in several ways. Myoclonic jerking may be more common with morphine or hydromorphone and is treated with opioid rotation or benzodiazepines (*Ann Pharmacother* 2006;4(11):2068-2070, *Br J Pain* 2017;11(1):32-35). Hyperalgesia can occur with high doses of opioids and results from sensitization of the CNS with a subsequent increase in pain signals (*Palliative Medicine* 2008). Hyperalgesia should be treated with decreased doses of opioids. Delirium is another adverse effect of opioids. Delirium, however, if it is significant, is unlikely to be from the opioid alone. Patients with delirium should have a full evaluation for the underlying cause including infection, constipation, urinary retention, other medications, electrolyte abnormalities, and presence of CNS disease.


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Chemical Coping & Addiction

In treating patients with chronic pain, minimizing risk is key. Prior to considering starting an opioid, the provider should take a history examining risk factors for opioid misuse, such as tobacco use, depression, history of substance abuse, personality disorder, somatization, and sexual abuse. It is important providers support their patients' psychological well-being and treat concurrent psychiatric illness, including anxiety and depression.

A screening tool such as the Cut-down, Annoyed, Guilty, and Eye-opener (CAGE); Screener and Opioid Assessment for Patients with Pain (SOAPP); Opioid Risk Tool (ORT); or Screening Tool for Addiction Risk (STAR) should be completed at the first visit to identify those at high risk for opioid misuse. If an opioid is prescribed, the provider should first review the state registry for prescribing of controlled substances. Informed consent, including education about addiction, tolerance, and opioid adverse effects, should be given to the patient. It is wise for the treatment to be multi-faceted, with opioids being just one of several methods to treat pain, including using non-pharmacologic approaches, psychotherapy, and non-opioid medications, such as NSAIDS or adjuvant analgesics, with the goal of always decreasing or avoiding automatic escalation of the opioids.

In patients at risk for opioid misuse, long-acting opioids should be used (such as fentanyl patches that, once used, are placed on a notebook and returned to the provider) and short-acting opioids should be limited (e.g., to fewer pills per day and shorter prescription duration) and discouraged. An opioid agreement outlining the expectations for appropriate behaviors and obligations for patients while on opioids (e.g., no early refills, no self-dose escalation, random urine drug screens, and pill counts) should be reviewed with the patient from the beginning. An assessment of pain level and function before and after initiation of opioids, as well as documentation of the "four A's" (analgesia, activities of daily living, adverse effects, and aberrant behavior) is standard of care. Work-up and documentation of pain etiology and diagnosis are also recommended (*JCO* 2014;32:16;1734-1738).

Chemical coping, a term first coined by Bruera, et al, describes when patients use medications, often opioids, in a non-prescribed way to cope with the various stressful events associated with the diagnosis and treatment of cancer (*J Pain and Symptom Manage* 2005;10:599-603). There are a range of opioid misuse behaviors that span from mild chemical coping associated with opioid dose escalation, increased pain expression, inability to discontinue opioids after resolution of the painful condition, to severe opioid addiction, associated with compulsive misuse of the opioid despite harm. In a study of 432 cancer patients, 76 (18%) of them were diagnosed as chemically coping. The diagnosis of chemical coping, however, was only documented in the record in 4 percent of

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RECRUITING

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event, it is useful to ask the applicant about their work, their career goals, and how they plan to achieve their goals. Most importantly, the dinner is an opportunity to gauge their emotional intelligence. Do they make eye contact? Do they listen? Do they ask follow-up questions? Do they have interests outside of medicine? How do they treat the wait staff? Do they have a sense of humor? Do they appreciate the massive talent of LeBron James?

8. **The interview.** There are many long articles written about how to conduct a job interview that go beyond this essay. I would simply suggest you search for interview questions that test emotional intelligence, find some that make sense to you, and use them. Very few people in academic medicine do so, because 100 percent of candidates tell me I ask different questions than anybody else does. An essential point to discover is whether the candidate can be an effective team member, or whether they are a lone wolf.

9. **Follow up.** It is very important the candidate knows what happens after they leave. Who is the contact person, and when will the next contact occur? Do not be vague about this, and if you say you will reach out to them next week, do so.

10. **Second visit.** Many times the highlight of the second visit is the candidate's talk. A good talk can seal the deal, at least in your mind. A bad talk will do the reverse. One key to a good talk is confidence without arrogance. Another key is assessing how the candidate answers questions. An applicant that handles tough questions with grace and honesty is usually a good person to try to hire.

11. **Verify.** If you are considering making an offer, you must call people who know the candidate and confirm (or refute) your thoughts about him or her. Letters are useful, but always talk to people who know the applicant.

12. **Make the offer.** The offer should be face to face at the end of the second or third visit. Agree on basic terms. Follow-up the conversation with a written confirmation of the terms. Keep the offer as concise as possible. Be mindful of the words of Joe Simone in *Simone's Maxims*: "The longer and more detailed the written offer to a new faculty recruit, the more likely both sides will end up unhappy."

13. **Show off your community.** Frequently, it is important for the candidate and their spouse to tour the area. Find an excellent real estate agent to do this, and use that agent repeatedly. If you are recruiting for a leadership position, consider hiring a professional relocation firm to "sell" your town. This is vital if you are recruiting to an area that is not exactly San Francisco, like, possibly….Cleveland, Ohio. The key is to show off the cool parts of your community.

14. **Red flags.** I have already mentioned some red flags—job hopping, any hint of problems with support staff, and somebody who flunks the interview or the dinner. One of the easiest red flag to spot is if the candidate does not respond to emails. If your recruiting coordinator is trying to arrange flights, and they do not respond, then they are not that in to you (yes, I know it's a movie title). If you arrange to have them meet with a real estate agent with their spouse and tour the area, and the spouse does not show up, then forget it. They will never come to your institution. I cannot tell you how many candidates verbalize great enthusiasm for a job with you, only to back out after an offer is made (and accepted); the reason for the change of heart is that their spouse is unwilling to move. I truly do not understand this behavior, but it sure is common. A true red flag is if they are dismissive to the recruiting coordinator. If so, they will be a management challenge in many ways. You are better off looking at others if they treat your staff poorly.

In closing, treat recruiting as a big deal, because it is. Nothing is more important than hiring excellent people. OT

OPIOIDS

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those patients. The CAGE questionnaire positivity, alcoholism, young age, higher reported pain, and other non-pain symptoms and higher functional status are associated with chemical coping (*The Oncologist* 2015;20:692-697). If a patient is chemically coping, psychological support, increased vigilance for structure (e.g., shorter intervals between visits and pill counts) and co-management with the interdisciplinary team and/or substance abuse specialist should be considered.

Existential Suffering

Opioids are often used in higher doses when the patient has related emotional pain, with associated complaints of severe, uncontrolled pain, often in many body areas, despite escalation of opioids and onset of adverse effects from these increasing doses. This constellation of symptoms may be related to existential suffering manifesting itself as physical pain. Patients with existential suffering require an interdisciplinary team approach to care including non-opioid pharmacological medications for mood and anxiety, as well as psychosocial and spiritual support.

Some neurobiological studies suggest there is a physical/social pain overlap where brain imaging studies revealed that experiences of social pain activate neural regions in the anterior cingulate cortex that are also involved in physical pain processing (*Psychosom Med* 2012;74(2):126-135). To the extent that physical and social pain rely on overlapping neural regions, individual differences in sensitivity to physical pain have been shown to relate to individual differences in sensitivity to social pain.

A study demonstrated that a genetic correlate of physical pain sensitivity, specifically variability in the mu-opioid receptor gene (OPRM1), where individuals who carry the rare G allele tend to experience more physical pain and require more morphine to alleviate pain, also report a sensitivity to social pain and rejection (*P Natl Acad Sci* 2009;106:15079-84). Acetaminophen, at doses of 1,000 mg/day, was shown to decrease self-reported hurt feelings over time when compared to placebo that showed no significant change (*Psychosom Med* 2012;74(2):126-135). More studies are needed to determine how opioids play a role in existential suffering.

Opioid Use in Cancer Survivors

After cancer treatment, many patients face chronic pain as a result of chemotherapy, surgery, or other procedures. They may have chronic, nonmalignant pain that predates their cancer diagnosis. Managing chronic pain in a cancer survivor should take into consideration the side effects and long-term effects of the treatment. NSAIDS have shown benefit for cancer-related pain (*Palliat Med* 2012;26:305-312). Adjuvant therapies such as antidepressants and anticonvulsants, as well as therapies such as physical therapy, exercise, mindfulness, acupuncture, and massage all show potential benefits. As previously stated, it is important to take a thorough pain history and determine etiology of the pain. Discussing goals of pain management with patients to maximize function, and not necessarily eradicate pain, is also an important step. Use of opioids in cancer survivors has not been well established and risks and benefits should be weighed carefully (*J Oncol Pract* 2016;12(8):757-762).

When a cancer patient has pain, it is important to complete a comprehensive pain assessment and use interdisciplinary, multimodality approaches to treat and address all aspects of pain, including the physical, psychosocial, and spiritual. When using opioids, the provider should assess risk for addiction and provide education to the patient of potential adverse effects. Ongoing monitoring and assessment of the four A's are important, and documentation of improvement in function and quality of life is always the goal. OT