Oxycodone Immediate Release for Cancer Pain Management in Turkey: Maximizing Value in Opioid Analgesics

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Abstract: Cancer pain can be severe, yet is often undertreated. In many parts of the world, there is a reluctance to prescribe narcotics for analgesia. Since the World Health Organization first published its "pain ladder" treatment paradigm in 1988, cancer pain is usually treated initially with nonopioids, then weak opioids, and finally strong opioids along with adjuvant agents as the pain intensifies. When initiating opioid therapy for cancer patients, the clinician must consider whether the patient is opioid naïve or opioid experienced. For naïve patients, opioid therapy must be started slowly, at a low dose initially, with adverse events anticipated and treated proactively. In all cases, opioid titration involves a controlled, stepwise increase of opioid dose until adequate (but not necessarily 100%) analgesia is achieved. A variety of opioid products are available, including immediate-release and controlled-release formulations. Immediate-release formulations are designed for easy titration to adequate analgesia; their rapid onset of action also makes them appropriate for managing breakthrough pain. Although morphine has long been considered the "gold standard" of cancer analgesics, oral oxycodone is increasingly used and is similar to morphine in efficacy and safety for cancer patients. Indeed, about 75% of morphine-tolerant patients can be successfully rotated to oxycodone. Adverse events with oxycodone are similar or perhaps favorable compared to those of other strong opioids. Because cancer pain can be challenging to treat, the addition of oral oxycodone IR is an important new tool for clinicians to consider when trying to control cancer pain.

Keywords: Cancer pain, oxycodone IR, new opioids, cancer in Turkey, analgesia in oncology.

INTRODUCTION

Despite tremendous advances in cancer treatments and developments in analgesics, much of the pain associated with cancer is inadequately treated [1]. Things have not improved much over the years: in 1994, an estimated 40% of cancer patients had under-treated pain [2] and in 2012, that number had reduced to only 33% [3]. Even cancer patients who report severe pain to clinicians may not receive adequate analgesia. In a study of breast, colorectal, lung or prostate cancer patients with pain, 19% had moderate to severe pain (n=584) at first assessment and of that group, 41% were not receiving any opioid analgesics and 20% received no analgesics of any kind [3]. In many parts of the world, physicians are reluctant to prescribe narcotic pain relievers, and patients may be fearful about taking opioids. There are many reasons for inadequate analgesia in cancer patients, including lack of education on the part of clinicians, government regulation and restrictions on some analgesics, availability and cost of pain medications, patients who may trivialize or deny their pain, and patients who lack the ability to adequately communicate with their healthcare providers [4]. Patients who experience cancer-related pain or who may dread pain may start to catastrophize, which, in turn, can worsen their perception of pain [5]. Pain is associated with worsened quality of life, can delay rehabilitation, and may prolong hospital stays [6, 7]. In one study, uncontrolled pain was even associated with increased mortality [8]. Moreover, pain causes patients and their families great suffering and distress, to the point that pain control has been put forth as a fundamental human right [9, 10].

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Pain is prevalent in cancer patients and often intensifies with disease progression, treatments, comorbidities, and other factors. Cancer patients may also suffer from concurrent but nonmalignant pain syndromes, such as osteoarthritis or low back pain. Pain in cancer patients is often multimechanistic, which requires an effective multimodal therapy to address [11]. See Table **1**.

Pain in cancer patients may relate to the underlying disease, tumor infiltration, treatments and surgeries, disease progression, and comorbid conditions; cancer patients, particularly the elderly, may have concurrent nonmalignant pain syndromes. Thus, cancer patients often present to the clinician with multiple pain sites and different types of pain. Owing to the nature of their condition, cancer patients experience pain that changes frequently and is subject to abrupt exacerbations. Cancer patients might not report changes in the nature or intensity of their pain, fearing it may relate to a worsening prognosis.

Advanced cancer treatments have extended the longevity and functionality of cancer patients. Thus, many cancer patients today require long-term pain therapy, which may result in protracted exposure to opioids [12].

Table 1: A Brief Overview of the Main Pain Classifications Observed in Cancer Patients. To Date, 22 Different Types of Cancer Pain Syndromes have been Identified

Name	Definition	How patient may describe it	Treatment options	Treatment considerations
Acute	Pain of short duration, often associated with surgery, treatments, or changes in disease	Tends to occur suddenly, be sharp and easy to localize, most patients can identify its cause	Nonopioid pain relievers, fixed-dose combination products, opioid agents	Acute pain often follows a defined trajectory and resolves gradually as the patient heals
Chronic	Persistent pain that occurs after the initial condition heals or for no obvious reason	Can be sharp or dull but tends to be diffuse and difficult to localize; may migrate	Nonopioid pain relievers, fixed-dose combination products, opioid agents	Chronic pain is associated with aberrant pain processing, central sensitization, and pain signal amplification
Nociceptive	Pain caused by a specific noxious stimulus	Tends to be sharp, stabbing, easy to localize, specific; most patients can identify its cause	Nonopioid pain relievers, fixed-dose combination products, opioid agents	Nociceptive pain is often associated with inflammation
Inflammatory	Pain caused by inflammation	Aching, dull, throbbing with abrupt exacerbations; easy to localize	NSAIDs may be more effective than other agents in reducing inflammation	Inflammatory pain can occur with other pain syndromes as well; it frequently accompanies nociceptive pain
Neuropathic	Pain caused by damage to nerves or aberrant neural processing; this can be the result of chemotherapy	“Electrical” sensations, sharp, stabbing, “pins and needles,” pain against a background of numbness or tingling; it may be persistent or occur intermittently and suddenly	Anticonvulsants, opioids	Conventional nonopioid analgesics are not often effective against neuropathy. About 40% of cancer patients will have some degree of neuropathic pain.[11]
Somatic	Pain medicated by nociceptors in the skin, deep tissue, and soft organs.	Aching, dull, gnawing, throbbing, or cramping pain which may be persistent or intermittent; it is easy for patient to localize	NSAIDs, bisphosphonates, opioids	This is the most common type of pain in cancer patients. Bone pain occurs in about 42% of cancer patients.[11]
Visceral	Pain mediated by nociceptors in the cardiovascular, respiratory, gastrointestinal, or genitourinary system	Intense and often moderate to severe pain, may be referred to other sites, difficult to localize, may be perceived by patient as diffuse but severe	NSAIDs or NSAID/opioid combinations may be more effective than opioids alone	Many internal organs have dense neural structures, making pain particularly severe. About 28% of cancer pain owes to visceral lesions [11]
Breakthrough	A sudden flare of worsened pain against a background of treated pain; breakthrough episodes are usually of short duration (< 1 hour)	Abrupt, intense, often unexpected, worsening of pain; patient reports the intensification but can also localize the pain	Rapid-onset opioids	Some breakthrough pain is incident pain (related to specific movements) and is thus more predictable

The evaluation of pain control techniques in a specific population must recognize that although pain is designated a fifth "vital sign" [13, 14] it remains a subjective patient experience [15]. Pain is the cumulative product of physical sensation, the intellectual contextualization of that sensation, and individualized emotional infusion into the experience. Pain can cause certain motor reflexes or other behaviors that may alter autonomic output. Thus, pain is a highly individual and subjective experience, and may be influenced by families, friends, ethnic groups, and culture. For example, enduring pain without complaint may be highly esteemed in some cultures as a sign of strength, while another individual may come from a family where pain is a way to get attention. This speaks to a long-term goal of pain medicine, namely tailored therapy which can be individualized to address the unique and specific needs of each individual patient. Thus, many different factors can influence prescribing choices even for two similar patients with the same condition.

Clinicians must also be cognizant of the potential for pain chronification, that is, the transition of an acute pain syndrome into chronic pain. Chronification often includes central sensitization, [16, 17] although the exact process has not been elucidated. Pain chronification might be prevented if the acute pain syndrome is interrupted, in other words, controlling acute pain both early and effectively can break the process that leads to chronic pain. Therefore, effective analgesia can play a prophylactic role as well as relieving the patient's immediate suffering and distress.

OPIOID ANALGESIA

The World Health Organization (WHO) in 1988 defined a treatment model for cancer pain that is still in widespread use. The WHO "pain ladder" describes three main steps that suggest using nonopioid pharmacological therapy for mild pain intensity, advancing to weak and then strong opioids as pain intensity increases [18]. See Figure **1**.

When considering a cancer patient for opioid analgesia, unless there is an oncologic emergency, it is first important to determine if the patient is opioid naïve or opioid experienced [19].

Opioid-Naïve Patients

No opioid-naïve patient should be initiated into opioid therapy without a frank discussion with the clinician, who can explain the risks and benefits of opioid analgesia. The patient and caregivers should be educated about the drug(s) and their possible side effects. Psychosocial support should be available to the patient, who is likely in great emotional stress over his disease and worried about his care options. As a rule of thumb, opioids should be used as little as possible and as late as possible without compromising pain control. Cancer patients may benefit from fixed-dose combination products, such as acetaminophen plus tramadol or an NSAID plus an opioid. These agents offer an opioid-sparing effect while providing effective and safe analgesia [20, 21].

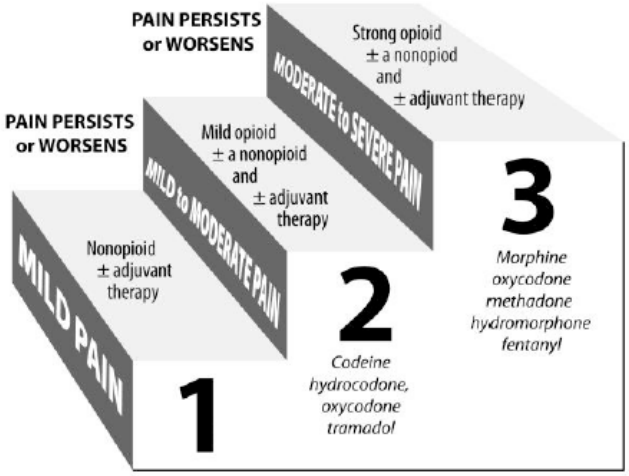

Figure 1: From the World Health Organization, a pain treatment paradigm for cancer pain which advocates progression from nonopioids to weak and then strong opioids as pain intensifies. This is an artist's depiction of the WHO pain ladder.

Opioids are associated with well-described side effects, many of which occur early in therapy of opioid-naïve patients and resolve over time [22]. Typical opioid-associated side effects include sedation, nausea, vomiting, constipation, dizziness, and respiratory depression. To the extent possible, the clinical team should anticipate such adverse events and address them. Opioid-naïve patients should begin a bowel regimen when starting opioid therapy to help treat constipation, a frequent and distressing opioid-associated side effect. Other side effects should be discussed with the patient, who should be encouraged to report them. Side effects should be managed quickly and as soon as possible, since adverse events can limit opioid treatment [22].

Pain assessments are an integral part of opioid therapy; using an 11-point numeric rating scale (NRS), patients can describe their pain along a continuum with

0 no pain at all and 10 the worst possible pain imaginable. In general, scores of <4 define mild pain, 4 to 6 describes moderate pain, and >7 is considered severe pain. Opioid-naïve patients should be considered for opioid therapy when their pain becomes moderate to severe and nonopioid agents are no longer effective. A good general rule of thumb is to commence therapy with a short-acting opioid and titrate to effective pain relief. Opioid titration involves a gradual, stepwise progression of analgesic agent until acceptable analgesia is achieved. Patients should be advised that complete pain relief may not be possible; it may be more appropriate to speak of "pain control" rather than "pain relief."

Some opioid agents, such hydromorphone or opioid transdermal patches (fentanyl and buprenorphine), are not appropriate for opioid-naïve patients, but can be suitable for patients who have some degree of opioid tolerance.

Opioid-Experienced Patients

The opioid-experienced patient has a degree of tolerance to opioids and therefore may not have side effects as frequently or as severely as their opioid-naïve counterpart. On the other hand, they will most likely require larger doses of opioid than the opioid-naïve for equivalent levels of analgesia. Although opioid-experienced patients likely have an understanding of the risks and benefits of opioid therapy and the nature of opioid-associated side effects, clinicians would nevertheless be wise to review the risks and benefits of opioids with them.

To manage an opioid-experienced patient, the clinician must first know the opioid and dose taken by the patient in the past 24 hours. If a different opioid is used, the clinician may have to rely on a dose conversion chart to determine the equivalent dose. Any opioid rotation should be treated as a discrete clinical trial, commencing with a much lower dose of the opioid (typically figured as a percentage of the dose taken the previous day) with efficacy and tolerability assessed after 60 minutes [23]. If the pain level is unchanged or increases, the clinician should consider increasing the dose and reassessing the patient at one hour. If the pain score has decreased and now falls in the range of 4 to 6, the previous dose can be repeated and the patient reassessed in an hour. In those patients who have pain scores that decrease to <3, it may be possible to continue the current dose, as needed, over the initial 24 hours.

It is important for the prescribing physician to recognize that there is variability among patients in terms of both responsiveness to opioid analgesia and tolerability. Thus, prescribers must assess and evaluate each patient individually.

Other Considerations for Opioid Analgesia

Cancer patients may be required to undergo surgery or painful procedures to treat their underlying disease or other conditions. When such events occur, the clinician must be prepared to control that pain as well [19].

Apart from such procedures and oncologic emergencies, cancer patients often require strong pain killers. A particular concern with analgesics as required is the possibility for so-called "analgesic gaps" or time periods when serum concentration of the analgesic agent has become too low to be efficacious in the patient and the new dose has not yet reached adequate serum concentration levels. End-of-dose pain can be distressing to the patients and may limit their function. Thus, dosing must be tailored to meet the needs of the individual patients and when analgesics are administered as required, patients and clinicians should be urged not to wait until significant pain has returned. Around-the-clock dosing can solve this problem, but many patients on continuous analgesic therapy still experience breakthrough pain. Breakthrough pain, discussed later in this article, differs from end-of-dose pain.

When considering opioid analgesics for cancer pain patients, physicians are often confronted with psychological barriers: fear of addiction, abuse and drug dependence. This in turn often leads to the undertreatment of pain due to a patient's hesitation to take opioids. When used safely and appropriately, opioid analgesics have been reported to be effective in treating cancer pain. However, there are many reports throughout the world indicating patients are at a constant fight against addiction, abuse, or drug dependence. In reality, patients with no history of addictive behavior rarely become addicted to opioids. In a retrospective review of 24,000 patients with no history of addiction, only 7 became addicted [24]. Though these effects can happen, it should be noted that they can be mitigated and prevented by a well-trained healthcare provider. Steps to reduce the risk include: proper education on addiction, abuse, and drug dependence; understanding of the mechanisms of action of opioids and their side effects; and

understanding the facts about pain management in relation to these adverse effects.

Clinicians must consider both controlled-release (CR) and immediate-release (IR) opioid formulations. In addition, certain opioid agents are pharmaceutically long acting (morphine, hydrocodone, oxycodone, and others) or pharmacologically long acting (levorphanol and methadone) [25]. Oral medications are optimal for outpatients, but their use is limited in patients who have difficulty swallowing [26] or those who are non-adherent to oral medications for various reasons (pill burden, carelessness). Transdermal patches and other routes of administration may provide better analgesic action in some individuals [27], but are only suitable for certain opioid-experienced patients.

There are no high-quality, large-scale, randomized clinical trials that demonstrate that one particular opioid agent is unequivocally superior in analgesic effect or tolerability over other agents in cancer patients [25]. On the other hand, patient response can vary among opioids making certain agents more advantageous for individual patients [23]. Morphine might be considered the "gold standard" opioid analgesic; oxycodone is widely used and in some geographies has usurped the role of morphine as the most frequently used analgesic agent [28, 29]. A short overview of key prescribing considerations and available options is given in Table **2**. The overarching goal is to achieve as much pain control as possible with the fewest and mildest side effects, knowing that complete pain relief and perfect tolerability may not be possible.

Combination or multimodal therapy is often necessary to treat moderate to severe pain associated with cancer. When selecting multiple analgesic and adjuvant agents, complementary mechanisms of action should be considered [30]. Many fixed-dose combination products are available which offer such appropriately combined analgesics.

OYXCODONE IR TO TREAT PAIN IN CANCER PATIENTS

Oxycodone immediate-release (IR) capsules (5, 10 and 20 mg) were specifically designed for patient-tailored pain control by facilitating dosing using this motto: titrate, tailor, and taper. Tailored oxycodone dosing can be particularly important in cancer patients, who over the course of their cancer may experience acute pain, chronic pain, pain associated with chemotherapy and other treatments, breakthrough pain, and postsurgical pain. Oxycodone IR was designed to facilitate dose titration, a stepwise progression of the drug dose until adequate analgesia is achieved. Further, the rapid onset of action of oxycodone IR can be helpful in treating breakthrough pain. This medication has recently been approved for use in Turkey and is available in other countries as well.

Pharmacology

Oxycodone can be classified as a mu-opioid receptor agonist. Although its *in-vitro* mu-opioid receptor binding affinity is less than that of morphine and oxymorphone, pharmacokinetic factors enhance its *in-vivo* analgesic activity. It has been suggested to have greater effect on mu-subreceptor type 1 than type 2, which may influence its pharmacologic profile [31]. Oxycodone binds to kappa-opioid receptors and delta-opioid receptors with affinity much lower than that associated with mu-opioid receptors. It has been speculated that the analgesic effects of oxycodone may be in part mediated indirectly by kappa-opioid receptor pathways [32]. Oxycodone's lipophilicity is similar to that of morphine but less than that of fentanyl. Its plasma-protein binding (about 40% to 50%) is similar to that of morphine (about 38%) [33]. Oxycodone is metabolized primarily in the liver. Most of its metabolites are excreted in the urine; only about 10% of the dose is excreted unchanged. The major route of metabolism is *N*-demethylation (catalyzed by CYP3A4 isoenzyme) to noroxycodone and *O*-demethylation (catalyzed by CYP2D6 isoenzyme) to oxymorphone [32].

Oxycodone IR Onset of Action

Rapid onset of action may be an important prescribing consideration for certain types of pain in cancer patients. The onset of action for oxycodone IR has been estimated to be in the range of 15 to 30 minutes [34-36]. The onset of action of three oxycodone products is depicted in Figure **2**.

Oxycodone IR Rotation

About 75% of morphine-tolerant patients can be successfully rotated to oxycodone therapy [32]. When converting from a strong opioid to oxycodone IR, an equianalgesic daily dose must be calculated. The rule of thumb conversion ratio for morphine is 50% (that is 20 mg of morphine is equianalgesic to 10 mg of oxycodone), and 100% for hydrocodone (10 mg of

Table 2: Prescribing Considerations for Cancer Patients in Pain. This Table is Not Exhaustive

Prescribing Considerations	Prescribing Choices	Comments
Type of pain	Nonopioid and opioids are effective in somatic, nociceptive, and visceral pain. Anticonvulsants may be required to address neuropathic pain.	Multimodal pain therapies are often effective. Physicians may have to conduct patient interviews to identify all pain components.
Exacerbation of pain	Progression from nonopioids to weak and then strong opioids per the WHO pain ladder; patients on opioid therapy may require dose escalation	Pure mu-opioid receptor drugs, such as morphine and oxycodone, have no clinically relevant ceiling effect with respect to analgesia[24]
Responsiveness	Wide inter-patient variability in opioid response; opioid rotation may be necessary	Responsiveness cannot be reliably predicted
Side effects	Opioid agents have similar and frequent side effects although rotation may sometimes improve tolerability.	Many side effects can be managed; proactive steps are effective. Note that these side effects can sometimes limit treatment
Disease progression	As the disease advances, pain is likely to worsen; the prescriber may have to rotate opioids, increase dosage, or consider other treatments to control pain	Patients may be reluctant to disclose worsening pain, fearing that it is associated with worsening cancer
Analgesic gaps	Consider around-the-clock dosing, transdermal patches, and controlled-release products	The end-of-dose phenomenon is different than breakthrough pain; end-of-dose can be managed by drug administration changes.
Breakthrough pain	Strong opioid agent with rapid onset of action	Start with about 10% to 20% of the patient's total daily opioid dose. Breakthrough pain is not related to end-of-dose analgesic gaps.
Incident pain	Strong opioid agent with rapid onset of action	Incident pain, such as pain associated with a specific movement or posture, may be a form of breakthrough pain and can be very severe.
Tolerance	Increase dose or rotate opioid	Patients may become opioid tolerant over time. Opioid-tolerant patients may demand more analgesia and exhibit behaviors that mimic drug-seeking ("pseudo-addiction") when, in reality, they need more pain control[29]
Compliance	Transdermal systems may be appropriate, if the patient is a candidate for this type of drug	Noncompliance encompasses both refusal to take the analgesic agent and taking it in ways other than as prescribed; patient education may be helpful
Treatment-related pain	Chemotherapy may induce peripheral neuropathy; such patients may benefit from adjuvant anticonvulsants. Surgery is associated with acute postsurgical pain that must be managed.	Chemotherapy-induced peripheral neuropathy may resolve when chemotherapy ceases[30]
Hyperalgesia	Opioid-induced hyperalgesia may lower the patient's pain threshold;[31] lower the dose of opioid therapy	Hyperalgesia may appear to be tolerance, but it is actually a condition caused by the opioid; lowering the dose might reinstate analgesia
Physical dependence	Physical dependence is not aberrant, abnormal, or unexpected in any patient on long-term opioid therapy; clinicians must determine if it is appropriate to increase opioid dose, rotate the opioid, or taper the patient off the drug	Dependence or withdrawal upon rapid opioid discontinuation is not equivalent to addiction (although all addicted patients are physically dependent)
Metastases	Pain may spread and worsen, necessitating a change in analgesic regimen or increased doses	Frequent pain assessments and discussions with the patient can help to manage metastatic pain better
Older age	Geriatric patients metabolize drugs differently, but generally tolerate opioid therapy.[32] Renal and hepatic insufficiency must be considered as these are more prevalent in seniors.	Fentanyl, buprenorphine, and hydromorphone are considered safe for patients with renal failure; morphine and meperidine must be avoided with renal dysfunction.[24]
Costs	Costs associated with analgesic therapy include the costs for the pain reliever and costs to manage associated adverse events; certain analgesic choices may be cost prohibitive.	Specific analgesics are not universally available, owing to regulatory rulings, commercial availability, and other factors.

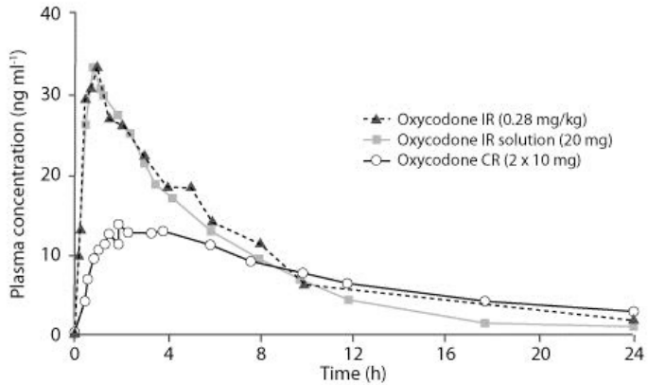

Figure 2: The onset of action of oral oxycodone IR, oxycodone IR solution, and oxycodone controlled-release (CR) formulation. This graph was created based on data from two studies by Mandema and Poyhia, respectively.

hydrocodone is equianalgesic to 10 mg of oxycodone) [37]. More details on equianalgesic doses are shown in Table **3**.

Table 3: Suggested Equianalgesic Factors for Calculating the Dose of Oral Oxycodone IR (for Titration to Stable Analgesia) Based on other Opioid Agents. Note that these figures should be used only as approximations. Calculate the oxycodone IR dose by multiplying the daily dose in mg of the current opioid by the equianalgesic factor. For instance, a patient taking a daily dose of oral morphine 20 mg would start with a daily dose of oral oxycodone IR at or around 10 mg (20 x 0.5 = 10)

Current Opioid	Equianalgesic Factor for Calculating Dose of Oral Oxycodone IR
Opioids as Monotherapy	
Hydromorphone	4
Levorphanol	7.5
Meperidine	0.1
Methadone	1.5
Morphine	0.5
Oxycodone	1
Opioid in a Fixed-Dose Combination Product	
Codeine	0.15
Oxycodone	1
Hydrocodone	0.9

Dosing in Special Populations

Opioids are considered to be safe and effective in the elderly, but must be administered with caution [38, 39]. The lowest possible dose should be administered initially and titrated carefully to achieve adequate pain control. Some elderly patients have mild to moderate renal dysfunction or mild hepatic dysfunction or both. Such patients—whether aged or not—must be carefully considered before commencing opioid therapy. In certain cases of renal and hepatic impairment, opioids may not be appropriate. If opioid therapy is indicated and the renal and/or hepatic dysfunction does not preclude the use of opioids, patients should begin with the lowest dose possible and then be titrated under close clinical supervision to pain control.

When using oral oxycodone IR to titrate to stable analgesia, it may be useful to estimate equianalgesia by taking the total daily dose of the current agent (in mg) and multiplying it by the equianalgesic factor to obtain the equianalgesic dose of oxycodone [40]. See Table **3**. Note that equianalgesic ratios are approximate and it is prudent clinical practice to round down.

The use of oxycodone IR in pediatric patients has not been studied.

Drug-Drug Interactions

Approximately one third of cancer patients are concomitantly receiving anticancer agents along with analgesic therapy to manage pain. Without proper pharmacovigilance, patients are at increased risk to experiencing a drug-drug interaction, which often results in an increase or decrease in the efficacy of one of the medications [41]. Many of the commonly used chemotherapy medications affect the main drug metabolizing enzyme, known as cytochrome P450 (CYP450). Many of the commonly used opioids also are metabolized through this enzyme and thus concomitant exposure of certain chemotherapy agents and opioids may result in an increase or decrease in opioid drug exposure [42]. Opioids that are generally not metabolized by CYP450 are morphine, hydromorphone, oxymorphone, and tapentadol. Others, such as tramadol, codeine, oxycodone, and methadone, pass through the CYP450 system and when used concomitantly with CYP450 inhibitors or inducers may have reduced efficacy and patients may experience unwanted side effects [43]. It is therefore very important for healthcare providers to review all current medications prior to adding additional treatments, especially during rounds of chemotherapy and pain management.

Clinical Studies of Oxycodone

Oxycodone has been evaluated in several clinical studies of cancer patients. For example, in a

randomized clinical trial of pancreatic cancer patients, oxycodone reduced pain scores on an eleven-point rating scale (where 0 is no pain and 10 is the worst pain imaginable) from 7.19 to 3.15 at four weeks with no difference in side effects compared to morphine [44]. A meta-analysis of 29 studies found no significant differences between oxycodone and other strong step III opioids (in particular, morphine and hydromorphone) in terms of the efficacy and safety of treating moderate to severe pain in patients with various types of cancer [45]. Oxycodone was compared to morphine and hydromorphone for the control of cancer-related pain in a meta-analysis of four studies that reported that oxycodone had similar efficacy and tolerability when compared to morphine [46]. In an analysis of a cross-sectional, longitudinal study of 258 palliative cancer patients, morphine, oxycodone, fentanyl, and buprenorphine were compared over a three-week period for pain intensity differences (PID) and response rates. Oxycodone, fentanyl, and buprenorphine patients had the most "full responders," defined as those who achieved ≥ 30% decrease in PID score [47]. The investigators noted different characteristics among these opioid agents and reported that of the four, oxycodone offered the best safety profile based on the incidence of reported side effects. In a meta-analysis of oxycodone versus morphine, codeine, and tramadol for control of moderate to severe pain in cancer patients (n=7 randomized clinical trials, 613 patients), reported that oxycodone offered significantly better pain relief (p=0.0002) and better improvement in pain intensity scores (p=0.01) compared to other drugs [48].

Oral oxycodone IR was compared to oral oxycodone CR in 83 cancer pain patients over a five-day period in a double-blind trial that measured pain intensity and how acceptable patients found the therapy [49]. Mean doses were 127 mg/d for oxycodone IR (range 40 to 640 mg/d) and 114 mg/d for oxycodone CR (range 20 to 400 mg/d). Oxycodone CR administered every 12 hours was as effective as oxycodone IR administered four times daily for moderate to severe cancer pain [49]. The discontinuation rates for adverse events were 11% for oxycodone IR and 7% for oxycodone CR.

Note that in the studies mentioned above, patients with various types of cancer were enrolled; the studies did not exclude certain types of cancer.

Breakthrough Pain Management

Breakthrough pain (BTP) is a transitory flare of pain, often severe or very severe, in a patient with controlled but persistent pain. As BTP reaches its peak intensity in a matter of minutes, patients can find these episodes both surprising and upsetting. The median duration of a BTP episode is about 30 minutes, and patients may experience multiple episodes in a day [50]. While some BTP is idiopathic and thus unpredictable, certain movements or conditions can initiate episodes of incident BTP [51]. BTP has been associated with poor outcomes and an increased burden on the healthcare system.

BTP can occur in both cancer and noncancer pain syndromes and is often under-treated [52]. The effective treatment of BTP requires a fast-acting analgesic agent [53]. It has been suggested that analgesics for BTP in cancer should be about 10% to 20% of the patient's total oral daily dose. For example, if a patient is taking 20 mg of oral oxycodone a day, BTP should be treated with 5 mg (approximately 20% of 20 mg) [19]. A particular benefit of oral oxycodone IR is its rapid onset of action, allowing the agent to address the sudden onset of BTP. Note that as patients increase their daily opioid dose over the course of time, the dose appropriate for BTP will rise correspondingly.

Managing Adverse Events and Safety Considerations

The adverse events associated with oral oxycodone IR are typical of those seen with other strong opioids. Common adverse reactions (defined as those occurring in 1% or more of patients) include gastrointestinal side effects (constipation, nausea, vomiting), central nervous system effects (headache, confusion, dizziness, sedation), cardiovascular events (orthostatic hypotension), respiratory side effects (respiratory depression, bronchospasm, dyspnea), rash, pruritus, sweating, and chills [54].

Certain opioid-associated side effects, such as headaches, nausea, and dizziness, may diminish with time as the body develops tolerance to the drug. Other side effects, such as constipation, may persist throughout the course of treatment [55]. It is important to educate patients about potential side effects and to manage adverse events proactively, when possible. For instance, nausea and vomiting can often be effectively treated with antiemetic therapy (for example, commencing with dopamine-receptor antagonists agents such as haloperidol or metoclopramide and advancing, as needed, to histamine-receptor antagonists, muscarinic receptor antagonists such as hyoscine, and serotonin-receptor antagonists such as

ondansetron). Constipation is a frequently occurring adverse event that patients often find very distressing [56]. A bowel regimen should be considered when a patient is started on opioid therapy.

The incidence of side effects, their severity and duration, as well as the patient's ability to cope with them can vary among patients. Patients should be encouraged to report side effects, since over time, opioid-associated side effects can be treatment limiting.

CONCLUSION

The clinician's goal in managing cancer pain is to adequately control the pain while at the same time keeping side effects to a minimum and minimizing risk of inappropriate use as much as possible. This is a dynamic balancing act, as many changing factors will influence the patient's use of opioids: disease progression resulting in pain exacerbations, therapy-related pain syndromes, and opioid tolerance. Despite the challenges, opioids, in particular oral morphine, have long been recognized as safe, effective, and appropriate therapy in certain cancer patients. Studies indicated that oxycodone can be considered as safe and effective as morphine in the treatment of cancer pain. Oral oxycodone IR was developed to address the unmet need of an opioid analgesic with a rapid onset of action and fast dose titration that could address moderate to severe pain, particularly pain associated with cancer. Oral oxycodone IR is likewise reported to be safe and effective in managing neuropathic pain (common in cancer patients treated with chemotherapy) and acute postoperative pain. Its adverse event profiles are similar or perhaps favorable to those of other strong opioid analgesics. Therefore, oral oxycodone IR may be considered when deciding on first-line opioid analgesic therapy options for cancer patients or as an opioid agent to be used in rotation. As with any pharmacotherapeutic approach, the initiation, use, and monitoring of opioid therapy in cancer patients requires sound clinical judgment and an individualized application.

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