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The Management of Cancer Pain: Should interventional therapies be approached as first-line treatment along with beginning an opioid regimen?

Sarah Holmes

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Introduction

Having active cancer pain has the potential to take a toll on a person's life in the worst ways. Sometimes their whole way of living must change while they try to adapt to the pain. It is projected that there will be 1,806,590 new cancer cases in 2020 with a death rate of 606,520 (Jemal, 2020). The cost for treatments for these types of patients can go up to as much as \$400,000 per year with one drug costing almost \$12,000 per year (Rimer, 2018). Statistics show that 33-59% of cancer patients experience pain (Dhingra, 2019). There is a cancer pain assessment that will be routinely performed for these types of patients in order to give them a therapeutic treatment plan. A pain scale that is currently used in combination with objective data often refers to a numerical scale from 0-10, 10 indicating the worst pain and 0 indicating no pain (Aono, 2020). Opioids are the first-line treatment for patients with cancer pain for their safety, flexibility, through dose titration, opioid rotation, by having multiple routes of administration, and effectiveness. Even so, there are many adverse effects, such as constipation, somnolence, and mental clouding resulting from the use of opioids, which may end up in a change of therapy for many patients (Ahmed, 2020). The next step in treatment after trying opioid and pharmacologic therapy is interventional therapy. There are many options for this approach in treatment, which also have great results. Some examples of these interventional therapies include nerve blocks, a kyphoplasty, a vertebroplasty, and joint injections (Copenhaver, 2019). Case studies show that the options for interventional therapies are very effective resulting in pain relief. For example, there is a 2017 explaining how 6 patients received joint injections because of tumors causing pain. The pain relief from these injections lasted about eight months with a decrease in the use of opioids as well (Gulati, 2016). Because of the positive results from the

interventional therapies, perhaps this line of treatment should be suggested as first-line along with opioid treatment, giving patients more options and advocacy for their plan of care.

Review of Literature

Cancer produces many symptoms, and pain is one of them. When a person is having pain due to cancer, many aspects of the person's life may be altered or inhibited; for example, activities of daily living may be difficult to perform, their psychological state may be altered, their social lives may be changed, and their overall physical function may be affected in a way that the person may need to modify what they typically do in a normal day. The pain a person experiences depends on the type of cancer, how far the cancer has progressed, and the treatment being performed. Statistics show that 33-59% of people who are undergoing cancer treatment experience chronic pain and increases to 64-74% in people with more advanced diseases (Dhingra, 2019). Because cancer results in a high prevalence of reported pain, patients should be routinely screened for pain through a cancer pain assessment.

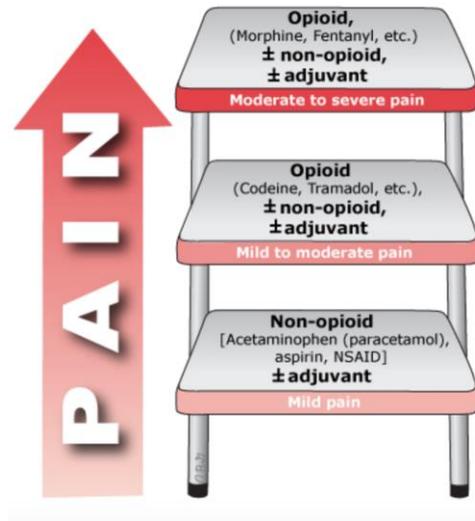
Because cancer pain is such a complex symptom of cancer, the cancer pain assessment should be an in-depth evaluation resulting in a specialized plan of care. The first step of this evaluation starts with a comprehensive assessment of their pain history, the cancer they currently have that is causing the pain, and the treatment they are receiving. One important aspect to assess is their psychosocial status along with their physical functioning status because, as previously stated, pain may alter these aspects of a person's life. A comprehensive physical exam and assessment of the pain location should be completed in addition to receiving a description of the pain from the patient. "The description of the pain must include the intensity, temporal features, location and patterns of radiation, quality, and factors that provoke or relieve the pain" (Dhingra,

2019). All of these things including the data received from imaging and other tests in combination help the professional medical team to determine the etiology and pathophysiology of the pain being experienced. In addition to the objective data, a numerical pain scale is used to determine the severity of the pain. The pain scale starts at 0 and goes to 10, 0 referring to no pain and 10 referring to the worst pain (Aono, 2020). After this is all retrieved, a diagnosis may be determined, and a plan of care is then formed in order to relieve the pain.

The goal of treatment is to maximize the functioning of the person while decreasing the possibility or presence of adverse effects occurring with the treatment being given. Routine cancer pain assessments are important because it allows the clinicians and practitioners to see the response to the treatment and find new targets for pain treatment. The pain being experienced may be reversible; however, persistent and chronic pain will most likely not be completely eradicated. “Persistent pain is defined as pain that continues beyond the expected time of healing, or for at least three to six months” (Galicia-Castillo, 2019). The goals must be realistic, which is why optimal functioning is a great goal to strive towards. Statistics show that there is a sufficient amount of pain relief in 70-90% of patients who abide by the treatment plan of care (Ahmed, 2019). Even with these statistics, there are cancer pain patients who are being undertreated or their goals are not being reached. In 2014, there was a systematic review performed that resulted in a decrease in 25% of undertreated patients between the years 2008 and 2013; however, there are still one-third of patients with cancer pain who are still being undertreated. There are many adverse effects on a person’s life when they are being undertreated, such as a poor ability to cope with the illness, dysfunction with activities of daily living, hardships with physical and social life, readmissions into the hospital, and interference with chemotherapy and radiation

treatments. This is another reason why it is important for cancer pain reassessments, which would aid in the redirection of treatment to a more effective plan of care.

The World Health Organization (WHO) analgesic ladder approach was published in the mid- 1980s, which gave clinicians and practitioners a stepwise or stepped care approach to strategize a therapeutic response from treatment depending on the description of the pain, ranking it from mild to severe. The ladder highlights opioids being prescribed for moderate to severe pain, along with suggesting combination therapy throughout and adjuvant analgesics. “Adjuvant analgesics (or coanalgesics) stands for any drug with a major clinical use other than pain that is used as an analgesic in selected circumstances” (Ahmed, 2019). The patient that describes their pain as moderate should be prescribed Acetaminophen or an NSAID initially. These analgesics may be combined with adjuvant drugs for additional analgesia, such as an analgesic antidepressant. The adjuvant drug may also be used to treat other adverse effects or other symptoms from the cancer pain. The ladder also emphasizes that patients with moderate to severe cancer pain or chronic pain should be treated with an opioid or if the NSAIDs are not reaching a therapeutic range. As previously stated, these drugs may also be paired with adjuvant analgesics. With the stepped care approach in older adults, the overall idea is that systemic medications are used later in treatment, or as the pain worsens, because of the potential for toxicity, adverse effects, and interactions with other prescribed medication. Interventional therapies should also be explored firsthand, and surgical intervention should be explored once a disease has progressed to a persistent pain state. There are also times when chemotherapy is given palliatively to treat pain as pancreatic cancer patients have a lot of pain. Chemo has the potential to shrink the tumor enough to hopefully alleviate some of the pain.



The use for opioid therapy is considered the first-line approach for cancer pain patients with moderate to severe pain, as shown by the WHO analgesic ladder. Opioids are a common therapy for cancer pain patients because of the safety with this therapy related to dose titration, the variety of routes used for administration, reliability, and effectiveness for many different types of pain (Ahmed, 2019). Opioids bind to many different kinds of receptors throughout the body, including in the peripheral and central nervous system. The most analgesic-producing receptors are the Mu receptors, which are what most opioids are targeted to bind to for highest rate of effectiveness. Chronic cancer pain is typically treated with a long-term treatment of pure Mu receptor agonists (Ahmed, 2019). Some examples of Mu receptor agonists are morphine, hydromorphone, oxycodone, oxymorphone, fentanyl, and methadone. Statistics show that chronic cancer pain is reported by about 30-50% of patients along with 75-90% of patients with other advanced diseases – these reports justify an opioid treatment plan (Ahmed, 2019).

The United States has assigned opioids as controlled substances under the Controlled Substances Act. This federal law places controlled substances under a list ranking the drugs from schedules of one to five based on the ability of the drugs to be abused – most opioids for cancer pain are schedule II, which would indicate a higher ability to abuse the drug. The government

has also taken steps to further prevent abuse and overdose from happening through two more opioid-regulating strategies. Through the Risk Evaluation and Mitigation Strategy (REMS), there are regulations on extended-release and long-acting opioids in addition to another regulation on transmucosal immediate-release fentanyl (TIRF) formulations (Ahmed, 2019). Because of this, the undergoing of opioid therapy must be performed with caution while having the patient on this therapy closely monitored with routine reassessments. Even so, there are clinicians and practitioners who are concerned about prescribing opioids because of these laws, which could potentially lead to the already spoken about undertreatment of pain. There are some questions that should be asked when starting a patient on an opioid regimen: “Is there an alternative therapy that is likely to have an equivalent or better therapeutic index for pain control, functional restoration, and improvement in quality of life?; Does the patient have medical problems that may increase the risk of opioid-related adverse effects?; Is the patient likely to manage the opioid therapy responsibility or relevant caregiver likely to responsibly co-manage? (Galicia-Castillo, 2019).” These are things to consider for the patient before starting an opioid treatment plan because of the numerous amounts of side effects and the potential to abuse the drugs.

There are many potential side effects or adverse effects from a plan of care involving opioid therapy for cancer pain. The use of opioids in general increases the risk of abuse or addiction without the proper monitoring and prescribing. Opioids work by activating the dopamine reward pathways in the brain that can release a euphoria effect, which makes the drugs easier to result in addiction and abuse (Ahmed, 2019). This abuse is not completely uncommon in patients with cancer pain, as a study of 432 patients with cancer pain using opioids for palliative care showed that 18% of these patients were using the opioids out of their prescribed plan of care to cope with the illness (Ahmed, 2019). The incorrect use of opioids for cancer pain

may interfere with the effectiveness of the treatment they are receiving. Even so, overdoses and hospitalizations for cancer pain related opioid use are uncommon. With the patients being closely monitored and reassessed, a risk assessment should also be performed to ensure the patient's safety: observe for a personal history of alcohol or drug abuse, family history of alcohol or drug abuse, and a major psychiatric disorder. Encouragement of the patient to adhere to the plan of care is crucial for their safety along with limiting the quantity of drugs used and no early refills. Pain contracts should be used in combination with drug screening to ensure the medications are being taken.

The most common side effects from opioids include gastrointestinal (GI) and neurological issues. Opioids are typically known for their GI effects, such as constipation. The cause of this is most commonly decreased activity of the GI tract, or decreased peristalsis. There are other results from this as well, such as nausea, pain, and bloating. In cancer patient using opioid therapy, rates of constipation are around 60-90% (Ahmed, 2020). Narcotic bowel syndrome is a term that can be used when the pain is significant in the abdomen with increasing the use of opioids. This is a paradoxical effect because the pain is worsening with opioid use even though opioids are a type of analgesic medication.

The other most common side effect is the neurological issues involving somnolence and/or mental clouding. These issues are typically at their worst when initiating opioid therapy or increasing the dose of the drug being used. The clinical manifestations vary depending on the person but can be shown in various degrees of inattention or fatigue, disorientation, severe memory impairment, or extreme confusion and delirium (Ahmed, 2020). There was a cross-sectional study performed involving 1915 patients with cancer who were beginning their opioid therapy treatment plan and had been taking opioids for at least three days. The study recorded the

degree of cognitive impairment based on the Mini-Mental Status Examination (MMSE). The results indicated that one-third of the population had scores less than 27, indicating slight cognitive dysfunction (Ahmed, 2020).

As previously stated, there are many side effects resulting from the use of opioids for cancer pain management; however, there are side effects that are not as common as others. Nausea and vomiting may occur at the initiation of the opioid therapy but does not persist because of the tolerance effect opioids can. A sign of neurotoxicity is myoclonus, which is the uncontrollable spasming of muscles. This is a sign that the dose is too high and is often accompanied by somnolence and mental clouding. In addition, there may be a decrease in sex hormones because opioids affect the hypothalamic-pituitary-adrenal axis. Some respiratory issues involve an opioid-induced sleep-disordered breathing, which would be caused by someone already having sleep apnea, and respiratory depression, which rarely happens even though it is commonly considered to be a serious adverse effect. In a systematic review and meta-analysis, there were reports of 91% of patients having sleep disordered breathing receiving opioids in sleep clinics and 63% of patients in pain clinics (Arif, 2020). Because of these statistics, these patients should be closely monitored. Pruritus is seen in about 2-10% of patients receiving opioid therapy along with the rare account of an allergic reaction. Urinary retention is a possibility because the opioids attach to a receptor that may result in total bladder relaxation. Infection risk has been shown by four different epidemiologic studies to be a side effect of opioids because some of them have immunosuppressive qualities. Finally, opioid induced hyperalgesia can occur, which is also a paradoxical response that is shown by a patient receiving opioids becoming more sensitive to some types of painful stimuli, or in extreme cases, experience pain from stimuli that typically would not be painful, or allodynia (Ahmed, 2020).

There are many things to consider when prescribing opioids to a patient with cancer pain. Each person is different, so every person will respond differently to the opioid treatment plan. This also includes each person's reaction to the adverse effects that go along with this kind of treatment, which may be because of many personal characteristics, such as age, genetics, other drugs they might be on, and comorbidities (Ahmed, 2020). There should also be consideration based on their social and psychological factors, such as depression, anxiety, coping skills, support, and financial status. Two comorbidities that are of great importance include renal insufficiency and liver failure. Because some opioids result in active metabolites accumulating then being excreted by the renal system, this would be unsafe for a patient with renal insufficiency because of side effects and potentially toxicity. Because most opioids are metabolized by the liver, patients with liver failure would be at risk for side effects (Ahmed, 2020). Other comorbidities to look out for include obesity, sleep disturbances, such as sleep apnea, dementia or any type of cognitive impairments, history of falls and uneasy gait, hypertension, congestive heart failure, and constipation.

As there are many risks to starting an opioid regimen for cancer pain, there are also many benefits. One benefit to the opioid plan of care is that there are numerous routes of administration, the favored routes being oral, transdermal, subcutaneous, intravenous, intrathecal, and intraspinal. The oral route is deemed the easiest by patients because there is flexibility to it and is extremely convenient (Ahmed, 2020). The transdermal route is often used for the use of chronic pain and may be favored over the oral route due to the GI effects caused by digestion of the medication, such as constipation; however, the patient must contain enough adipose tissue for the transdermal route to result in therapeutic treatment. The subcutaneous and intravenous routes are typically only temporary, and these regimens begin when other routes

need to be switched for a period of time. Finally, the intrathecal and intraspinal routes have been shown to be extremely effective in the controlling of the cancer pain and produce fewer side effects (Ahmed, 2019).

As previously stated, each person with an opioid regimen will respond to each drug in a different and nonpredictable way. This is very much involved in dose titration, which is another benefit of an opioid regimen. Each regimen is individualized, based on needs and desired outcomes for each patient. The goal of dose titration is to have a therapeutic analgesic response with the fewest side effects possible; however, that is not always the case. The dose will be increased until the person experiences the analgesia with side effects or until the side effects become unbearable for the patient. During the dose titration process, each patient is monitored extremely closely for side effects and especially toxicity. If a dose becomes extremely high, there will be a reassessment to make sure that specific drug is still beneficial for the patient and their treatment plan (Ahmed, 2019). Even so, cancer patients typically do not have extremely high doses.

There is a point in dose titration where a patient may be deemed poorly responsive to the opioid regimen because of side effects or the benefits no longer outweigh the adverse effects, which could lead to multiple options being explored to reach analgesia. There could be a trial of another opioid being used, direct management of the side effects, or adding other therapies to the equation, such as nonopioids, adjuvant analgesics, or nonpharmacologic therapy. The action of trying a different opioid rather than the one being used previously is called opioid rotation (Ahmed, 2019). This is a great option for when a patient responds poorly to another opioid. The idea and goal of this action is to provide a balance between analgesia and side effects, which would be another benefit to an opioid regimen – it is flexible. Another aspect to this idea of

being poorly responsive to a regimen, is that a person could potentially become tolerant to the adverse effects of the drugs over a few weeks of treatment (Ahmed, 2019). Even so, if the patient were to switch to another drug during a time of opioid rotation, the new opioid could have even stronger effects, which might not be worth the waiting time for tolerance to begin.

There is an analysis of Cochrane reviews (152 studies, including 13,524 patients) that resulted in 19 out of every 20 people with the description of pain being moderate to severe cancer pain on an opioid regimen should have had their pain reduced to mild or moderate or no pain within fourteen days. Most of the patients experienced adverse effects, and one to two of every ten patients being treated would find these adverse effects intolerable, leading to a change in treatment (Ahmed, 2019). Even so, the studies included small group settings for review and few follow-up meetings with the patients, so the level evidence is not very high.

Patients who do not tolerate first-line treatments, such as opioids, should explore interventional therapies. Interventional refers to therapies that are invasive with the goal of analgesia with many options, such as injection therapies, spine-related injections, vertebroplasties and kyphoplasties, neural blockades, neuraxial infusions, intrathecal catheter placement, and intraventricular opioid delivery. These approaches are oriented towards giving safe and effective pain relief. The idea of interventional therapy is used when the benefits no longer outweigh the risks for pharmacotherapy. Although the effects tend to be positive, because they are invasive, they automatically increase the risk for infection.

Cancer pain patients have effective options to attempt with the goal of effective pain relief. Soft tissue and joint injections are a great option for cancer pain patients as long as there are no contraindications for injections, such as coagulopathy, leukopenia, pneumothorax, or infection. One of the benefits to this type of interventional therapy is that the pain from the

injection is relieved for days or even weeks. Another type of interventional therapy is the spine-related injection, which are typically for acute and chronic, non-cancer, low back and neck pain but can also be useful for patients with cancer pain involving other approaches including epidural steroid injections, facet joint injections, facet denervation approaches, and sacroiliac injections. One 2017 case study consisting of 6 patients each receiving joint injections because of sacroiliac tumors causing pain. Pain scales were recorded before and after the procedures, resulting in a significant pain improvement that lasted for about eight months for each person. In addition, each person decreased their use of opioids because of their pain relief from the procedure (Gulati, 2016).

Other options for interventional therapies include a vertebroplasty and kyphoplasty. Vertebroplasties involved the injection of a medical cement into a vertebral body known as a compression fracture in order to stabilize the spine. Kyphoplasties involves something called a “inflatable bone tamps,” which is basically a balloon that is inflated and releases the pressure from the collapsed vertebral body creating an area where cement may be injected like the vertebroplasty (Copenhaver, 2019). There is a 2016 case study performed on 158 patients with 228 cancer-related vertebral compression fractures who had chosen to do the kyphoplasty. The results were recorded right after the procedure and three months after. The result of the study concluded a decreased mean pain score from 7.5 to 3.6 with a decreased disability index from 50 to 42. Cement leaks are a rare complication; however, in this study, there was a result of 31% (Hargunani, 2016). The results showed that pain was relieved and controlled in over one-half of the patients, which also resulted in a decrease in medications for pain management and pain disability scores. In addition, the kyphoplasty procedures resulted in the decreased need for medications of any kind, walking aids, such as canes and braces, and a decreased prevalence for

bedrest (Copenhaver, 2019). The benefits from these procedures are strong; however, there are still some complications and things to take account for, such as a pulmonary embolism, spinal cord compression, and paraplegia. Even so, the risk of these adverse effects happening is relatively low.

The next interventional therapy that will be discussed are neural blockades. The procedure of nerve block injections includes injecting a drug within close proximity of a nerve in hopes for a result of pain relief. Therapeutic nerve blocks are providing pain relief for a longer period of time. Nerve blocks can be divided into a neurolytic procedure or a nonneurolytic procedure (Copenhaver, 2019). A neurolytic procedure involves the alteration of a nerve, potentially permanently injuring it. A nonneurolytic procedure involves preserving the nerve with no injury. The experience with these types of procedures for cancer pain has shown to be beneficial through the recording of case reports and other clinicians and practitioners. Yes, these procedures are beneficial; however, nerve blocks should not be considered until all other options have been explored. This is because of the risk of neuritis, which is a type of nerve pain, the possibility of some type of neurological compromise, tissue damage resulting from the neurolytic procedures, and insufficient reach of therapeutic levels of analgesia (Copenhaver, 2019). There is a block, though, that is safe and effective and used routinely for cancer pain patients when their first-line therapy with medication does not suffice. This blockade is called the Celiac Plexus Neurolysis (CPN), which is commonly used for pain occurring because of some type of abdominal cancer, typically pancreatic cancer (Copenhaver, 2019). For neurolytic blockades in general, there are many risks that are involved with the procedures. For example, there could be a result of some type of autonomic dysfunction, bladder and/or bowel dysfunction, orthostatic hypotension, neuritis, and anesthesia.

One interventional therapy that includes targeted drug delivery is neuraxial infusion. This type of drug therapy involves using a neuraxial space, such as an epidural space and intrathecal space. There are multiple options for the infusion of this drug therapy, such as different infusion devices along with different drugs available. This treatment is optimal for cancer pain patients because the pain is targeted and has a high potential for the relief of this pain. Even so, the risks and benefits need to be weighed. One type of neuraxial infusion that has been very successful is the intrathecal drug delivery. This therapy involves the same targeted therapy as stated before and is typically used for cancer pain patients. The final type of neuraxial infusion discussed is the intraventricular opioid therapy, which involves a drug being injected into the cerebral ventricles in the brain through an infusion device. The evidence proving this therapy is greater than opioid therapy is extremely weak; however, the experience from the procedure has shown 50-90% of cancer pain patients have strong pain relief (Copenhaver, 2019).

There was a case study performed recording the beneficial aspects of using intrathecal drug delivery. The case study involved a randomized trial consisting of 202 patients with cancer pain that was not being managed and treated in the most efficient way. The pain was not controlled. The requirement for the patients to receive the intrathecal drug delivery was that they had to tolerate intrathecal morphine administration over a four-week assessment. The other option for the patients was a conventional medical management therapy, which involved any therapy other than spinally administered medication. Both groups increased cancer pain relief, however, there was a greater than 20% difference in the intrathecal group with the most pain relief. They also reported a decrease in toxicity from 58% to 38%. There were also decreased amounts of side effects resulting from the intrathecal therapy along with a longer survival period

being about six months longer. There was a six month follow up after the study was performed, and the results remained the same (Copenhaver, 2019).

Conclusion

Overall, opioid therapy treatment has been effective, even though there are many possible adverse effects. Because the adverse effects can be so prominent, patients tend to try other options to treat their pain, such as interventional therapies, nonpharmacologic therapies, and combination therapies. There are many options to attempt resolving pain in cancer patients, which is necessary because cancer pain is complex. The option of interventional therapies should be approached alongside opioid therapy in the first-line of treatment because they are extremely effective. There are more invasive procedures; however, case studies and reports have shown that the interventional therapies could be equally if not more effective than opioids, depending on the person and their preferences. Multiple options for treatment should be addressed, and patients should play a role in managing their pain. Educating patients about the risks and benefits of treatment modalities should be done so that the provider and patient can make an individualized treatment plan.

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