Managing Cancer Pain Poorly Responsive to Systemic Opioid Therapy

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By Russell K. Portenoy, MD [2]

Large surveys of populations with cancer pain indicate that as many as 90% of patients can attain adequate relief of pain using optimal, systemic, opioid-based pharmacotherapy. Skilled clinicians should be able to achieve

**Introduction**

Systemic opioid pharmacotherapy is widely accepted as the major approach to the management of cancer pain.[1-6] More than three-quarters of cancer patients can achieve adequate relief with long-term treatment.[1,7-13] If undertreatment, which continues to be a significant problem,[14] were eliminated, most patients would be able to cope with the disease and its treatment without the profound burden of unrelieved pain.

These statistics are reassuring, but should not deflect attention from the subgroup of patients that does not respond adequately to an initial trial of systemic opioid therapy. These patients experience an unsatisfactory balance between analgesia and side effects, despite efforts to individualize the dose. They are poorly responsive to the opioid therapy and must be considered for alternative analgesic strategies.

**The Concept of Opioid Responsiveness**

The potentially confusing nomenclature applied to the outcome of opioid therapy is exemplified by the term “efficacy.”[15] Pharmacologists use the term “intrinsic efficacy” to indicate the proportion of receptors that must be occupied to yield a given effect, and apply the unmodified label “efficacy” to either the effect produced by a given dose of drug or the maximal effect that can be produced by the drug (also called maximal efficacy). None of these usages may resonate with the clinician, who typically describes an opioid therapy as efficacious if it yields a favorable balance between analgesia and side effects. For the patient, the maximal efficacy of a morphine-like opioid agonist is not determined by the effect at a given dose, or the ceiling effect above which dose increments yield no additional analgesia. Rather, clinical efficacy is determined by the degree of analgesia reported before treatment-limiting toxicity occurs.

In an effort to clarify this terminology, the term “responsiveness” was proposed to characterize the outcome of opioid therapy.[16,17] Opioid responsiveness is defined as the probability that adequate analgesia (satisfactory relief without intolerable and unmanageable side effects) can be attained during dose titration. Alternatively, responsiveness can be used to depict the degree of analgesia obtained at dose-limiting toxicity. This might be viewed as maximal efficacy from a clinically relevant perspective.

There is remarkable variability in the responsiveness of individual patients to different opioids and the responsiveness of different patients to the same opioid. For example, a patient with stable pain may develop severe somnolence at a morphine dose associated with acceptable analgesia, then demonstrate dose-limiting nausea without somnolence at a dose of hydromorphone associated with lesser, equal, or better analgesia. Among those who are treated with morphine for metastatic bone pain, some achieve a highly favorable balance between analgesia and side effects, whereas others experience treatment-limiting toxicity before any meaningful analgesia is reported. Thus, the overall high rate of responsiveness to long-term opioid treatment in the population of patients with cancer pain actually subsumes wide variation in outcomes. The mechanisms that underlie variability in opioid responsiveness are not known, but are presumably multifactorial and related to characteristics of both the pain syndrome and the patient. Among the factors related to pain that appear to reduce opioid responsiveness are a neuropathic mechanism and the presence of severe breakthrough pain.[18] The most important patient-related factor is a propensity to adverse
opioid effects, which may be determined by advanced age, major organ failure, or other factors. Presumably, genetic factors also play an important role in determining this propensity. The existence of factors that increase or decrease opioid responsiveness should not be taken to mean that any factor, or group of factors, imparts opioid resistance. Indeed, no factor is sufficiently predictive to preclude outcome in any individual case. A neuropathic mechanism, for example, may reduce opioid responsiveness overall, but the population of patients with neuropathic pain presents a range of outcomes that includes some who do very well.[19-22] Moreover, the variable responsiveness to different opioids in the same patient implies that a poor response to one drug should not be interpreted as a poor response to opioid therapy overall.

**Analgesic Strategies for Poorly Responsive Patients**

Recognition that some patients do not attain a favorable balance between analgesia and side effects during systemic opioid therapy should lead to an assessment that allows rational selection of an alternative analgesic strategy. Unfortunately, this selection is hampered by the absence of comparative clinical trials. Given the lack of science, it often appears that the choice of one therapy over another is determined more by the expertise, availability, and biases of providers than by the clinical characteristics of the patient.

There are four major strategies that may be applied to the management of pain in cancer patients who demonstrate poor responsiveness during a trial of systemic opioid therapy (Table 1):

**Expanding Therapeutic Window**

First, it may be feasible to continue the same opioid if more aggressive side effect management is possible. Effective treatment of a limiting side effect can “open” the therapeutic window and potentially allow even higher doses of the opioid if required to improve analgesia. The most significant advance in this strategy is the expanding use of psychostimulant drugs to treat opioid-induced somnolence and mental clouding.[23,24]

**Opioid Rotation**

Second, the observation that a poor response to one opioid does not predict an equally poor response to another suggests the utility of sequential trials.[25,26] This technique, which is now termed opioid rotation, is widely used and accessible to all clinicians. It requires an understanding of the relative potency between opioids and the practical use of the equianalgesic dose table.[27]

**Invasive Techniques**

Third, it may be possible that a pharmacologic technique that reduces the systemic opioid requirement may yield equal or better analgesia with less drug. If opioid requirement is reduced, the dose that is ultimately needed may be associated with a more favorable balance between analgesia and side effects. Conceptually, the use of intraspinal opioid therapy may be considered under this strategy, which also includes the use of systemically administered nonopioid or adjuvant analgesic drugs (Table 2).[28]

**Nonpharmacologic/Neurosurgical Techniques**

Fourth, there are a large number of nonpharmacologic analgesic approaches that may result in a lower opioid requirement. These approaches may be categorized as anesthesiologic (eg, chemical neurolysis), neurostimulatory (eg, transcutaneous electrical nerve stimulation and dorsal column stimulation), surgical (eg, cordotomy), rehabilitative (eg, an orthosis to brace a painful region), psychologic (eg, cognitive interventions for pain control), and complementary alternative. Although linked conceptually, the scope of these therapies is obviously very broad and there are substantive differences in their indications and implementation.

**Assessing the Poorly Responsive Patient**

Faced with such a diversity of analgesic strategies, the clinician must perform a detailed assessment of the patient and the pain syndrome to rationalize decision-making.[2,29] Without comparative data to illuminate the relative risks and benefits of different approaches in carefully defined populations, recommendations must be based on this knowledge of the patient and on an understanding of the available techniques.

Pain should be described in terms of severity, location, temporal features (duration, pattern, and course), quality, and factors that provoke or improve it. This information, the findings from a physical examination, and the results of appropriate laboratory and imaging studies usually clarify the most likely etiology of the pain and the syndrome that best characterizes it.[29] This information also allows classification of the pain according to the broad type of pathophysiological processes that are likely to be sustaining it.
In the cancer population, the most prevalent pathophysiology is termed nociceptive. Nociceptive pain can be attributed to a site of ongoing tissue injury (usually somatic, sometimes visceral). A substantial minority of patients have pain that is neuropathic or can be attributed to aberrant processing in the peripheral or central nervous system. Mixed pathophysiologies are also common. The assessment also must clarify the goals of care, which ultimately inform all therapeutic decisions. Many patients experience a period during which primary treatment of the disease is not possible or desired because of the burden of the therapy. Some of these patients emphasize goals related to comfort combined with the maintenance or restoration of function. Others, particularly those at the end of life, emphasize comfort above all else. The fluctuation of these goals mandates repeated assessment, particularly when decisions must be made about new therapies.

A comprehensive evaluation of the pain should also include detailed information about physical and psychosocial comorbidities. The status of the disease and its complications have obvious implications for the selection of alternative analgesic strategies. The presence of coagulopathy, electrolyte abnormalities, major organ dysfunction, or metastatic disease in critical locations must be clarified. The performance status of the patient should be noted and the specific impact of pain on functioning should be determined. Functional impairment that is believed to be caused by unrelieved pain is less likely to exclude an alternative analgesic strategy than is impairment perceived to be related to progressive disease and short life expectancy.

The social situation of the patient also has clear implications for the choice of analgesic approaches. Interventions that require careful monitoring may not be feasible if the patient lives alone and adequate home care nursing cannot be arranged.

Selection of an alternative analgesic approach may also be influenced by other considerations. Obviously, a treatment will not be possible unless there are clinicians who can implement it and a protocol for reliable follow-up. Economic considerations, such as insurance coverage for invasive approaches or nursing care, may be a very salient issue for some patients.

The Use of Intraspinal Therapy

Following a comprehensive assessment of the cancer patient whose pain does not respond adequately to a systemic opioid trial, the clinician may consider using several alternative analgesic strategies. For example, a relatively simple approach, such as opioid rotation or the addition of an adjuvant analgesic, may be considered along with a trial of an intraspinal opioid. The patient’s wishes must guide prioritization of these options. The patient should also be informed about the possible risks and benefits associated with each option. Many benefit from the knowledge that there is no strong scientific evidence favoring one treatment approach over another, and that, ultimately, decisions must be based on the best judgment of the clinician and the desires of the patient. In many cases, the best decision-making in this setting is collaborative.

Many factors influence the perceived utility of an intraspinal opioid trial in patients with poorly responsive pain (Table 3).[30] These factors may be related to the patient, the pain, or the system of care.

**Patient Factors and Intraspinal Therapy**

Intraspinal approaches are contraindicated in the setting of severe thrombocytopenia or irreversible coagulopathy, systemic infection, or local infection in the region of the catheter insertion. Severe immunocompromise should also be considered a relative contraindication, but does not exclude the approach if refractory pain cannot be managed in other ways. Multilevel epidural disease may eliminate the option of intraspinal therapy.

Performance status and life expectancy are also important considerations. Life expectancy influences the use of any type of invasive approach, including intraspinal therapy. If intraspinal therapy is pursued, life expectancy is one of the most important factors when deciding among the various approaches to long-term therapy. These approaches include simple percutaneous catheters, tunneled catheters, and implanted pump systems.[31] The more sophisticated approaches are more durable, and are preferred when life expectancy is longer (usually greater than 3 months).

The patient’s cognitive and psychosocial status also may influence decisions concerning intraspinal therapies. Truly informed consent may not be possible if cognitive impairment is significant. Untreated depression or anxiety can undermine judgment and prevent an appropriate evaluation of risks and benefits. As noted, the social situation of the patient may become important if careful monitoring is needed at home and can only be accomplished by family or others in the home.

**Pain-Related Factors and Intraspinal Therapy**

The characteristics of the pain also influence the decision to pursue intraspinal therapy. For example,
intraspinal approaches are generally most favored when pain is located below midthorax. Patients with head and neck cancer are considered poor candidates.

The predominating pathophysiology of the pain also may be relevant, particularly when considering the potential for nonopioid drug administration. Local anesthetics are commonly coadministered with an opioid during epidural administration,[32,33] and anecdotal experience suggests that this approach may be particularly effective in the management of refractory neuropathic pain. Epidural clonidine (Duraclon) is analgesic and has the greatest benefit in patients with neuropathic pain.[34] The availability of opioid-local anesthetic-clonidine mixtures for epidural administration may influence the decision to begin a trial of intraspinal treatment in patients with severe neuropathic pain earlier than would be the case if opioid therapy alone were the only option. The role of intraspinal therapy may expand if other drugs with special efficacy by this route become available. As described previously, the type of side effect that precludes systemic opioid therapy may also influence the decision to implement a trial of intraspinal therapy. Central nervous system toxicity, such as sedation, mental clouding, or frank confusion, more strongly suggests the utility of this approach than does gastrointestinal toxicity such as nausea. These impressions are based on anecdotal experience, but have a strong influence on practice.

**System Issues and Intraspinal Therapy**

Patients should not be considered for intraspinal therapy unless systems are in place to monitor and adjust treatment in the home.[35] These systems must allow for a quick response to emergencies at any hour of the day or night and should provide access to skilled nursing support and a knowledgeable physician.

Intraspinal therapy is relatively expensive and the decision to implement an intraspinal approach must address the availability of reimbursement. An important concern is reimbursement for an inpatient trial period, which is strongly favored as a prelude to long-term treatment.[36] The long-term costs of intraspinal therapy vary with the specific approach[37] and the variation in cost must also be considered during treatment selection. For example, long-term epidural administration requires more nursing involvement than subarachnoid administration via an implanted pump; over time, the cumulative costs of epidural administration exceed subarachnoid administration. This may be more or less an issue for the individual patient, depending on the insurance coverage available.

**Conclusions**

A minority of cancer patients demonstrate poor responsiveness during systemic treatment with an opioid drug. The selection of a therapeutic strategy, such as intraspinal therapy, depends on a careful assessment of the patient, the pain, and the available system of care. Clinicians must be knowledgeable about the many options that exist for the management of these refractory pain patients and must be able to implement those options within the purview of the primary caregiver and refer appropriately for others.

**References:**


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