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Indications for intrathecal therapy in cancer patients

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An essential component of cancer treatment and management is effective pain control, which is vital to the preservation of functioning, quality of life, and potentially survival time. Unfortunately, not all patients with chronic cancer-related pain can be controlled with comprehensive medical management and it is important to consider other modalities of treatment, including intrathecal (IT) therapy for these patients. The indications for IT therapy in patients suffering from chronic pain resulting from cancer or the treatment of cancer are explored here. Generally, IT therapy is indicated for patients with greater than 3 months of life expectancy who have continuing neuropathic and/or somatic/visceral pain despite an optimized pharmacologic treatment regimen or who experience intolerable side effects from medications. In these refractory patients, IT therapy can provide targeted, effective analgesia with fewer adverse effects, leading to quality-of-life--enhancing pain relief.

It is estimated that 116 million Americans suffer from chronic pain, with 5 to 7 million of these cases attributable to cancer-related causes.[1] Approximately 90% of cancer patients will experience pain at some point during the course of their disease, and the resulting loss of function and negative psychological impacts can be devastating to the patient, with adverse consequences extending to family, friends, and overall societal productivity.[2,3] Chronic persistent cancer pain can result directly from disease growth into adjacent structures, as for sarcomas or lymphomas, or be a consequence of progression via metastasis into structures such as bone.[3,4] Protracted and debilitating pain can also be caused by cancer treatments. Surgical excision can result in postcraniotomy, post radical neck dissection, postthoracotomy, postmastectomy, postnephrectomy, post liver resection, and postinguinal lymphadenectomy pain syndromes. Likewise, patients may develop peripheral neuropathies after chemotherapy with agents such as vincristine, vinblastine, cisplatin, paclitaxel, docetaxel, bortezomib, or thalidomide. Fortunately, 90% to 95% of these patients can achieve adequate pain control with aggressive pharmacologic intervention using opioids and their adjuvants, although it is important to recognize that 5% to 10% of patients will require more invasive therapy.[5] Intrathecal (IT) pump placement is an important option to consider for patients who have optimized pharmacologic therapy that is not providing adequate pain control or who have intolerable side effects that preclude the ability to increase medications to therapeutically effective levels.

IT devices can deliver a variety of opioid and nonopioid medications directly into the cerebrospinal fluid, allowing central nervous system receptors to be more effectively and selectively targeted. This leads to better pain relief with a smaller dose of drug and a more exact delivery mechanism and thus patients experience fewer adverse systemic effects with little to no loss of motor function.[5] Cancer patients were the first group to benefit from implantable IT devices[6] and IT therapy is still indicated for many of these patients, particularly those with mixed neuropathic and somatic/visceral pain. These pain components are addressed with care-

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ful titration of opioids, bupivacaine and clonidine, first with an epidural trial to gauge whether pain is successfully controlled before a permanent IT pump is implanted.[5] Indeed, it is extremely important to provide adequate analgesia in the cancer patient population because there is evidence to suggest that good pain control may positively influence survival.[7-9] In non-cancer-related chronic pain, IT devices may be indicated for those who are not surgical candidates and who do not have any contraindicated medical conditions or underlying psychological problems. Examples of such potential patients include those suffering from postherpetic neuralgia, patients with complex regional pain syndromes type I or II, arachnoiditis, and chronic pancreatitis.[10] Moreover, IT therapy has been found useful in patients with acquired immune deficiency syndrome related pain.[11] It is also notable that patients with spasticity from multiple sclerosis, cerebral palsy, or brain injury can also benefit from an implantable pump that can deliver muscle relaxant medications intrathecally.[10]

There is mounting evidence that that IT therapy is superior to comprehensive medical management (CMM) in achieving clinical pain control and reduction in drug toxicities. In 2002, Smith et al[7] conducted a randomized clinical trial comparing IT therapy (or implantable drug delivery system) to CMM in patients with refractory cancer pain. This trial showed that 84.5% of patients receiving IT therapy achieved clinical success, which they defined as greater than or equal to 20% reduction in pain scores or equal scores with a 20% or greater reduction in toxicity, whereas the only 70.8% of the CMM group achieved the same ($P = 0.05$). In the IT group, visual analog pain scores fell by 52% compared to the CMM group, which had a 39% reduction ($P = 0.055$). The IT group also had a statistically significant reduction in fatigue and oversedation ($P < 0.05\%$). The study also found that patients with pain controlled with IT therapy had improved survival with 53.9% alive at 6 months compared to 37.2% of the CMM patients, although it is important to note that survival was not a designated endpoint in the design of the study and that the study did not have the statistical power to evaluate this problem.

In 2005, Smith et al[8] again compared implantable drug delivery systems to comprehensive medical management in the same type of patient population with the goal of investigating if IT therapy success was maintained over time. He compared the same endpoints of pain reduction and toxicities at 4 weeks and again at 12 weeks. He again found that patients treated with IT therapy had reduced pain scores and fewer side effects from pain medications at both 4 weeks and 12 weeks. At 4 weeks 88.5% of IT patients had achieved clinical success with 82.5% at 12 weeks, compared to the CMM group, which achieved 71.4% and 77.8% at 4 and 12 weeks, respectively ($P = 0.02$ at 4 weeks, $P = 0.55$ at 12 weeks). The reduction in drug side effects in patients on IT therapy was 55% at 4 weeks and 66% at 12 weeks, compared to 20% and 37% and 4 and 12 weeks in the CMM group ($P = 0.002$ at 4 weeks, $P = 0.23$ at 12 weeks). Additionally, at the end of 6 months, patients on IT therapy were again found to have higher survival rates, with greater than 50% still alive compared to 32% of patients on CMM who had not crossed over to IT therapy, although again survival was not a designated endpoint of the trial and further studies are needed to confirm this result.

Despite the effectiveness of IT therapy for pain management, however, it is not appropriate for all patients, and potential candidates must be carefully evaluated to optimize treatment outcomes.[5,8] Lifespan is 1 of the first considerations that must be taken into account. IT therapy is indicated for patients with greater than 3 months to live as it will provide a more permanent means of pain management. In those patients with less than 3 months to live, pain can be effectively managed with an epidural catheter.[5]

When evaluating a patient for IT therapy, the source of the patient's pain must be identified so the proper medications can be used and an appropriate site for catheter placement can be planned.[8] This can be achieved through a careful history and physical and diagnostic testing.[5] IT therapy is effective in patients with visceral pain, commonly the result of soft-tissue tumors originating from the pancreas, lung, or liver. It can also be effective therapy for somatic pain, which is often the result of bone metastases. IT therapy is also indicated for neuropathic pain, which can occur when tumor tissue compresses or invades nerves.[8] Somatic and visceral pain is effectively managed with administration of IT opioids, while neuropathic pain should be managed with IT bupivacaine and/or clonidine. Medications can also be administered concurrently for patients suffering from mixed nociceptive and neuropathic pain components.[5]

Once the source of pain is identified, a measure of pain intensity should be obtained with a numerical score or another means of qualification to determine if the patient has a pain level in a range to warrant IT therapy and to obtain a baseline, help with titration of medications, and monitor the success of the treatment.[8] IT therapy is indicated for patients with moderate to severe pain intensity despite systemic medication administration.

The results of prior therapies can also be important to determining if IT therapy is indicated. In practice, it has been noted that patients who have a history of poor pain control with failure of noninvasive pharmacologic measures or those who have difficulty tolerating systemic opioids and/or adjuvants achieve better pain control with IT therapy.[3,8] IT therapy should be considered in patients with complex pain that is poorly managed and in patients who have difficulty tolerating systemic opioids, anticonvulsants, tricyclic antidepressants, or dual reuptake inhibitors. Moreover, it has been suggested that it could also be used in patients with conditions that make opioid-related toxicities especially dangerous, such as morbid obesity, sleep apnea, or other forms of respiratory compromise.[3] However, longitudinal studies have not been conducted to corroborate this suggestion.

It is important to recognize when IT therapy is indicated because not all patients can be managed effectively with systemic medications and suitable pain control is necessary for quality of life, functioning, and psychological well-

being. In carefully selected patients, IT therapy with multiple agents is associated with a high degree of success and, with the development of IT therapy, chronic pain can now be appropriately managed in almost all patients.[5]

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