

Narrative Review

Rationale and Recent Advances in Targeted Drug Delivery for Cancer Pain: Is It Time to Change the Paradigm?

Denis Dupouiron, MD¹, Rui Duarte, PhD², Gabriel Carvajal, MD³, Frederic Aubrun, PhD⁴, and Sam Eldabe, PhD⁵

From: ¹Anesthesiology and Pain Department Institut de Cancérologie de l'Ouest Paul Papin - Angers - France; ²Liverpool Reviews and Implementation Group, University of Liverpool, Liverpool - UK; ³Centro Nacional De Control del Dolor y Cuidados Paliativos, San José - Costa Rica; ⁴Anesthesiology and Critical Care Department Centre Hospitalier Universitaire Lyon - France; ⁵Department of Pain Medicine, The James Cook University Hospital, Middlesbrough - UK

Address Correspondence:
Denis Dupouiron, MD
Anesthesiology and Pain, Institut de Cancérologie de l'Ouest
2 rue Moll
Angers, 49933 France
E-mail:
denis.dupouiron@ico.unicancer.fr

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Background: Cancer pain prevalence remains high with more than 60% of patients with advanced cancer experiencing cancer-related pain. The undertreatment of pain due to concerns of opioid dependence or diversion, as well as the potential effect of opioids on tumor neogenesis, add to the suffering among cancer populations.

Objectives: The aim of this narrative review was to assess evidence on the effectiveness, safety, cost-effectiveness, and advances of Intrathecal (IT) Drug Delivery Systems (IDDS) for the management of cancer pain.

Study Design: The present review was performed by searching for articles indexed in PubMed, MEDLINE, SciELO, Google Scholar, and Scopus.

Methods: Studies were included if they investigated patients with chronic cancer-related pain treated with IDDS and assessed experienced pain. We performed a narrative synthesis.

Results: IDDS have demonstrated efficacy in relieving cancer pain even in the challenging treatment of head and neck cancer pain. IDDS is also associated with a large reduction in serum opioid concentrations limiting adverse effects. When combined with other analgesics commonly used in the spinal space, but not systemically, pain relief may be dramatically improved. Advances in IT drug diffusion, including mixtures created with pharmaceutical compounding, improve the safety and accuracy of this therapy. IDDS is cost-effective and safe yet remains underutilized in this patient population.

Limitations: Despite numerous clinical studies, only a small number of randomized trials have been conducted to evaluate the effectiveness of IDDS for cancer pain.

Conclusions: This article presents an overview of the current state of evidence on the effectiveness, safety, cost-effectiveness, and advances of IDDS for the management of cancer pain. Despite current evidence, IDDS remains underutilized for people with cancer pain. Potential areas to facilitate its use are discussed. A shift in the paradigm of cancer pain treatment should be considered given the undertreatment rate, lack of benefits, and considerable risks associated with oral opioid medication in many patients who suffer from chronic cancer pain.

Key words: Cancer pain, intrathecal drug delivery systems, narrative review, opioids, undertreatment

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Considerable progress has been made in recent years in treatments for cancer, including a wider variety of drug options available to treat different cancer pathologies at different stages

of the disease. However, cancer pain remains a major issue that becomes more problematic especially at later stages of the disease (1-3). Although greater rates of remission are now observed, patients often continue

to suffer consequences from the cancer itself or from the cancer treatments received. For example, kidney cancer mortality rate has decreased 1% per year, from 2007 to 2016, due to the availability of targeted cancer therapies (4). While these patients are in a stable disease state, pain may remain problematic because of tumor invasions of neural structures and somatic tissues.

The prevalence of pain in patients with cancer has been reported as 39.3% after curative treatment; 55.0% during anti-cancer treatment; 66.4% in advanced, metastatic, or terminal disease; and 50.7% in studies that included all cancer stages (2). In addition, a literature review has suggested that 31.8% of cancer pain was inadequately treated (5). Long-term pain control through administration of opioids has been called into question due to concerns about opioid harms, opioid abuse, and dependence (6), as well as the effect of opioids on tumor neogenesis (7). Moreover, 28% of patients experience cancer pain with neuropathic features, which may be resistant to opioids (8). Even when treatment is well managed, between 10% to 15% of patients can suffer from refractory pain (9).

It has been demonstrated that pain is a contributing factor in the reduction of life expectancy (10). For this reason, a fourth step of the World Health Organization (WHO) ladder was proposed (11) for patients presenting a high level of pain or adverse effects of treatments despite a well-managed pain program following the WHO ladder. This fourth step calls for the use of interventional techniques, including targeted drug delivery. Despite increasing evidence in the literature demonstrating the efficacy, safety, and cost-effectiveness of intrathecal (IT) therapy, it remains underused in the cancer population for poorly controlled, severe pain.

Principles of IT Analgesia

IT analgesia is a targeted therapy where analgesics are administered into the cerebrospinal fluid (CSF) close to their specific site of action at the spinal cord. The efficacy of IT analgesia was first demonstrated in an animal study conducted by Yaksh et al (12) and confirmed in the first human study published in 1979 (13). The use of IT Drug Delivery Systems (IDDS) subsequently grew following the development of fully implantable pumps.

The administration of low doses of analgesics directly into the CSF facilitates effective pain relief, while reducing systemic adverse effects. The targets for IT treatment are the A delta and C fiber synapses located on laminae I, II, and III of the dorsal horn of the spinal

cord (14). Understanding CSF drug diffusion is essential to improving the efficacy of IT treatments. Recently, great strides have been made toward a better understanding of CSF circulation and IT drug diffusion due to magnetic resonance imaging (15). It is now understood that CSF circulation is only pulsatile and that its pace is set by heartbeat- and intrathoracic respiratory-induced pressure variations (16). However, opioid movement within the CSF is not only pulsatile, but there is also bulk flow, as evidenced by radioactively labeled morphine injected into the lumbar CSF, appearing in the brain over time. (17). Accordingly, the most important factors in IT drug diffusion are, firstly, the level of infusion and, secondly, the volume and flow rate.

Technical Tips

Trials, Device Choice, and Catheter Placement

Contrary to nonmalignant pain, a trial of IT analgesia and preimplant psychological evaluation are not mandatory for patients suffering from cancer-related pain, but should be reserved for the few where there remains lack of clarity about pain etiology or response to a particular class or mixture of drugs (18). External devices are recommended for patients with a short life expectancy, usually less than 3 months, while internal pumps are used in patients with longer life expectancy. However, life expectancy can be challenging to evaluate, and severe pain, as well as adverse effects of large doses of systemic analgesics, may skew judgment (19). When implanting the catheter, care should be taken to place the tip close to the dermatomes involved in the nociceptive signal in the dorsal CSF (20). Recent availability of multilayered catheters has greatly facilitated catheter tip placement, especially in higher cervical positions for head and neck cancer pain via lumbar puncture, thus widening the scope of application of IDDS (21). Although nonprogrammable IDDS devices remain available in some countries, programmable infusion pumps have dominated clinical practice for the last decade (21).

Complications

Postdural puncture headache (PDPH) is one of the most frequent complications with an incidence ranging from 1% to 30% for cancer patients (22). Several options for management of PDPH have been described in the literature, including conservative management, the use of epidural blood patches, or preventative fibrin glue application (23). The potential for complications

following epidural blood patch in an immunosuppressed population needs to be taken into account when considering risk vs benefit fibrin glue application has been described as a treatment of PDPH but remains experimental as a prevention measure (24). Infection of the pump pocket ranges from 0% to 9% (25). Infections are more likely to occur in cases of cancer due to immunosuppressive treatments. However, in a recent evaluation of 270 cancer patients receiving antineoplastic treatment or systemic corticosteroids within 30 days before IDDS implant, the infection rate was only 0.9% (95% confidence interval, 0.1% to 3.3%) (26). The risk of bleeding has been estimated to be 0.9% and the risk of neurologic injury as 0.4% (27). Catheter dislodgment, breakage, and kinking are frequently discovered after an unexpected loss of efficacy of the IDDS with an incidence of 1.31% to 3.19% (28). Drug complications are outside the scope of this article.

Contraindications

Intracranial hypertension, as well as localized infections at the site of spinal catheter or pump pocket implant and systemic infection (sepsis), are considered absolute contraindication to IDDS. Similarly, an obstacle to CSF circulation, like spinal stenosis secondary to tumor, may block correct catheter positioning and the physician may select an intraventricular catheter placement to address challenging types of pain. Guidelines have been established by the Polyanalgesic Consensus Conference (PACC) (21,22) for surgical recommendations in patients who have ongoing localized infections, are on anticoagulants, have thrombocytopenia, or have leukocytopenia. The PACC have also suggested that factors, including the presence of major psychiatric disorders, insufficient acceptance and understanding of the procedure, lack of social support, significant substance abuse/addiction, and significant cognitive disruption may be contraindications (19) for IDDS. These factors should be carefully considered in cancer pain patients and whether the potential benefits of IDDS may outweigh the risks. Consideration of risk benefit should take into account the patient's cancer stage, life expectancy, as well as the availability of other potential therapeutic options.

IT Drugs

Drugs must meet certain criteria to be IT administered. Molecules must be diffusible through the spinal fluid and remain in solution at body temperature (29). Hydrophilic medications IT administered may have a

clinical advantage as they have longer half-lives, reflecting a faster clearance into the vasculature as demonstrated by lipophilic agents. In addition, drugs must be stable in pumps and nontoxic for the spinal cord. An overview of commonly used IT drugs is presented in Table 1. Starting dose, maximum dose, concentration, and titration of IT drugs should follow best practice recommendations (19).

Future Drugs

Dexmedetomidine is an alpha-2 adrenergic agonist with high selectivity at 8 times that of clonidine and was observed to have a synergistic effect with morphine in one study (30). Fadolmidine is another alpha-2 adrenergic agonist that produces fewer hemodynamic effects and less sedation (31). Quinoxaline-based kappa-opioid receptor agonists downregulate the proliferation, activation, and secretion of cytokines. Antisense oligonucleotides could attenuate mechanical allodynia following peripheral nerve injury. Resiniferatoxin TRPV1 receptor agonist and botulinum toxin are potential drugs for IT use (32). Synthetic botulinum toxin has demonstrated effects in pain relief of inflammatory and neuropathic pain in mouse models (33). Mycolactone is an endotoxin produced by the bacteria *Mycobacterium ulcerans* and IT acts by the activation of angiotensin 2 receptors (34).

Compounded drug combinations are commonly used to address multiple pain receptors. Several combinations have been shown to be effective (19,35). Device manufacturers and the US Food and Drug Administration have recommended the use of single drug, on-label-only medications. However, for cancer patients, complex combination therapies are utilized in 97% of IDDS formulations (18). The prescription of these treatments often requires complex calculations (36). In addition, preparation of these mixtures requires high levels of accuracy and sterility that only compounding pharmacies can achieve. Such high standards are recommended by the PACC (22). Moreover, conducting systematic assays on mixtures after preparation improves safety, accuracy, and reduces the risk of errors, as well as the monitoring of formulation contaminants and drug stability (37).

Rationale for IT Treatment for Cancer Pain

The effectiveness of IDDS for the management of pain has been reported in several studies (38,39). A study (38) of 202 patients with refractory cancer pain randomized to receive IDDS or comprehensive medical

Table 1. Commonly used IT administered drugs for the management of cancer pain.

Drug	Target	Mechanism of Action	Indication	Commonly reported side-effects	PACC recommendation cancer pain with localised nociceptive or neuropathic pain (16)	PACC recommendation cancer pain with diffuse nociceptive or neuropathic pain (16)
Opioids						
Morphine	Mu-type opioid receptor (agonist)	Morphine and other opioids binding to opioid receptors blocks transmission of nociceptive signals, signals pain-modulating neurons in the spinal cord, and inhibits primary afferent nociceptors to the dorsal horn sensory projection cells. Morphine has a time to onset of 6-30 minutes and has a lasting effect.	Nociceptive and neuropathic pain	Respiratory depression, granuloma, endocrine disruption, urinary retention, peripheral oedema, immunosuppression, hyperalgesia, cognitive impairment	First-line (1A) = morphine Second-line= +clonidine or +ziconotide Third-line= +bupivacaine+clonidine or +bupivacaine+ziconotide	First-line (1A) = morphine First-line (1B)= +bupivacaine Second-line= +clonidine or +ziconotide Third-line= +bupivacaine+clonidine or +bupivacaine+ziconotide
	Kappa-type opioid receptor (agonist)					
	Delta-type opioid receptor (agonist)					
Hydromorphone	Mu-type opioid receptor (agonist)	Analgesic effect suggested to be related to the effect on the mu-opioid receptors. It has been reported to also have a minor affinity for the delta and kappa receptor. Onset of action of the immediate release form of hydromorphone is achieved in 15-20 minutes and has a lasting effect for 3-4 hours while the extended-release form onset of action is of 6 hours lasting for about 13 hours.	Nociceptive and neuropathic pain. Suitable for pain relief in patients that do not tolerate the side effects of morphine		Second-line=hydromorphone or +bupivacaine or +clonidine or +ziconotide Third-line= +bupivacaine+clonidine or +bupivacaine+ziconotide	First-line (1B)=hydromorphone or +bupivacaine Second-line= +clonidine or +ziconotide Third-line= +bupivacaine+clonidine or +bupivacaine+ziconotide
	Kappa-type opioid receptor (agonist)					
	Delta-type opioid receptor (partial agonist)					
Fentanyl	Mu-type opioid receptor (agonist)	Produces strong analgesia through its activation of opioid receptors, especially the mu opioid receptor. It has a duration of action of several hours and a wider therapeutic window as patients develop tolerance to opioids.	Nociceptive and neuropathic pain		First-line (1B)=fentanyl or +bupivacaine Second-line= +clonidine or +ziconotide Third-line= +bupivacaine+clonidine or +bupivacaine+ziconotide	Third-line= +bupivacaine+clonidine or +bupivacaine+ziconotide
	Delta-type opioid receptor (agonist)					

Table 1 (cont.). Commonly used IT administered drugs for the management of cancer pain.

Drug	Target	Mechanism of Action	Indication	Commonly reported side-effects	PACC recommendation cancer pain with localised nociceptive or neuropathic pain (16)	PACC recommendation cancer pain with diffuse nociceptive or neuropathic pain (16)
Sufentanil	Mu-type opioid receptor (agonist)	Highly selective binding to mu-opioid receptors. Has been reported to be as much as 10 times as potent as fentanyl. Opioids decrease cAMP (affecting neural signalling pathways), decrease neurotransmitter release, and cause membrane hyperpolarization, all of which contribute to the relief of painful symptoms.	Nociceptive and neuropathic pain		Third-line=sufentanil Fourth-line= +ziconotide or +bupivacaine or +clonidine Fifth-line= +bupivacaine+clonidine or +bupivacaine+ziconotide or +clonidine+ziconotide	Third-line=sufentanil Fourth-line= +ziconotide or +bupivacaine or +clonidine Fifth-line= +bupivacaine+clonidine or +bupivacaine+ziconotide or +clonidine+ziconotide
Non Opioids						
Ziconotide	Voltage-dependent N-type calcium channel subunit alpha-1B (inhibitor)	Inhibits N-type calcium channels involved in nociceptive signalling, primarily in the dorsal horn of the spinal cord. N-type channel activation in lightly myelinated Aδ- and C-fibres is known to mediate the release of neurotransmitters substance P, calcitonin gene-related peptide, and glutamate, which influence downstream neural activation and pain perception. Binding is reversible, however, careful dosing is required to ensure therapeutic effects while minimizing adverse effects. Ziconotide has been described as possessing a narrow therapeutic window.	Nociceptive and neuropathic pain. Suitable for patients who cannot tolerate, or who have not responded adequately to other treatments such as intrathecal morphine and systemic analgesics	Cognitive and neuropsychiatric symptoms, reduced levels of consciousness, elevated serum creatine kinase levels, may increase the risk of infection including serious cases of meningitis	First-line (1A)=ziconotide Second-line= +morphine or +hydromorphone Third-line= +bupivacaine or +clonidine or +morphine+bupivacaine or +hydromorphone+bupivacaine or +fentanyl+bupivacaine Fourth-line= +sufentanil or +bupivacaine+clonidine Fifth-line= +sufentanil+bupivacaine or +sufentanil+clonidine	First-line (1A)=ziconotide Second-line= +morphine or +hydromorphone Third-line= +bupivacaine or +clonidine or +morphine+bupivacaine or +hydromorphone+bupivacaine or +fentanyl+bupivacaine Fourth-line= +sufentanil or +bupivacaine+clonidine Fifth-line= +sufentanil+bupivacaine or +sufentanil+clonidine

Table 1 (cont.). Commonly used IT administered drugs for the management of cancer pain.

Drug	Target	Mechanism of Action	Indication	Commonly reported side-effects	PACC recommendation cancer pain with localised nociceptive or neuropathic pain (16)	PACC recommendation cancer pain with diffuse nociceptive or neuropathic pain (16)
Bupivacaine	Sodium channel protein type 10 subunit alpha (inhibitor)	Bupivacaine blocks the generation and the conduction of nerve impulses, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. Prevents depolarization by binding to the intracellular portion of sodium channels and blocking sodium ion influx into neurons. Short onset of action.	Noiceptive and neuropathic pain. Used in combination for severe pain conditions where opioids alone are not sufficient to obtain satisfactory pain relief	Numness, weakness, urinary retention and hypotension	First-line (1B) = +morphine or +fentanyl Second-line = +hydromorphone Third-line = +morphine+clonidine or +hydromorphone+clonidine or +fentanyl+clonidine or +ziconotide or +morphine+ziconotide or +hydromorphone+ziconotide or +fentanyl+ziconotide Fourth-line = +sufentanil or +clonidine+ziconotide or +clonidine Fifth-line = +sufentanil+clonidine or +sufentanil+ziconotide Sixth-line = +opioids+clonidine+adjuvants*	First-line (1B) = +morphine or +hydromorphone Third-line = +morphine+clonidine or +hydromorphone+clonidine or +fentanyl+clonidine or +ziconotide or +morphine+ziconotide or +hydromorphone+ziconotide or +fentanyl+ziconotide Fourth-line = +sufentanil or +clonidine+ziconotide or +clonidine Fifth-line = +sufentanil+clonidine or +sufentanil+ziconotide Sixth-line = +opioids+clonidine+adjuvants*
	Alpha-2A adrenergic receptor (agonist)	Functions through agonism of alpha-2 adrenoceptors which is coupled to G-proteins. It has effects such as lowering blood pressure, sedation, hyperpolarization of nerves and decrease transmission of pain signals at the spine. It has a long duration of action.	Noiceptive and neuropathic pain. Used in combination for severe pain conditions where opioids alone are not sufficient to obtain satisfactory pain relief	Sedation and hemodynamic side effects such as hypotension and bradycardia	Second-line = +morphine or +hydromorphone or +fentanyl Third-line = +morphine+bupivacaine or +hydromorphone+bupivacaine or +fentanyl+bupivacaine or +ziconotide Fourth-line = +sufentanil or +bupivacaine+ziconotide or +bupivacaine Fifth-line = +sufentanil+bupivacaine or +sufentanil+ziconotide Sixth-line = +opioids+bupivacaine+adjuvants*	Second-line = +morphine or +hydromorphone Third-line = +morphine+bupivacaine or +hydromorphone+bupivacaine or +fentanyl+bupivacaine or +ziconotide Fourth-line = +sufentanil or +bupivacaine+ziconotide or +bupivacaine Fifth-line = +sufentanil+bupivacaine or +sufentanil+ziconotide Sixth-line = +opioids+bupivacaine+adjuvants*
Clonidine	Alpha-2B adrenergic receptor (agonist)					
	Alpha-2C adrenergic receptor (agonist)					

management demonstrated improved clinical success with IDDS in pain control along with a significant reduction of common analgesic drug toxicities and improved survival. A double-blind placebo controlled randomized study (39) of 111 patients with cancer or AIDS-related pain found that IT administered ziconotide provided clinically and statistically significant analgesia at the cost of a higher rate of adverse events.

Although randomized trial evidence is limited, IDDS is a well-accepted management option for cancer pain, and as such, clinical equipoise, essential for the conduct of a randomized trial, may no longer be present unless to evaluate new IT drugs. Observational studies, although having inherent limitations due to its design, can provide a better representation of the effectiveness of IDDS in routine clinical practice. IDDS with ziconotide alone or in combination with other analgesics has also been reported to be highly effective in various observational studies (21,35) with a positive impact on pain and quality of life outcomes. Several recent observational case series (21,40-42) confirmed the efficacy of IDDS, including low-dose ziconotide mixtures in cancer pain treatment, with pain score improvements of more than 50%. Additionally, highly specific studies have demonstrated efficacy in the control of pancreatic (40,43) and head and neck (44) cancer pain. A 2016 literature review (45) of IDDS in cancer-related pain concluded that although IT therapy has been shown to provide pain relief in these patients, the decision to implant an IDDS must be based on an appropriate risk/benefit ratio that weighs the possible benefits (ie, pain relief) and harms (eg, surgery risk, drug management issues) of IT treatment against palliative care options (eg, hospice). The authors also pointed to increases in cancer survival prompting a paradigm shift in the treatment of cancer-related pain from a short-term palliative care approach to a long-term management of chronic pain approach and that IDDS may well fit within the long-term therapy paradigm (45). Finally, in the largest prospective follow-up study to date of 1,403 patients, Stearns et al (46) reported significant improvements in pain and quality-of-life scores following IDDS even in advanced stages of the disease.

Cost-effectiveness of IDDS

Studies (47-49) have shown that IDDS are not only effective, but also economically efficient. Brogan et al (47) showed that IDDS for the management of refractory cancer pain reaches the break-even point after 6 months of use through reduced costs of medication

and less time spent in the hospital. Moreover, costs of treatment with IDDS were observed to stabilize, while those of conventional treatments steadily increased. In the same vein, Stearns et al (48), using the Truven Health MarketScan Commercial Claims and Encounters Database, have shown that at 12 months, pharmacy costs were \$9,264 higher for IDDS, while medical costs were \$12,459 lower compared to conventional medical management (CMM), achieving total cost savings of \$3,195 for IDDS. Using the same database with more recent data (49), from January 1, 2009 to September 30, 2015, the authors showed more than \$63,000 cost savings after 12 months and more than \$15,000 after 2 months of treatment with IDDS.

Recommendations on the Use of IDDS for Cancer Pain

Cancer pain management is globally based on WHO recommendations published in 1986 and updated in 2019 (50). These recommendations, while appropriate from a global perspective, have not taken into consideration neither the increased cancer survival nor the long-term consequences of chronic systemic opioid therapy. Recently, concern over the harmful effects of long-term systemic opioids led to the retraction of the WHO on its 2011 guidance for availability and accessibility of controlled medicines (51). A cohort study (9) observed that despite adherence to the WHO guidelines the efficacy of cancer pain treatments was inadequate for 14% of the study patients. The addition of a fourth step, to include interventional therapies to the WHO ladder, has been suggested (11). Based on the recognition of the harms of long-term systemic opioids, more patients are being offered interventional techniques, as opposed to opioid therapy for chronic cancer pain. IDDS for cancer pain is routinely commissioned in the United Kingdom (52), Netherlands and Belgium (53), France (54), and Spain (55). Likewise, the European Society of Medical Oncologists has recently proposed IDDS as a management option for cancer pain with a Level IIB recommendation (56). An evidence-based medicine review (57) classifies IDDS amongst the treatments that must be used for cancer pain, even if the level of evidence has been deemed as moderate. The same publication rejected ketamine, intravenous lidocaine, steroids, and anticonvulsants. The latest PACC awards the strongest grade IA recommendation for the use of IDDS for the management of cancer pain (19). Recently, recommendations from The American Society of Pain and Neuroscience for reducing pain and suffer-

ing associated with malignancy also awarded the same grade IA level for IDDS and stated that this intervention should be strongly considered in patients with cancer-related pain that is not responding to, or who develop side effects from, CMM (58).

Given its stated goal of reduction of pain to a level that allows for a quality of life that is acceptable to the patient, it is difficult to understand why the WHO continues to ignore interventional cancer pain treatment options (50), even when the WHO recommends that after an abrupt reduction in pain (such as, after a nerve block or neuro-ablative procedure), clinicians may consider reducing the dose of opioid until it can be stopped (59). The above can only be understood within the context of a global view of cancer pain where interventional techniques, such as IDDS, are only.

Rationale for Early IT Treatment

IT treatments are often introduced late. This is demonstrated by mean daily morphine equivalent doses of systemic opioids of patients referred for IDDS reported of 805 mg/d (60), 360 mg/d (40), or 453 mg/d (42). In addition, it appears that patients are often referred when their overall health has already deteriorated. For instance, Stearns et al (46) reported the American Society of Anesthesiologists (ASA) physical status of III or IV in 91.1% of 1,403 patients enrolled in a prospective IDDS registry. Similarly, Sindt et al (61) found 93.5% of patients at ASA III or IV. However, the main factors predicting early pain relief post-IDDS have been reported to be preimplant low systemic morphine equivalent doses and the patient's level of functioning Performance Status (PS) from the Eastern Cooperative Oncology Group (62). Moreover, survival is significantly better in active patients with a PS of 0 or 1, with a greater improvement in pain scores in patients receiving early pain relief (63).

Given the above, coupled with the long-term safety track record of IDDS (46), it may be reasonable to conclude that earlier consideration of IDDS in the course of the disease may yield better long-term outcomes.

The management of neuropathic cancer pain is challenging, with relatively high rates of failure and side effects with conventional treatments (1). It is estimated that 20% of cancer pain is purely neuropathic (8). However, when mixed neuropathic-nociceptive pain is included, approximately 40% of patients with cancer are affected by neuropathic pain (1). Specific drugs commonly used for neuropathic pain include gabapentinoids (e.g., gabapentin and pregabalin)

and antidepressants (e.g., tricyclic antidepressants, duloxetine, and venlafaxine). Antidepressants were reported to have a number needed to treat of 3.6 in a Cochrane review (64). An evidence-based review of effective management of pain in patients with advanced cancer found very limited evidence for the efficacy of anticonvulsants or antidepressants in cancer pain. Their addition to opioids was also not shown to improve pain compared to opioids alone (57). Updated WHO recommendations for cancer pain management do not recommend anticonvulsants and antidepressants (50). Haumann et al (1) incite the rapid development of therapeutic alternatives. In this context, IT analgesia offers pain relief options using specific treatments, such as local anesthetics, clonidine, and ziconotide (32).

Adverse Effects of Opioids on Cancer Evolution

Since the 1990s, opioid analgesic use has increased for the treatment of severe cancer pain in the United States. Common safety concerns have been raised over time, including opioid-induced respiratory events (6).

More recently, concerns regarding a potentially higher systemic infection risk among opioid users has been reported after an association between opioids and immunosuppression was investigated both in vitro and in vivo (65). Systemic opioids have been found to impair the function of macrophages, natural killer cells, and T-cells and to increase susceptibility to specific bacteria in humans. These immunosuppressive effects of systemic opioids may be associated with negative clinical outcomes, particularly in patients with known risk factors, such as cancer (66).

Systemic opioid use for cancer pain treatment is concerning due to the potential role of opioids in tumor growth. Some tumors overexpress a mu opioid receptor involved in tumor angiogenesis, especially in small cell lung cancer (7) and some breast tumors (67). In vitro studies (66,67) suggest that opioid pathways may be involved in tumor growth, though more evidence is required. On the other hand, IDDS is associated with a dramatic reduction in serum opioid concentrations with most patients having undetectable serum levels (68).

Moreover, in the opioid crisis context, the risk of opioid misuse is significant. In a study (69) of cancer patients screened with specific scales to assess for the risk of substance use disorder with prescribed opioids, 29% were found to be at high risk. This was particularly true for younger individuals and those with high levels of anxiety/depression. Systemic opioid elimination

could be accomplished after IDDS implantation in most cases (70). Furthermore, in pancreatic cancer, it is the only treatment providing prolonged pain relief, while also eliminating systemic opioids (40). Smith et al (38) revealed a significant reduction in all adverse effects of analgesics. Today, as stated by Pittelkow et al (71), it is challenging to understand why this technique is implemented so late, while relatively low levels of systemic opioids are a factor in early pain relief (68).

How to Facilitate IDDS for Cancer Patients

Despite the available evidence and recommendations for the use of IDDS, a substantial gap has been reported between the number of patients with refractory cancer pain in England potentially eligible to receive IT therapy and the actual provision of this management option, with the number of patients receiving an implant not increasing since 2015 (72). Furthermore, few cancer patients are referred to pain clinics, only 23% in the largest European survey (73). This probably helps to explain the late and infrequent use of IDDS in cancer pain care. Moreover, this therapy is sometimes seen as aggressive and burdensome by physicians in the context of palliative care, while some countries limit access to the technique either by restricting the number of devices to be implanted annually or by mere financial management of health care, as in Ontario, Canada (74). It must also be noted that IDDS is available only in expert centers, and few physicians are trained in managing implantations and patient follow-up. Moreover, in some countries, physicians do not have access to the required medications for IT use (eg, concentrated bupivacaine in France, ziconotide in Belgium).

Several strategies can facilitate access to IDDS. Firstly, new technologies, such as video conference, can be used for multidisciplinary meetings to share knowledge and recommend the best treatments available. Compounding pharmacies can also easily provide refill mixtures for nearby hospitals or for their patients, to avoid displacing frail cancer patients. Moreover, refills performed by trained nurse practitioners at home with support from a medical specialist, as is already the case in the Netherlands for spasticity (75), should allow for a wider adoption of the technique. Finally, the inclusion of a fourth step in the WHO ladder to include interventional procedures could potentially raise awareness in clinicians, patients, and caregivers for the availability of IDDS as a management option for cancer pain.

CONCLUSIONS

IDDS technique has improved over the past few decades. Its effectiveness, safety, and cost-effectiveness has been widely evaluated via good-quality randomized controlled trials and economic evaluations. Based on this evidence, IDDS is a recommended therapy for cancer pain in several countries. Devices and treatments allow the targeting of all types of pain that remain difficult to treat by conventional routes. For refractory cancer pain, IDDS markedly reduces the risks associated with systemic treatments, such as opioids. The limited access to IDDS therapy can potentially be improved with implantations carried out by expert centers, refills, and follow-ups managed closer to patients' home with the help of compounding pharmacies and advanced nurse practitioners.

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