Intra-Thecal Drug Therapy in Cancer Pain

Abstract

This case outlines the difficulties and multidisciplinary nature involved in the management of complex cancer pain. Cancer pain is multifactorial and as such often needs multiple treatment approaches including Surgery, Radiotherapy, Hormonal treatment and Analgesics. Conventional analgesics may be ineffective in controlling pain in patients with cancer or lead to intolerable systemic side effects.

Intra-thecal or Epidural Drug Delivery systems have been used in cancer pain where conventional treatment has failed. The case described shows how efficacious intra-thecal therapy can be in providing pain relief. It also outlines the critical importance of good patient selection and psychological assessment.

Modalities of management of cancer pain are reviewed and the potential benefits and problems of Intra-Thecal Drug Delivery Systems in cancer pain are discussed.

Case Presentation

The case presented is that of a 62-year old man diagnosed with metastatic prostatic adenocarcinoma with pain refractory to conventional analgesic management.

He had no significant past medical history and lived alone. He initially presented to his GP with a six-month history of paraesthesia and numbness in
his left foot and leg followed by developing sudden onset left sided lower back pain. He reported difficulty moving his left leg normally and was noted to have a foot drop.

As part of his investigations, his GP performed a prostate specific antigen (PSA) test, which was 60ng/ml (highly elevated) so he was referred to a Urology team for further investigation and management. They noted an enlarged prostate on rectal examination and proceeded to perform an MRI scan which is shown in Figure 1.

This demonstrated a prostatic mass with large volume pelvic nodes and sacral metastatic deposits. Mass lesions in the sacrum involved the 2nd, 3rd and 4th segment with encroachment on the sacral canal at S4/5. Independently there was evidence of L4/5 nerve root impingement by enlarged nodes. Increased metabolic activity in these regions was confirmed by a radioisotope bone scan. A provisional diagnosis of metastatic prostatic adenocarcinoma was made and was confirmed by tissue biopsy. A CT of his chest, abdomen and pelvis revealed no intra-abdominal, or thoracic metastatic deposits.

**Figure 1: MRI Scan of patient’s lumbar and sacral spine**

Sagittal View
Due to the extent of disease, surgical treatment was not possible. Because of neurological compromise, he was treated with dexamethasone 16mg/day for potential spinal cord compression and started on Degarelix. This is a
Gonadotrophin Releasing Hormone (GnRH) Receptor Antagonist that reduces the secretion of Testosterone from the testes. This reduces the growth of hormone dependent tumours such as prostate adenocarcinoma. Afterwards he was started on Goserelin (GnRH Agonist) implants to continue hormonal suppression.

Because of bony tumour involvement and bone pain he was treated with Zolendronic Acid (a bisphosphonate) 4mg once monthly as an intra-venous infusion. He then received radiotherapy; 30 Gy to his Sacrum and L5 vertebra in 10 divided fractions. The tumour responded well to treatment and his PSA level dropped to undetectable (<0.1ng/ml).

Unfortunately, after radiotherapy his pain became worse. He had increasing pain focally in his sacrum and radiating down his leg. His Palliative Care Team prescribed Paracetamol 1g four times daily and Sevredol 10mg PRN. His requirements for Sevredol rapidly escalated and soon Morphine slow release tablets (MST) were added and titrated to 40mg BD. Gabapentin (300mg TDS), Nabumetone (1g OD) and TENS were added with no relief of symptoms. The patient was referred to the Pain Team.

**Pain Management**

On assessment by the Pain Team, the patient described a severe pain in his left sacrum and buttock, which often radiated down the lateral aspect of his leg. It did not affect the sole of his foot. This had become much worse since
radiotherapy, to the extent that he could not sleep on that side or on his back. He described it as a cigarette burning into an area the size of a two pence coin on his left sacrum/buttock with electric shocks going down the leg. Numeral Rating Scores (NRS) for the pain were 8/10 at background with 10/10 incident pain. He had a marked limp and quadriceps weakness on the left. A diagnosis of bony metastatic pain with neuropathic radicular pain was made.

On further questioning the patient stated that not only were his current analgesics ineffective at treating his pain he was getting significant side effects. These included general malaise and lethargy, nausea and constipation. He was desperate for superior analgesia with less systemic side effects.

His social history was that he was a retired engineer. He lived alone in a second floor flat with no lift and was having great difficulty with the stairs due to his limp. He did not consume alcohol, tobacco or recreational drugs. He was fairly socially isolated with financial concerns. He had no history of mental health problems and did not appear depressed or particularly anxious. He was however very specific in his questioning, wanting to know large amounts of detail about all investigations and treatments. His Hospital Anxiety and Depression score (HADS) was 7 for depression and 12 for anxiety. Apart from this he was not formally assessed by psychological services.

After discussion with the patient a decision was made to implant an Intrathecal Pump to improve his pain relief and side effects. A Synchromed II Intrathecal pump and catheter system with a 40ml reservoir was implanted
under general anaesthetic by the neurosurgeons (Figure 2). This was filled with 20ml of 0.5% Bupivacaine and 600mg of preservative free morphine.
The pump was started at 3mg of Morphine (0.5mg Bupivacaine) per 24 hours. The patient self-discharged against medical advice after pump insertion.
but represented a day later with evidence of opioid toxicity and symptoms of nausea, sweating and sedation. The patient had had a fall as a result of this, resulting in a haematoma around the pump site, which resolved spontaneously. He required naloxone and his pump was temporarily stopped but then slowly titrated up to 1.5mg(0.25)/24 hours.

When assessed two weeks post insertion the patient had dramatically better pain control (NRS 1-2/10) with no opioid or local anaesthetic side effects. The only addition analgesia required was PRN paracetamol. Unfortunately he was very unhappy with the cosmetic result of his pump as he thought it protruded too much and rubbed on his pelvis and lower costal margin. He initially wanted the pump removed but did not wish the pain to return. He also did not wish it moved too centrally as he had a large peri-umbilical tattoo which he did not want damaged.

After much debate, the pump was switched to a 20ml reservoir to protrude less and moved slightly medially to reduce rubbing on the costal margin. The patient was much happier with the cosmetic result of the new pump although remains very preoccupied with the appearance and functioning of his pump. Pain remains extremely well controlled with NRS 1/10 with his new intrathecal pump.
Discussion

Cancer Pain

Cancer pain is common affecting 64% of patients with advanced incurable disease and can be difficult to treat. It often has multiple mechanisms including direct compression or erosion by tumour as well as neuropathic and ischaemic elements as illustrated in table 1. The exact mechanism may vary by site within an individual patient. It is also modulated by the psychological status of the patient. The case discussed is that of a patient with metastatic vertebral bone pain and radicular pain.

Table 1: Mechanisms of Cancer Pain

<table>
<thead>
<tr>
<th>Tumour Related</th>
<th>Treatment Related</th>
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<tbody>
<tr>
<td>Direct Compression → Nociceptive pain</td>
<td>Chemotherapy induced painful peripheral neuropathy</td>
</tr>
<tr>
<td>Nerve Compression → Neuropathic pain</td>
<td>Mucosititis secondary to chemotherapy / radiotherapy</td>
</tr>
<tr>
<td>Secretion of pro-inflammatory chemicals → Inflammatory pain</td>
<td>Post Radiation Neuropathy / Plexopathy</td>
</tr>
<tr>
<td>Alterations in blood flow → Ischaemic pain</td>
<td>Chronic Post Surgical Pain</td>
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<tr>
<td>Bony Metastatic Pain</td>
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Bony Metastases

Bony metastases occur commonly in breast, thyroid, kidney and prostate cancers. Bony involvement can lead to pain, fractures, nerve root or spinal cord compression and hypercalcaemia. The most frequent presentation is gradual onset of localised pain with severe incident pain on movement. Metastases most commonly occur in the axial skeleton particularly in vertebrae and ribs.

Vertebral metastases commonly involve the pedicle, which may result in nerve root compression or erode into the vertebral body leading to collapse. This can lead to localised pain or nerve root / spinal cord injury. Invasion of the vertebra alone can also cause pain.

The exact mechanism for why localised tumour invasion of the vertebra even without collapse leads to pain is not fully understood. The predominant theory is that osteoclast proliferation, seen in both osteolytic and osteoblastic tumours, leads to increased acidity within the tumour micro-environment. This reduced pH in turn activates TRPV1 receptors resulting in nociceptive pain.
Treatment of Cancer Pain

Treatment of cancer pain is multimodal as illustrated in table 2. A significant aspect of pain management is good oncological management as reducing tumour size often leads to reduced pain. However this needs to be combined with a suitable analgesic regime and holistic psychological care.

Table 2: Modalities Of Treatment of Cancer Pain

<table>
<thead>
<tr>
<th>Modality</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Surgery</td>
<td>Reduce tumour size / Stabilise Bone</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Reduce tumour size</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Reduce tumour size</td>
</tr>
<tr>
<td>Hormonal Treatment</td>
<td>Reduce tumour size / growth for hormone sensitive tumours</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Reduce bony metastatic pain</td>
</tr>
<tr>
<td>Analgesics</td>
<td>Varies by drug</td>
</tr>
<tr>
<td>Psychological / Spiritual Support</td>
<td>Enhances descending modulation</td>
</tr>
</tbody>
</table>

Surgery is often inappropriate in advanced cancer management but procedures such as vertebroplasty to treat pain from vertebral collapse fractures or fixation of long bone fractures may lead to significant relief. Radiotherapy is the main modality of treatment for bony cancer pain. Chemotherapy and hormonal treatments can reduce tumour growth and thus symptoms but can lead to significant side effects.
Bisphosphonates are widely used for the treatment of bony metastases. They bind to calcium and are then absorbed by osteoclasts. This inhibits osteoclast function and leads to apoptosis. Thus they both reduce bony pain and tumour growth within bone\textsuperscript{4}.

**Intra-Thecal Drug Therapy\textsuperscript{5}**

Because of the multiple mechanisms and severity of cancer pain, some patients do not respond to conventional analgesic regimens. This may be because they are ineffective or more commonly the dose required is so high it leads to intolerable side effects such as sedation, nausea, vomiting and constipation.

Intra-Thecal drug therapy delivers the drugs directly onto the nerve roots and the spinal cord where it can have a local effect. This aims to provide effective analgesia at much lower doses, leading to less systemic side effects. The first reported case of treatment of Cancer pain with intra-thecal morphine was by Wang in 1979\textsuperscript{6}.

Many systems for intra-thecal drug therapy exist; ranging from single shot injection to tunnelled catheters in sub-arachnoid space to sophisticated indwelling Intra-Thecal Drug Delivery Systems (IDDS). Tunnelled systems are effective but have a higher rate of infection and significantly reduce patient mobility as they are permanently attached to a pump.
Fully internalised IDDS consist of a catheter in the cerebro-spinal fluid in the sub-arachnoid space connected to a pump with an integral drug reservoir in a subcutaneous pocket (See Fig 2). The pump has its own battery power supply and can be programmed to deliver the drug in the reservoir at a specified rate. Programming the pump is performed by transcutaneous telemetry, enabling the whole system to be internal, reducing infection risk. If desired the patient can deliver boluses for breakthrough pain.

Following the British Pain Society Guidelines, all patients who are being considered for an IDDS should have a full multi-professional assessment of their underlying disease progression, analgesics, social and psychological wellbeing and alternatives available\textsuperscript{5,7}. This is procedure involving surgery that has incipient risks and significant financial costs so needs to be targeted at the correct individuals.
Drug Options

Drugs used in IDDS include: Opioids, Local Anaesthetics, Clonidine, Baclofen and Ziconotide. For drugs to be suitable, they need to be preservative free, stable at body temperature for prolonged periods, not precipitate or be significantly neurotoxic.

Opiates suitable for IDDS use include; morphine, hydromorphone and fentanyl. They act by binding to opioid receptors within the dorsal horn and are the first line agent for intrathecal drug therapy. Opioid sparing adjuncts include Local Anaesthetics and Clonidine. Local Anaesthetics block sodium channels in the dorsal horn and on nerve roots within the CSF. They are particularly useful for neuropathic pain. However as would be expected their use can result in sensory deficit and motor weakness. Clonidine is an $\alpha_2$ adrenoreceptor agonist leading to pre-synaptic hyperpolarisation and reduced neurotransmitter release.

Other intrathecal agents include Ziconotide, which is a drug derived from the cone snail $\omega$-conotoxin that blocks N-type calcium channels in the dorsal horn. It frequently leads to severe nausea, vomiting dizziness and ataxia so is analgesic used only when other intrathecal therapy has failed because of cost and its significant side effect profile. Baclofen is a $\text{GABA}_B$ agonist used purely for the management of spasticity often in the context of multiple sclerosis.
Problems With IDDS

Problems associated with IDDS can be divided into surgical insertion complications, which are usually self limiting, drug side effects, infection, catheter granuloma and pump failure. These are outlined in table 3.

Table 3: Risks associated with IDDS\textsuperscript{5,8}

<table>
<thead>
<tr>
<th>Type of risks</th>
<th>Examples</th>
</tr>
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<tbody>
<tr>
<td>Surgical risks of insertion</td>
<td>Bleeding</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
</tr>
<tr>
<td></td>
<td>Low Pressure Headache</td>
</tr>
<tr>
<td>Drug Effects</td>
<td>Nausea, Vomiting, Constipation, Respiratory Depression</td>
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<tr>
<td></td>
<td>Endocrine Dysfunction</td>
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<tr>
<td></td>
<td>Sensory &amp; Motor Deficits (Local Anaesthetics)</td>
</tr>
<tr>
<td>Infection</td>
<td>Pump Pocket Infection</td>
</tr>
<tr>
<td></td>
<td>Meningitis/ Epidural Abscess</td>
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<tr>
<td>Catheter Granuloma</td>
<td></td>
</tr>
<tr>
<td>Device Failure</td>
<td>Disconnection Hygroma, Catheter kinking, Pump Failure</td>
</tr>
</tbody>
</table>

Infections can either be localised to the pump or wound site or can be neuroaxial i.e. meningitis or encephalitis. The most common infective organism is \textit{Staphylococcus Aureus}. Incidence of wound site infection is estimated at 12%,
Meningitis is estimated at 2%⁹ Overall infection risk is approximately 0.7% per year and is increased in diabetic or immno-compromised patients¹⁰.

Catheter tip granulomas are seen in approximately 0.5% of IDDS patients. They are a non-infectious inflammatory mass at the catheter tip between the spinal cord and dura most commonly in the thoracic spine. They have are seen most commonly with high dose opiates and present with analgesic failure and new neurology secondary to cord or nerve root compression. The mechanism is unclear but may be due to morphine acting as a mitogen, via nitric oxide release or via μ-opioid receptor activation. It is not fully understood whether they are due to the total dose or the concentration of opiate¹¹. It is recommended to keep the concentration of morphine below 25mg/ml and the daily dose below 10mg, however 39% of granuloma occurred at a concentration <25mg/ml and 30% at a dose <10mg/day⁹.

Granulomas enhance on T₁ weighted gadolininium MRI scanning and often mandate surgical removal of the pump. To avoid them it is advisable to keep the dose and concentration of opiate to a minimum and to consider using opiate sparing adjuncts such as bupivacaine or clonidine. Using hydrophilic opiates such as morphine enable the catheter to be placed below the conus in the lumbar spine with less potential for cord compression if granulomas occur¹².
**Effectiveness**

There are few randomised controlled trials looking at IDDS and cancer pain. A systematic review in 2011 only identified 5 reports, only one of which was an RCT\textsuperscript{13} & \textsuperscript{14-18}. These all looked at morphine alone. They all found an improvement in VAS for neuropathic and non-neuropathic pain, and reduced toxicity compared to conventional medical management. They classified the evidence for IDDS for cancer pain as Level IIB. A randomised controlled trial by Smoth et al sound that not only did IDDS improve pain scores, it also prolonged patient survival\textsuperscript{15}.

**Cost Effectiveness**

IDDS has substantial costs associated due to the high initial pump and insertion costs (~10,000 $) and ongoing relatively low maintenance and refill costs. In comparison conventional medical management costs steadily increase with disease progression in cancer pain. A recent study on 36 cancer patients showed that cost neutrality was predicted in patients on high costs conventional regimes after 7 months\textsuperscript{19}. Factors associated with cost neutrality were high opiate use, parenteral regimes and non-generic drugs use. Other Research has shown cost neutrality for IDDS in cancer pain at 3-6 months and for non-cancer pain at >11-22 months\textsuperscript{20}. 
Conclusions

This case highlights the challenges of cancer pain management and the efficacy of IDDS in refractory cases. It also demonstrates the importance of good patient selection and psychological screening as if more thorough screening had been performed, invasive treatment may well have been deemed unsuitable in this patient.

IDDS have been shown to be effective in cancer pain, have less systemic side effects than conventional therapy and may even prolong survival. This must however be balanced against the significant costs associated and potential for adverse consequence including granulomata.

Clearly this is an exciting modality for the treatment of cancer pain but further research is clearly needed to define which patients would benefit most and what would be the ideal drug regime.
References


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