

## **Author Information**

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## **Case Information**

**Presenting Symptom:** Uncontrolled pain from metastatic breast cancer

**Case Specific Diagnosis:** Intrathecal drug delivery systems (IDDS) for cancer pain

### **Learning Objectives:**

- To present the World Health Organization (WHO) Pain Ladder
- To understand the indications for IDDS
- To understand the risks and complications associated with IDDS

### **History:**

The patient is a 66-year-old female with intractable pain secondary to metastatic breast cancer to the spine, lung, and liver. She has received palliative chemotherapy and radiation therapy, but the pain is unchanged. She reports the pain at rest is a 9 out of 10 and located in the middle of her back. Pain is worse with any kind of movement. She denies any numbness or tingling in her lower extremities. She has had a 35 pound weight loss over the past six months.

Initially, her pain was managed with Acetaminophen and Ibuprofen by her oncologist. Eventually she was transitioned to opioids when the non-opioid medications were not managing her pain. She had been on multiple opioids in the past and while higher doses managed her pain better, she felt drowsy and didn't like how she felt at those dosages. She was currently prescribed Morphine ER 15mg every 12 hours and Oxycodone 5mg every 4 hours as needed. She reports her current regimen "only helps a little bit and for not very long." The medication is also associated with significant constipation as well as transient sedation. She's here to discuss different pain control options to better manage her pain and limit any side effects.

### **Pertinent Physical Exam Findings:**

- Accompanied by husband and daughter
- Using wheelchair to get around
- Cachectic appearance
- Friendly demeanor, converses easily, positive outlook
- Diffuse tenderness to palpation throughout lower back
- Strength is 4/5 throughout BL UEs and LEs
- Sensation intact to light touch throughout BL UEs and LEs
- Reflexes 2+ throughout BLEs

### **Diagnostic Imaging and Results:**

- CMP: elevated liver enzymes, otherwise WNL
- CBC: H/H 9.3/28.2, otherwise WNL
- Coagulation panel: WNL
- Spine X-ray:
  - Multifocal lytic lesions throughout the thoracic spine concerning for metastatic disease.
  - No pathologic fractures seen.
- PET/CT:
  - Multiple lytic lesions noted throughout the thoracic spine. Likely metastatic disease.
  - No spinal stenosis or nerve root impingement seen.
  - As X-ray stated, no pathologic fractures identified.

### **Diagnosis:**

- Opioid tolerance
- Terminal breast cancer

### **Medications and Interventions:**

The patient was initially started on Acetaminophen and Ibuprofen. This eventually did not manage her pain and she was started on opioids. She has been on multiple opioids and opioid regimens in the past, but was currently prescribed Morphine ER 15mg every 12 hours and Oxycodone 5mg every 4 hours as needed. This regimen was helping her pain for short periods of time and the patient was seeking better options. Because the patient was not getting adequate pain relief but also could not tolerate higher dosages of medications, an IDDS was recommended.

### **Case Discussion**

- ***History***
  - The WHO Pain Ladder was developed in 1986 to guide the management of cancer pain (1). It is described as a “three-step ladder” of increasingly strong medications to appropriately treat pain. Cancer pain treatment starts with non-opioids, such as Ibuprofen and Acetaminophen (Step 1). If pain persists, a mild opioid (codeine) may be added (Step 2). Lastly, if adequate pain control is still not achieved,

the patient should be started on strong opioids (morphine) until the patient is pain-free (Step 3). Drugs should be dosed every 3-6 hours, rather than “as needed”. Adjuvants for anxiety and depression should also be considered.

- In 1994, the WHO ladder was modified to include the use of interventional options to improve pain control in those patients who follow the WHO ladder but continue to have severe pain or side effects that limit their ability to increase their dosages (2).
- IDDS was first introduced in the 1980’s. It is a method to deliver medications directly and continuously into the central nervous system. This allows smaller dosages of medications, which potentially improves pain control and reduces side effects. With technological advancement and the WHO recognizing the importance of interventional options for pain control in cancer patients, IDDS became much more popular in the 1990’s.
- **Evidence-based IDDS Use**
  - In 2002, Smith et al. performed a RCT comparing pain control in cancer patients using comprehensive medical management (CMM) versus IDDS and CMM (3). A total of 143 patients completed the study, 71 IDDS and 72 CMM patients. Inclusion criteria included uncontrolled pain ( $\geq 5$  on VAS) at two measurements despite 200 mg/d of oral morphine or an equivalent, or had side effects limiting their ability to increase their dosage. All patients had advanced cancer, severe pain, were 18+ years of age, had an expected life span  $\geq 3$  months, and were appropriate candidates for IDDS. Treatment success was defined as  $\geq 20\%$  reduction in VAS, or equal scores with  $\geq 20\%$  reduction in toxicity as measured by the Common Toxicity Criteria used by the National Cancer Institute. Patients were evaluated four weeks after treatment initiation. Overall, 60/71 IDDS patients (84.5%) achieved clinical success compared with 51/72 (70.8%) CMM patients ( $p=0.05$ ). The CMM VAS score decreased from 7.81 to 4.76 and the IDDS VAS decreased from 7.57 to 3.67 ( $p=0.055$ ). Just as importantly, the CMM toxicity scores fell from 6.36 to 5.27 while the IDDS scores decreased from 7.22 to 3.59 ( $p=0.004$ ). The IDDS group also had reductions in fatigue and drowsiness ( $p<0.05$ ), and had improved survival compared to the CMM group ( $p=0.06$ ).
  - A year later, Rauck et al. conducted a prospective multi-center study of 119 implanted IDDS patients (4). Pain relief, systemic opioid use reduction, and opioid-related complications reduction were analyzed. Clinical success was defined as  $\geq 50\%$  reduction in an 11-point Numeric Analog Score from the Brief Pain Inventory,  $\geq 50\%$  reduction in use of systemic opioids, or  $\geq 50\%$  reduction in opioid complication severity index. Patients were eligible for enrollment if they had a life expectancy of  $\geq 4$  months, were at least 18 years of age, were ineligible for tumor resection for pain control, and had no contraindications to IDDS. At 1 month, NAS decreased from 6.1 to 4.2 and this was

maintained at 7 months ( $p<0.01$ ) and 13 months ( $p<0.05$ ). Systemic opioid use decreased throughout the study ( $p<0.01$ ). At 13 months >70% of patients reported a >50% reduction in systemic opioid use and more than half of the patients reported no use of systemic opioids at all. Opioid-related complications were reduced at all time points ( $p<0.01$ ). Impressively, 83%, 90%, 85%, and 91% of patients experienced a 50% or greater reduction on at least 1 of the 3 outcome measures from months 1, 2, 3, and 4, respectively.

- Recently, a 2018 retrospective study by Sayed et al. reviewed the results of 160 IDDS patients from a single large academic institution (5). Metastatic disease was documented in 93% of patients. The most common type of cancer was pancreatic (20%). Pain was assessed with the 10-point VAS. The median pain decreased from 7.1 at baseline to 5.0 one month after implantation and these results were maintained at three months. Patients with an average pain score >6 experienced a greater reduction in pain scores following IDDS implantation. Five patients (3.1%) had their pumps explanted due to infection.
- The Polyanalgesic Consensus Conference (PACC) using USPSTF criteria reported there is Level I-A evidence for the use of intrathecal therapy in active cancer-related pain using both opioids and ziconotide (6).
- **Indications**
  - There are no definite indications for IDDS. In general, patients experiencing significant side effects that limit appropriate medication titration or those patients who do not achieve adequate pain control despite high dose opioids should be considered for IDDS.
- **Patient Selection**
  - Multiple factors beyond inadequate pain control and side effects need to be considered before IDDS implantation. These include patient's previous treatment adherence, reliable follow-up, disease state and prognosis, psychological state, and ability to undergo a surgical procedure. IDDS is contraindicated in these situations: unwilling to have pump refilled, coagulopathy or presence of therapeutic anticoagulation, hemodynamically unstable, cerebrospinal fluid outflow obstruction, intracranial hypertension, sepsis, infection at site of catheter or pump insertion, and severe wasting preventing device implantation (2).
  - However, the PACC recommends that cancer patients with imminent death or a relatively short life expectancy do not need a thorough psychological screen because palliative care is the goal of IDDS therapy in these cases (6).

#### **Treatment recommendations for this case:**

A conversation with the patient's oncologist revealed a poor prognosis and an estimated life expectancy between 6-12 months. After a thorough discussion of the

risks and benefits of IDDS along with the patient not having any contraindications to IDDS implantation, a single shot intrathecal injection of fentanyl was performed to test her response to intrathecal opioids. She reported significantly better pain control following the injection. An operative day was scheduled and the patient received implantation of an IDDS without any issues. She was started on a morphine infusion and with appropriate titration over the course of a month she was feeling significantly better pain control and had an improved quality of life. A patient controlled bolus was added to her settings after her daily dose was stabilized for breakthrough pain. She no longer required oral opioids.

**Discussion**

- The complications after IDDS implantation include: dislocation of the catheter from the pump or intrathecal space, catheter breakage, pump failure, medication errors with pump refill, bleeding, infections (superficial and deep), post-dural puncture headaches, and catheter granuloma (2).
- ***Anticoagulation Recommendations***
  - The PACC has issued specific time period recommendations for the discontinuation of anticoagulation medications (6). See Table 1 below.

Table 1. PACC Anticoagulation Discontinuation and Restart Recommendations for Trials and Permanent Implants

<b><u>Medication</u></b>	<b><u>Discontinue</u></b> (time prior to procedure)	<b><u>Restart</u></b> (after trial or implant)
Warfarin	5-7 days, INR <1.5	24 hours
LMWH (therapeutic)	24 hours	24 hours
Clopidogrel	High risk at least 5 days, Low risk 7-10 days	24 hours
Ticlopidine	14 days	24 hours
GPIIb/IIIa inhibitors	3 days	24 hours
Dipyridamole	7 days	24 hours
NSAIDs	7 days	24 hours
Aspirin	7 days	24 hours
Herbals	7 days	24 hours
Direct thrombin inhibitors	5 days	24 hours
Heparin IV	Case-by-case basis	Case-by-case basis
Heparin SQ	Case-by-case basis	Case-by-case basis

- ***Infection Prevention and Management***
  - Infection rates for IDDS have ranged from 2-8% in several large-scale studies (7).
  - In 2016 Neurostimulation Appropriateness Consensus Committee (NACC) released recommendations for infection prevention and management during IDDS (8). They recommend:

- Patient Factors: diabetes control, smoking cessation, limit perioperative steroids, treatment of ongoing infections (i.e. dental, urinary, etc.), preoperative *S. aureus* testing
- Surgical Factors: preoperative hair removal, procedural antibiotics (Cefazolin as first line, Clindamycin if beta-lactam allergy, Vancomycin if known MRSA colonization), surgeon preoperative surgical scrub, chlorhexadine-based skin preparation, maximum sterile precautions, surgeon double gloving, careful tissue handling, incision irrigation with bulb syringe and normal saline, thoughtful wound closure
- Postoperative Factors: use of sterile occlusive dressings for 24-48 hours, patient and family education on signs/symptoms of SSI, if infection suspected obtain neuraxial imaging
- ***Intrathecal Granuloma Formation and Treatment***
  - The risk of catheter-tip granuloma formation is increased with longer duration and higher concentration of intrathecal opioid therapy (9). Morphine and hydromorphone are the cause in most cases. Granulomas may occur in 3% of cases, but most are asymptomatic and go unrecognized (10).
  - When suspected, intrathecal opioids should be discontinued. If neurological symptoms are present, a neurosurgery consult should be placed and neuraxial imaging obtained. Replacement of intrathecal opioids with preservative-free saline will often lead to resolution of the granuloma and this treatment can be initiated if surgery is not indicated. The typical presenting symptom of granuloma formation is increased pain despite increasing opiate infusion. Thus, vigilant clinical suspicion and evaluation are paramount to diagnosis (10).
  - Recommendations for max concentrations and doses can be found below in Table 2 (6).

Table 2. PACC Maximum Concentrations and Daily Doses of IT Medications

<b><u>Drug</u></b>	<b><u>Max Concentration</u></b>	<b><u>Max Dose per Day</u></b>
Morphine	20 mg/ml	15 mg
Hydromorphone	15 mg/ml	10 mg
Fentanyl	10 mg/ml	1000 mcg
Sufentanil	5 mg/ml	500 mcg
Bupivacaine	30 mg/ml	15-20 mg
Clonidine	1000 mcg/ml	600 mcg
Ziconotide	100 mcg/ml	19.2 mcg

**Take Home Points:**

- The WHO Pain Ladder follows a step-wise approach to pain management in cancer patients by first using non-opioid medications, before initiating weak opioids and finally stronger opioids. Recognizing the need for more options

in these patients, the pain ladder was expanded to include interventional modalities.

- IDDS is a powerful pain control option with Level I-A evidence for patients with inadequately controlled cancer pain. IDDS should be considered for any cancer patient experiencing significant side effects that limit appropriate medication titration or those patients who do not achieve adequate pain control despite high dose opioids.
- There are strict contraindications to IDDS use and these guidelines must be followed. Patients must be appropriately screened and their past medical history reviewed before IDDS is recommended.
- Evidence-based guidelines regarding anticoagulation handling, infection prevention, and complication reduction have been created and should be strictly followed. These recommendations set the framework for a successful treatment plan for the patient.

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