

CLINICAL VIGNETTE

Complicated Pain Control Requiring Palliative Sedation in Metastatic Gastric Cancer

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Introduction

Cancer-related pain can be difficult to manage, especially during end of life care. We describe a case of intractable cancer pain despite escalating pain regimen including intravenous hydromorphone, intrathecal hydromorphone, continuous ketamine and lidocaine infusions, and topical fentanyl and lidocaine. We report this unusual case that ultimately required palliative sedation at the end of life.

Case Report

A 50-year-old man with history of metachronous recurrent gastric cancer presented with gastrointestinal obstruction and chronic pain. His cancer was initially treated with adjuvant chemotherapy and partial gastrectomy 15 years prior. He later developed unresectable esophagogastric stricturing and underwent palliative gastrojejunostomy and enteroenterostomy, followed by chemotherapy with appropriate response. His home pain regimen consisted of transdermal fentanyl 50mcg/hr every 3 days and oral immediate release oxycodone 20mg 2-3 times per day. He had no history of substance abuse and was doing well for the next 3 months before developing dysphagia, nausea, and vomiting. Upon admission, palliative care was consulted for nausea management with recommendations for scheduled prochlorperazine, ondansetron, and prn lorazepam and promethazine. Endoscopy revealed angulation of the gastrojejunostomy without specific blockage. A stent was placed to correct this angulation but it avulsed, complicated by esophageal perforation. After endoscopic correction, the patient was discharged home on TPN and continued NPO. His pain was controlled with hydromorphone patient-controlled analgesia (PCA), fentanyl patch 75 mcg/hr, and rectal acetaminophen 650mg every 6 hours as needed.

Several days later he developed worsening nausea and jaundice with high-volume ascites and was re-admitted. This was managed with therapeutic paracentesis, which revealed only atypical cells. CT of abdomen and pelvis showed dilation of the intrahepatic and extrahepatic bile ducts with a nondraining pancreatic biliary limb. He underwent exploratory laparotomy, which confirmed extensive carcinomatosis, with lysis of adhesions, placement of peritoneal drainage catheter, and

placement of enteric tube for decompression and feeding. He tolerated the surgery well and his post-operative severe lower abdominal pain and moderate, intermittent, epigastric pain were initially managed with PCA using hydromorphone (1mg/hr infusion, 1mg bolus, every 10 minute interval, maximum 6 times per hour). His oral morphine milligram equivalent (MME) requirement was approximately 830mg.

Over the next 3 weeks, his abdominal pain increased despite escalating opioid dosing which caused severe fatigue and hypoactive delirium. His pain medications increased: fentanyl patch 125 mcg/hr and hydromorphone PCA to 1.5mg/hr infusion, with 2mg bolus, every 10 minutes. On post-operative day 20, he was started on an intrathecal pump with hydromorphone at rate of 0.3 mg/day to improve pain control and decrease the lethargy from the PCA. He continued to complain of pain at the lumbar incision and right shoulder over subsequent days despite increasing the fentanyl patch to 150 mcg/hr, plus lidocaine patches to either shoulder 12 hours on and 12 hours off. His pain persisted post-operative day 23, after starting continuous ketamine infusion at 0.15 mg/kg/hr. By postoperative day 26, the intractable pain persisted despite multiple agents with MME approximately 1,040 mg. Following discussion with the patient and his family, he no longer wished to pursue chemotherapy for his gastric cancer, and goals were clearly identified for comfort at the end of life. He was therefore admitted to inpatient hospice for aggressive management of his severe pain and delirium.

The ketamine infusion was uptitrated over 3 days to 0.27 mg/kg/hr and lidocaine infusion was started at 1 mg/kg/hr. His fatigue and hypoactive delirium continued, with improved abdominal pain control, but persistent, severe, bilateral, referred shoulder pain and intermittent agitation due to the pain. As he became more delirious and unable to use his PCA at the end of life, the hydromorphone was switched to intravenous administration by the nurse as needed for pain. The dose was increased to 4mg and the fentanyl patch was increased to 300 mcg/hr to replace hydromorphone PCA infusion as he was switched to nurse administration. Sublingual methadone 10 mg every 12 hours was tried in an attempt to wean off ketamine and lidocaine infusions so he could return home. The methadone

was stopped 2 days later when patient became more agitated and continued to require same high doses of opioids. Although the patient was sleepy most of the day, anytime he awakened, he complained of pain, and used his PCA to fall back asleep. Pain remained intractable in the setting of mixed terminal delirium which includes hyperactive and hypoactive delirium, without preserved meaningful interaction. After discussion with his health care proxy, he was started on Palliative Sedation (PS) for symptom control at the end of life. Midazolam was started at 2mg/hr and titrated to 5mg/hr over one day with PS achieved. Patient thereafter appeared more comfortable with MME of approximately 940mg, allowing for the ketamine infusion rate to be lowered. He remained comfortable until he died 4 days later. His wife expressed contentment with the end of life process for her husband.

Discussion

Uncontrolled cancer pain is a multidimensional syndrome involving nociceptive and neuropathic pain, and associated with depression, insomnia, and decreased quality of life.^{1,2} In palliative care, patients with debilitating illnesses often identify a priority to maintain their quality of life through aggressive management of pain and other symptoms.

A refractory symptom is one that is defined as a “symptom for which all possible treatment has failed, or that no methods are available for palliation within the time frame and the risk:benefit ratio that the patient can tolerate.”³ The most common refractory symptoms in end of life care are delirium and dyspnea, followed by pain, nausea, and emesis.⁴

In this patient with cancer at the end of life with prognosis of days to weeks, who has expressed desire for aggressive control of symptoms, pain remained uncontrolled despite multiple modalities. He ultimately chose to weigh pain control over alertness and consciousness at the end of life. With the patient comfort request, expressed earlier in the hospital course and with the verbalized concurrence of the patient’s proxy healthcare decision maker, we ultimately pursued Palliative Sedation (PS) to manage his refractory pain complicated by mixed delirium.

In the context of palliative care, PS involves the intentional use of sedative medications to adequately control one or more refractory symptoms in patients at the end of life by reducing their level of consciousness.³ The three types of sedation include ordinary sedation, proportionate PS, and PS to unconsciousness. Specialists concur on the definition of PS including that of PS to unconsciousness. Most providers do not consider ordinary sedation to be PS, and there is not agreement on whether proportionate sedation is always PS. Ordinary sedation in palliative medicine is meant to control anxiety, restlessness, and other nonphysical symptoms without reducing consciousness. Proportionate PS aims to manage unbearable physical symptoms that are inadequately controlled by all other possible interventions. The dose is titrated up until symptom relief is achieved. This can be distinguished from PS to

unconsciousness when the dose is rapidly uptitrated until patient is completely unconscious.

Coordinating with medical providers, including but not limited to physicians, nurses, and care partners about the intent of PS is essential. This includes addressing any concerns and providing time for discussion before initiating PS. Of note, PS’s goal is to achieve a level of sedation that precludes patients from verbally communicate with their families.

The most common medication used for PS in the setting of palliative care is midazolam, a benzodiazepine, given its rapid onset of action and short half-life. This is appropriate for the first phase of sedation which requires careful titration.⁵ If ineffective, the next agent used is generally a barbiturate, such as phenobarbital. Less widely used drugs for PS include haloperidol, levomepromazine, chlorpromazine, ketamine, propofol, and dronabinol. Importantly, although opioids are first line agents for severe pain and should be continued with PS, opioids should not be used for the secondary effect of somnolence to achieve sedation.⁵

Guidelines for PS recommend close monitoring of patient symptoms, level of consciousness, and potential adverse effects of sedation while titrating dose. Although monitoring sedation is well-established (eg, Richmond Agitation-Sedation Scale), assessing symptom relief in unconscious patients can be difficult. Tools evaluating verbal or facial expression, body movements, and response to nonpainful stimuli may be valuable (eg, Critical-Care Pain Observation Tool, Pain Assessment in Advanced Dementia scale). Monitoring level of consciousness can be a substitute for evaluating symptoms.^{5,6}

Conclusion

Health care professionals should integrate the values, goals, and wishes of the patient when considering options that would best meet their needs at any stage of illness. PS does not hasten death although it reduces the likelihood of patients being able to verbally communicate with others. For the appropriate patient, we urge clinicians to consider PS to manage refractory symptoms that are causing unbearable distress at the end of life when all other options have been thoroughly considered and exhausted. We recommend a palliative care specialist be involved in all cases of PS to unconsciousness to assure best symptom control and provide support to the family and medical care team.

REFERENCES

1. **Pachman DR, Barton DL, Swetz KM, Loprinzi CL.** Troublesome symptoms in cancer survivors: fatigue, insomnia, neuropathy, and pain. *J Clin Oncol.* 2012 Oct 20;30(30):3687-96. doi: 10.1200/JCO.2012.41.7238. Epub 2012 Sep 24. Review. PubMed PMID: 23008320.
2. **Fürst P, Lundström S, Klepstad P, Runesdotter S, Strang P.** Improved Pain Control in Terminally Ill Cancer Patients by Introducing Low-Dose Oral Methadone in

Addition to Ongoing Opioid Treatment. *J Palliat Med.* 2017 Aug 9. doi: 10.1089/jpm.2017.0157. [Epub ahead of print] PubMed PMID: 28792784.

3. **Cherny NI, Radbruch L; Board of the European Association for Palliative Care.** European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. *Palliat Med.* 2009 Oct;23(7):581-93. doi: 10.1177/0269216309107024. PubMed PMID: 19858355.
4. **Maltoni M, Scarpi E, Rosati M, Derni S, Fabbri L, Martini F, Amadori D, Nanni O.** Palliative sedation in end-of-life care and survival: a systematic review. *J Clin Oncol.* 2012 Apr 20;30(12):1378-83. doi: 10.1200/JCO.2011.37.3795. Epub 2012 Mar 12. Review. Erratum in: *J Clin Oncol.* 2012 Sep 20;30(27):3429. PubMed PMID:22412129.
5. **Schildmann EK, Schildmann J, Kiesewetter I.** Medication and monitoring in palliative sedation therapy: a systematic review and quality assessment of published guidelines. *J Pain Symptom Manage.* 2015 Apr;49(4):734-46. doi: 10.1016/j.jpainsymman.2014.08.013. Epub 2014 Sep 19. Review. PubMed PMID: 25242022.
6. **Gurschick L, Mayer DK, Hanson LC.** Palliative Sedation: An Analysis of International Guidelines and Position Statements. *Am J Hosp Palliat Care.* 2015 Sep;32(6):660-71. doi: 10.1177/1049909114533002. Epub 2014 May 7. Review. PubMed PMID: 24807825.

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