Published in final edited form as:

Pediatr Blood Cancer. 2015 July ; 62(7): 1237–1244. doi:10.1002/pbc.25493.

Patient-Controlled Analgesia at the End of Life at a Pediatric Oncology Institution

Doralina L. Anghelescu, MD [Member],

Pediatric Medicine, Division of Anesthesiology; Director, Pain Management Service, St. Jude Children's Research Hospital

Jennifer M. Snaman, MD [Clinical Fellow],

Department of Oncology, St. Jude Children's Research Hospital

Luis Trujillo, MD [Assistant Member],

Pediatric Medicine, Division of Anesthesiology, St. Jude Children's Research Hospital

April D. Sykes, MPH [Biostatistician],

Department of Biostatistics, St. Jude Children's Research Hospital

Y Yuan, PhD [Assistant Member], and

Department of Biostatistics, St. Jude Children's Research Hospital

Justin N. Baker, MD [Associate Member]

Department of Oncology, St. Jude Children's Research Hospital

Abstract

Background—Patient controlled anesthesia (PCA) is increasingly used to manage pain in pediatric cancer patients and is important in the treatment of escalating pain at the end of life. The description of the use of opioid PCA in this population has been limited.

Procedure—This retrospective chart review of the last 2 weeks of life addressed the following objectives: 1) to describe the patient population treated with opioid PCA; 2) to describe the morphine-equivalent doses (MED) (mg/kg/day); and 3) to describe the pain scores (PS).

Results—Twenty-eight percent of inpatients used opioid PCA for pain control during the last 2 weeks of life. The mean MED (mg/kg/day) (SD) at 2 weeks prior and the day of death were 10.7 (17.9) and 19 (25.8). The mean MED increased over the last 2 weeks of life for all patients and across age groups and cancer diagnoses (all $p < 0.05$). The mean MED was significantly higher in the younger age group (age < 13 vs. age ≥ 13) on the day of death ($p < 0.04$). There was a significant change in mean PS over the last 2 weeks of life ($p < 0.001$), with the highest PS on the day before death. The most frequently used concurrent medications were benzodiazepines (91%).

Conclusions—Children and young adults with cancer experience high opioid requirements and significant dose increases during the last 2 weeks of life. Additionally PS increase toward the end

of life. Opioid rotation and addition of adjuvant medications merit consideration in the context of escalating opioid requirements.

Keywords

Opioid analgesics; Pediatric pain control; Pain control

Introduction

Pain is the most prevalent symptom in children with cancer at the end of life, reported in 76% of children, and appreciated as producing “a great deal” or “a lot” of suffering in 66% of cases.[1] The proportion of patients with progressive malignant disease reporting pain increases at the end of life increased from 70.6% at the time of palliative care consultation to 91.5% in the last month of life.[2] Of the patients who were treated for symptoms at the end of life, treatment of pain was successful in only 27% of cases [1] and the proportion of children who experience pain at the end of life has remained unchanged over the past 2 decades. However, in children dying of cancer, the proportion who suffered “a great deal” or “a lot” decreased from 66% to 47% over the eras of 1990-1997 and 1997-2004.[3]

Patient-controlled analgesia (PCA) is reported to be safe and efficacious in children with moderate to severe pain from surgery [4-6], burns [7], mucositis [8,9], bone marrow transplantation [10], sickle cell disease [11,12], and cancer [13-15]. Opioid use at the end of life in children, including those with cancer, has previously been characterized [16-23] and some of these series have described continuous opioid infusion.[16-18,20,21] PCA allows rapid opioid titration and improved pain control for children with difficult to manage pain at the end of life. Despite the importance of PCA in management of pain at the end of life, the description of the use of PCA in this setting has been limited.[23]

The aims of this review were: 1) to describe the patient population treated with opioid PCA over the last 2 weeks of life; 2) to describe the morphine-equivalent doses (MED) (mg/kg/day) over the last 2 weeks of life; and 3) to describe the pain scores (PS) over the same time frame.

Methods

St. Jude Children's Research Hospital (St. Jude) specializes in treating catastrophic childhood diseases. The St. Jude Institutional Review Board approved this study and waived consent. We retrospectively reviewed the use of opioid PCA during the last 2 weeks of life in patients treated at our pediatric oncology institution, including all patients that used opioid PCAs at any point during their last 2 weeks of life (or longer). Patients who were intubated and mechanically ventilated were excluded, since they were not controlling the use of PCA. The day of death is noted as “day 1”; “day 14”, “day 7” and “day 2” are defined as 2 weeks, and 1 week before death, and the day before death, respectively. We collected the following data from the medical records of all inpatients who used PCA during their last 2 weeks of life between February 2004 and January 2011: demographics (age, sex, and weight), cancer diagnosis, daily PS, daily PCA settings, morphine equivalent doses (MED) (mg/kg/day), opioid medications used (including opioid rotations), concurrent medications,

location within the hospital (ward or ICU), and complications associated with opioid use including naloxone use or mechanical ventilation. Patients were divided into age groups based on the age-specific pain assessment tools (age <4 years, 5-7, and >7 years) and the standard definition of adolescent and young adult patients (AYA) (<13 years). Data were collected for each day that the PCA modality was used.

The initial PCA settings and subsequent changes over time included the selection of a continuous infusion and boost dose, based on the institutional guidelines and tailored to individual patient medical status. The standard starting doses of opioid bolus, which are available on the hospital's intranet site, are: morphine, 0.02 mg/kg; hydromorphone, 0.004 mg/kg; and fentanyl, 0.5 mcg/kg, with a 15-minute lockout interval for all three. When a background infusion is indicated, the recommended starting hourly dose is equivalent to the bolus dose. Any physician or advanced practice nurse can order a PCA without consultation from our institution's pain service.

Pain assessment

Pain intensity scores were assessed and documented as per institutional clinical standards and were retrospectively collected and reported as daily maximum, minimum, and mean scores. Assessments were made using age-appropriate tools: Faces-Legs-Activity-Consolability-Cry (FLACC), for children <4 years [24], the Wong-Baker FACES scale for children 4-7 years [25], and the numerical pain scale [26] for children >7 years old. Per institutional policy, pain was assessed and documented at least every 4 hours on the ward or 2 hours in the ICU and 1 hour after any intervention to address pain.

Patient-Controlled Analgesia

Opioid doses were converted to morphine equivalent doses (MED) (mg/kg/day) on the basis of opioid equianalgesic potency, using the following potency relationships: 100:1 for fentanyl:morphine, 5:1 for hydromorphone:morphine, and 1000:1 for sufentanil:morphine. The dose data for the day of death was standardized by multiplying the mean intravenous MED per hour by 24. The choice of opioid by PCA was based on clinical judgment. The PCA-related data was collected beginning with day 14 for patients previously on a PCA or from the time of PCA initiation if duration was shorter than 14 days, and included opioid type, the 24-hour total dose, and the mean dose per hour.

Statistical Analysis

Descriptive statistics (number and percentage, mean and standard deviation, or median and range) were calculated for patient demographic and clinical characteristics. The mean MED between age groups (<13 and ≥13 years) and between diagnosis groups (leukemia/lymphoma and solid tumor/brain tumor) were compared at days 14, 7, 2 and 1, by using the Wilcoxon rank sum test.

The mixed effects linear model for repeated measures was used to assess the change in MED and PS over the last 2 weeks (days 14 to 1) and last week of life (days 7 to 1) for all patients. The mixed effects linear model was also used to assess the change in MED over the last 2 weeks of life within age and diagnosis groups. Time (days 14 to 1 or days 7 to 1) was

included in the model to assess the change. The unstructured correlation structure was selected to account for the correlation among repeated measurements made on the same patient for all models. One patient had unusually high MED and PS values and was considered an outlier in the data. Thus, a sensitivity analysis was conducted for all objectives that excluded the patient outlier. All analyses were conducted using SAS 9.3 software (SAS Institute, Cary, NC). All statistical comparisons were 2-sided; a P value <0.05 indicated a significant difference.

Results

Patients

Forty-four of 159 (28%) inpatients used opioid PCA during the study time frame. Patient demographics and clinical characteristics are summarized in Table I. The median age at time of death was 14.7 years (range 1.2 to 24). Sixty-four percent of patients were in the AYA group. Thirteen patients older than 18 years of age are included in this report, as our pediatric oncology institution provides care beyond the strictly defined pediatric age. The majority of patients had diagnoses of leukemia or lymphoma (59%) and 41% of had diagnoses of solid tumor or brain tumor. Sixty-one percent of patients were receiving treatment on the ward 2 weeks prior to death; the remaining 39% were located in the ICU. The opioids used at 2 weeks prior to death were fentanyl (32%), morphine (32%), and hydromorphone (30%). One-fifth (23%) of patients had opioid rotations in the last 2 weeks of life. The median duration of PCA use before death was 31 days (range 3 to 172) (Table I).

One patient required massive opioid doses at the end of life and was considered an outlier in the dataset; therefore his data was excluded from further analyses. This patient was a 9 year-old African American boy with spleen angiosarcoma with multiple liver and bony metastases unresponsive to chemotherapy and radiotherapy [27].

Morphine-Equivalent Dose

Twenty-seven of 43 (63%) patients included in the analysis used PCA for at least the last 2 weeks of life, 38 (88%) for the last 7 days, and 43 (100%) for the last 3 days of life (Table II).

The mean MED (mg/kg/day) (SD) for the entire group were 10.7 (17.9) and 19 (25.8) at day 14 and day 1, respectively. The mean MED (SD) in young patients (<13 years) at day 14 and day 1 were 12.8 (24.3) and 27.4 (31.5), respectively, and 9.5 (13.6) and 14.5 (21.5) in AYA patients. The MED was significantly higher in the younger patient group on the day of death ($p=0.040$), while the difference between age groups was not significant at either day 14, 7, or the day before death (Table II).

The average MED (mg/kg/day) (SD) for patients with a diagnosis of solid tumor was 9.5 (14) on day 14 and 17.9 (16.1) on day 1. For patients with a diagnosis of leukemia/lymphoma, the mean MED (SD) at these time points was 11.5 (20.2) and 19.7 (30.9). There was no significant difference in average MED by tumor diagnosis at the time points of day 14, 7, and day 1 (Table II).

Pain Scores

Pain scores are described in 25 of 43 patients for whom data were available (Figure 1). The highest mean (SD) PS was recorded on the day before death (day 2) and was 6.7 (2.3), as compared to 4.6 (3.3) on the day of death.

Changes in Morphine-Equivalent Doses over Time

Using a linear mixed model, there was a significant increase in the MED during the last 2 weeks of life ($p<0.001$, Table III). The increase in MED over this time period was consistent by age group (age <13 , $p=0.027$ and age ≥ 13 , $p=0.004$) and between tumor types (leukemia/lymphoma, $p=0.01$ and solid tumor, $p<0.001$). The increase in MED for the entire group over the last week of life demonstrated a trend toward significance ($p=0.149$, Table III).

Changes in Pain Scores over Time

There was a significant increase in the mean PS during the last 2 weeks of life ($p<0.001$); however, the change was not found to be significant over the last week of life ($p=0.418$, Table III).

Concurrent Medications and Complications

Benzodiazepines were the most frequently used class of medications concurrently with the opioid PCA. Thirty-nine of 43 patients (91%) received a benzodiazepine at some point during the last 2 weeks of life, and 12 of 43 (28%) received benzodiazepines every day. The number of patients receiving benzodiazepines increased toward the end of life, from 35% of patients on day 14 to 77% on day 1.

Haloperidol was administered to 2 patients during the last several days of life. Gabapentin was prescribed to 13 of 43 patients (30%) at some point during the last 2 weeks of life, and for 7 patients gabapentin was initiated during the last week of life. Four patients were treated with methadone during the last 2 weeks of life and 3 of them started methadone during the last week of life. Two patients received low-dose ketamine infusions for analgesia for 4 and 5 days, respectively; these infusions were discontinued prior to the last week of life. No patients in this analysis required palliative sedation with propofol. There were no documented complications (respiratory depression or apnea) that required naloxone administration or mechanical ventilation.

Discussion

This study analyzes both pain intensity scores and opioid PCA dose requirements in children with cancer at the end of life and presents the changes in these measurements over the 2 weeks preceding death; this is the largest study to date of a group of pediatric cancer patients receiving parenteral opioids by PCA at the end of life. The major findings of this study are a significant increase in the mean opioid MED over the last 2 weeks of life. Additionally we report the highest mean MED (mg/kg/day), specifically 10.7 on day 14 and 19.0 on day 1, as compared with the MEDs previously reported in children at the end of life, including those with cancer [16,17,19,21-23] (Table IV). Pain intensity scores increase over the last two weeks of life, with the highest PS recorded on the day prior to the last day of life.

Most of the previous pediatric studies have been retrospective case series; some studied children who died in hospital and others in hospice; some analyzed cancer patients while others included varied diagnoses. Comparisons are difficult due to variable measures of intravenous opioid doses (mean vs. median vs. maximum MED, daily vs. hourly doses, doses corrected for body weight or not) (Table IV).

The only report on the use of opioid PCA at the end of life in pediatric cancer described opioid use in 8 children during the last week of life. The reported median MED (mg/kg/day) on the last day of life was 2.21 (range, 0.32-18.76) [23], which is markedly lower than the median MED in our study group of 9.7 (0.1-116.9) on the last day of life. Sirkiä et al. described treatment with parenteral morphine at the end of life in 40 of 70 children who died of cancer. In the 30 children who received morphine continuous intravenous infusions, the “standard dosage” was 0.85-4.9 mg/kg/day [21] (Table IV).

Although mean dose values are generally comparable across studies, individual dose requirements at the end of life are highly variable.[28] This finding is consistently reflected in the large ranges of MED reported, including our findings.

The higher MED values in our study compared to other pediatric studies (except two reports by Collins et al. [18,20] which described cases with “massive opioid infusions” defined as >3 mg/kg per hour of intravenous morphine dose equivalent, or 100-fold greater than standard starting infusion rates) may reflect the requirement to escalate dose over time given the development of tolerance, as 50% of patients in our study had been on opioid PCA for 30 days or more at the time of death. Additionally, a large majority of patients at our institution are pretreated and present with recurrent or refractory disease. These patients are rarely opioid naive and/or have significant disease burden, necessitating earlier initiation of opioid infusion or higher doses for adequate treatment of disease related pain.

Unlike Collins et al. [18] who found an overrepresentation of patients with solid tumors in a subgroup of patients requiring massive opioid infusions at the end of life, we did not find a significant difference in the average MED requirement between tumor types. The average MED increased similarly between these groups during the last 2 weeks of life.

No previous study has evaluated the opioid requirement during the last 2 weeks of life in AYA patients compared to younger patients. We found a significant difference in the mean MED by age only on the last day of life, with patients younger than 13 years requiring higher doses of opioids. One could speculate that the increase in MED during the last day of life in younger patients may reflect differences in the pathophysiology of pain in this patient population, related to oncology diagnosis or drug metabolism. However, our study did not find any significant difference in the MED between oncology diagnoses, suggesting that this is not an important factor driving the difference in MED between age groups. Any differences in drug metabolism should have been seen as a consistent higher MED in younger patients over time, not just on the last day of life. We propose that the increased opioid consumption in younger patients on the last day of life may be a reflection of the increased perception of pain by caregivers (parents and the medical team) in the context of

imminent death – this perception would drive an increased delivery of opioid PCA, either as proxy or by encouraging PCA self-boosting.

Despite the high MED in our patients and the high percentage of patients with concomitant use of other sedating medications such as benzodiazepines, we found no complications (respiratory depression or apnea) that required naloxone or assisted ventilation. Fears of side effects such as respiratory depression and hastening death may prevent aggressive titration of opioids or addition of other medications for symptom management which may have concurrent respiratory and/or sedating effects.[29] Therefore, it is important to highlight the dual findings of the high opioid MED needed to control pain at the end of life and concurrent use of benzodiazepines, and the lack of respiratory complications in our study.

Only one other study has reported pain intensity in conjunction with opioid requirements [23] (Table IV). The pain scoring instruments differed between that study and ours, making comparison of analgesic efficacy difficult. Although the MED increased over time in our study, the PS also increased during the last 2 weeks of life, with the highest PS on the day prior to death. The increasing MED values may be partially due to progressive disease and development of tolerance to opioids. However, the increase in PS during the last 2 weeks of life indicates that patients at the end of life may need more aggressive titration of pain medications. Additionally, the increasing pain at the end of life despite ongoing opioid titration highlights the role of treatment strategies such as opioid rotation and addition of adjuvant medications, especially NMDA receptor antagonists. The decrease in PS on the day of death as compared to the previous day may indicate that the rapid titration of the opioid PCA at the end of life and use of appropriate adjuvant medications is effective in controlling pain in these patients. However, it is more likely that this is a reflection of increased somnolence and decreased alertness associated with the dying process.

We found that benzodiazepines were used in a large percentage of pediatric patients with cancer with increasing use toward the end of life. The high proportion of patients receiving benzodiazepines in the last 2 weeks of life is suggestive of their use for various clinical indications. Lorazepam is commonly used to control nausea and vomiting in patients with cancer. Additionally, in patients on high opioid infusions, benzodiazepines may be used to manage dyspnea, especially in patients with anxiety – a common symptom at the end of life. [30]

Patients who continue to have intractable distress despite maximal titration of opioids and benzodiazepines for symptom control at the end of life may require palliative sedation. [27,30]

The use of gabapentin, methadone, and ketamine in our study may be suggestive of a neuropathic component of pain in pediatric cancer patients at the end of life; nevertheless, the design of this study did not aim to provide evidence to support this association. Collins et al. identified tumor spread to nerves or spinal cord compression as causes of massive opioid requirements at the end of life due to difficult to control pain.[18] Authors who examined the prevalence of neuropathic pain in a systematic review of 22 studies in adult and teenage patients with cancer indicated that 40% of patients may be affected by

neuropathic pain, either as pure neuropathic pain or as mixed nociceptive neuropathic pain. [31] However, the escalation of pain medications does not necessarily provide evidence for the presence of a neuropathic pain component at the end of life. One must carefully consider the potential contributing factors to escalation of analgesia requirements at the end of life, including neuropathic pain [18,32], increasing source of nociceptive pain, unrecognized opioid hyperalgesia, and “pain from suffering”. [33,34] Patients with a neuropathic pain component may benefit from early addition of adjuvant medications specific for neuropathic pain to improve pain control and/or reduce opioid consumption. The use of opioids remains appropriate for uncontrolled neuropathic pain at the end of life, based on a shorter time to effect and faster up-titration than medications specific for neuropathic pain, such as gabapentinoids and tricyclic antidepressants. Despite the known long time to effect of gabapentinoids for neuropathic pain, their addition for seven patients in the last week of life may reflect a “kitchen sink” approach to treatment of severe pain at the end of life, with additions of multiple medications in the face of intractable symptoms. However, if patients in the terminal phase can be adequately identified, improved selection of adjuvant medications to include ketamine or methadone would be beneficial based on their efficacy in treating neuropathic pain through NMDA receptor antagonism effect which may augment the opioid effect at the mu receptor and allow for improved pain control with lower opioid use. [35,36]

This study of patients treated at a single pediatric oncology center may not be generalizable to all pediatric oncology patients due to specific institutional approaches to end-of-life care in the inpatient versus the hospice and home care settings as well as the fact that a large majority of patients at our institution are pretreated and present with recurrent or refractory disease. Another limitation is the retrospective nature of this study, which precludes inferences about causality. This study includes a large proportion of patients requiring long-term PCA which may lead to overall increased MED around the time of death due to opioid tolerance and dependence in the context of chronic use. Finally, this study was limited to information documented in the medical records due to its retrospective design.

In conclusion, our study found a high opioid requirement at the end of life in children and young adults with cancer and a significant increase in the use of opioids during the last 2 weeks of life as well as an increase in PS, with the highest mean PS on the day prior to the day of death. On the last day of life, AYA patients had significantly lower opioid requirement than the younger patient group. The use of adjuvant medications was common and we suggest that it may be beneficial early in the context of escalating opioid needs. It is important for clinicians to be aware of the need for opioid escalation at the end of life, so that pain and suffering can be aggressively addressed. As pain is a prevalent and distressing symptom in this patient population, further studies of PCA use at the end of life are recommended to better identify patients who would benefit from rapid escalation of opioids and/or the addition of adjuvant medications to improve pain and symptom control.

Acknowledgments

We thank Sharon Naron for scientific editing advice and Tracie Blancett, RN and Brenda Steen, RN, MSN for assistance with data collection.

Funding: This study was supported by the National Cancer Institute Cancer Center Support Core Grant 5P30CA-21765-35 and the American Lebanese Syrian Associated Charities (ALSAC), neither of which had a role in its planning, conduct, analysis, and reporting.

References

1. Wolfe J, Holcombe E, Grier MD, Klar N, Levin SB, Ellenbogen JM, Salem-Schatz S, Emanuel EJ, Weeks JC. Symptoms and suffering at the end of life in children with cancer. *The New England Journal of Medicine*. 2000; 342(5):326–333. [PubMed: 10655532]
2. Goldman A, Hewitt M, Collins GS, Childs M, Hain R. Symptoms in children/young people with progressive malignant disease: United Kingdom Children's Cancer Study Group/Paediatric Oncology Nurses Forum survey. *Pediatrics*. 2006; 117(6):e1179–1186. [PubMed: 16740818]
3. Wolfe J, Hammel JF, Edwards KE, Duncan J, Comeau M, Breyer J, Aldridge SA, Grier HE, Berde C, Dussel V, Weeks JC. Easing of suffering in children with cancer at the end of life: is care changing? *J Clin Oncol*. 2008; 26(10):1717–1723. [PubMed: 18375901]
4. Gaukroger PB, Tomkins DP, van der Walt JH. Patient-controlled analgesia in children. *Anaesth Intensive Care*. 1989; 17:264–268. [PubMed: 2774144]
5. Berde CB, Lehn BM, Yee JD, Sethna NF, Russo D. Patient-controlled analgesia in children and adolescents: a randomized, prospective comparison with intramuscular administration of morphine for postoperative analgesia. *J Pediatr*. 1991; 118(3):460–466. [PubMed: 1999793]
6. Rodgers BM, Webb CJ, Stergios D, Newman BM. Patient-controlled analgesia in pediatric surgery. *Journal of Pediatric Surgery*. 1988; 23(3):259–262. [PubMed: 3357143]
7. Gaukroger PB, Chapman MJ, Davey RB. Pain control in pediatric burns: the use of patient-controlled analgesia. *Burns*. 1991; 17:396–399. [PubMed: 1760109]
8. Mackie AM, Coda BC, Hill HF. Adolescents use patient-controlled analgesia effectively for relief from prolonged oropharyngeal mucositis pain. *Pain*. 1991; 46(3):265–269. [PubMed: 1758710]
9. Collins JJ, Geake J, Grier HE, Houck CS, Thaler HT, Weinstein HJ, Twum-Danso NY, Berde CB. Patient-controlled analgesia for mucositis pain in children: a three-period crossover study comparing morphine and hydromorphone. *J Pediatr*. 1996; 129(5):722–728. [PubMed: 8917240]
10. Dunbar PJ, Buckley P, Gavrin JR, Sanders JE, Chapman CR. Use of patient-controlled analgesia for pain control for children receiving bone marrow transplant. *J Pain Symptom Manage*. 1995; 10(8):604–611. [PubMed: 8594121]
11. Trentadue NO, Kachoyanos MK, Lea G. A comparison of two regimens of patient-controlled analgesia for children with sickle cell disease. *J Pediatr Nurs*. 1998; 13(1):15–19. [PubMed: 9503762]
12. Melzer-Lange MD, Walsh-Kelly MD, Lea G, Hillery CA, Scott JP. Patient-controlled analgesia for sickle cell pain crisis in a pediatric emergency department. *Pediatric Emergency Care*. 2004; 20(1):2–4. [PubMed: 14716157]
13. Angelescu DL, Burgoyne LL, Oakes L, Wallace DA. The safety of patient-controlled analgesia by proxy in pediatric oncology patients. *Anesth Analg*. 2005; 101(6):1623–1627. [PubMed: 16301231]
14. Angelescu DL, Faughnan LG, Oakes L, Windsor KB, Burgoyne LL, Deqing P. Parent-controlled PCA for pain management in pediatric oncology: is it safe? *J Pediatr Hematol Oncol*. 2012; 34(6):416–420. [PubMed: 22767126]
15. Angelescu D, Kaddoum RN, Oakes L, Windsor KB, Faughnan LG, Burgoyne L. An update: The safety of PCA by proxy for pain management in pediatric oncology: 2004 to 2010. *Anesth Analg*. 2011 in press.
16. Miser AW, Miser JS, Clark BS. Continuous intravenous infusion of morphine sulfate for control of severe pain in children with terminal malignancy. *Journal of Pediatrics*. 1980; 96(5):930–932. [PubMed: 7365606]
17. Miser AW, Davis DM, Hughes CS, Muine AF, Miser JS. Continuous subcutaneous infusion of morphine in children with cancer. *Am J Dis Child*. 1983; 137(4):383–385. [PubMed: 6187211]
18. Collins JJ, Grier HE, Kinney HC, Berde CB. Control of severe pain in children with terminal malignancy. *Journal of Pediatrics*. 1995; 126(4):653–657. [PubMed: 7535354]

19. Siden H, Nalewajek G. High dose opioids in pediatric palliative care. *Journal of Pain and Symptom Management*. 2003; 25(5):397–399. [PubMed: 12727032]
20. Collins JJ, Berde BC, Grier HE, Nachmanoff DB, Kinney HC. Massive opioid resistance in an infant with localized metastasis to the midbrain periaqueductal gray. *Pain*. 1995; 63(2):271–275. [PubMed: 8628594]
21. Sirkia K, Hovi L, Pouttu J, Saarinen-Pihkala UM. Pain medication during terminal care of children with cancer. *Journal of Pain and Symptom Management*. 1998; 15(4):220–226. [PubMed: 9601156]
22. Drake R, Frost J, Collins JJ. The symptoms of dying children. *J Pain Symptom Manage*. 2003; 26(1):594–603. [PubMed: 12850642]
23. Schiessl C, Gravou C, Zernikow B, Sittl R, Griessinger N. Use of patient-controlled analgesia for pain control in dying children. *Support Care Cancer*. 2008; 16(5):531–536. [PubMed: 18274785]
24. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: A behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs*. 1997; 23(3):293–297. [PubMed: 9220806]
25. Hockenberry, MJ.; Wilson, D. *Wong's essentials of pediatric nursing*. Mosby; St. Louis: 2009.
26. von Baeyer CL, Spagrud LJ, McCormick JC, Choo E, Neville K, Connelly MA. Three new datasets supporting use of the Numerical Rating Scale (NRS-11) for children's self-reports of pain intensity. *Pain*. 2009; 143(3):223–227. [PubMed: 19359097]
27. Angheliescu DL, Hamilton H, Faughnan LG, Johnson LM, Baker JN. Pediatric Palliative Sedation Therapy with Propofol: Recommendations Based on Experience in Children with Terminal Cancer. *Journal of Palliative Medicine*. 2012; 15(10):1082–1090. [PubMed: 22731512]
28. Zernikow B, Michel E, Craig F, Anderson BJ. Pediatric palliative care: use of opioids for the management of pain. *Paediatr Drugs*. 2009; 11(2):142.
29. McGrath PJ, Finley GA. Attitudes and beliefs about medication and pain management in children. *Journal of palliative care*. 1996; 12(3):46–50. [PubMed: 8885571]
30. Thielking PD. Cancer pain and anxiety. *Current pain and headache reports*. 2003; 7(4):249–261. [PubMed: 12828874]
31. Bennett MI, Rayment C, Hjermstad M, Aass N, Caraceni A, Kaasa S. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. *Pain*. 2012; 153(2):359–365. [PubMed: 22115921]
32. Dougherty M, DeBaun MR. Rapid increase of morphine and benzodiazepine usage in the last three days of life in children with cancer is related to neuropathic pain. *J Pediatr*. 2003; 142(4):373–376. [PubMed: 12712053]
33. Berde C, Wolfe J. Pain, anxiety, distress, and suffering: interrelated, but not interchangeable. *J Pediatr*. 2003; 142(4):361–363. [PubMed: 12712049]
34. Strasser F, Walker P, Bruera E. Palliative pain management: when both pain and suffering hurt. *Journal of palliative care*. 2005; 21(2):69–79. [PubMed: 16114805]
35. Jackson K, Ashby M, Martin P, Pisasale M, Brumley D, Hayes B. “Burst” ketamine for refractory cancer pain: an open-label audit of 39 patients. *Journal of pain and symptom management*. 2001; 22(4):834–842. [PubMed: 11576800]
36. Toombs JD, Kral LA. Methadone treatment for pain states. *American family physician*. 2005; 71(7):1353–1358. [PubMed: 15832538]

Figure 1.
Boxplot of Pain Scores During the Last Days of Life (N=36)

Figure 2.
Plot of Average MED (mg/kg/day) by Tumor Diagnosis (A) and Patient Age (B) During the Last Days of Life (N=43)

Table I
Patient Characteristics (N=44)

	N	%
Gender		
Female	16	36
Male	28	64
Age at death (years)		
Age 0-4	6	14
Age 5-7	4	9
Age 8-12	6	14
Age 13-18	15	34
Age >18	13	30
Mean (SD)	13.6 (6.6)	
Median (range)	14.7 (1.2 to 24.0)	
Diagnosis		
Leukemia/Lymphoma	26	59
Solid Tumor/Brain Tumor	18	41
Location on day 14 of PCA		
ICU	17	39
Ward	27	61
PCA duration (days)		
Mean (SD)	38.3 (35.8)	
Median (range)	31 (3 to 172)	
Initial opioid		
Fentanyl	14	32
Hydromorphone	13	30
Morphine	14	32
Remifentanyl	1	2
Sufentanyl	2	5
Number of opioid rotations		
0	34	77
1	9	20
2	1	2
Type of opioid rotation		
Fentanyl/Hydromorphone	2	20
Hydromorphone/Fentanyl	2	20
Hydromorphone/Morphine	1	10
Morphine/Fentanyl	3	30
Morphine/Hydromorphone	1	10
Morphine/Hydromorphone/Fentanyl	1	10

PCA = patient controlled anesthesia; SD = standard deviation.

Table II

Comparison of MED (mg/kg/day) by Tumor Diagnosis and Patient Age (N=43)

Diagnosis							
All			Leukemia/Lymphoma		Solid Tumor/Brain Tumor		
Day	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	P
14	27	10.7 (17.9)	17	11.5 (20.2)	10	9.5 (14.0)	0.744
7	38	14.7 (26.2)	22	16.1 (32.4)	16	12.9 (14.6)	0.337
2	43	16.3 (22.7)	26	17.1 (26.2)	17	15.0 (16.4)	0.576
1	43	19.0 (25.8)	26	19.7 (30.9)	17	17.9 (16.1)	0.339

Age							
All			<13		13		
Day	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	P
14	27	10.7 (17.9)	10	12.8 (24.3)	17	9.5 (13.6)	0.633
7	38	14.7 (26.2)	13	19.1 (38.4)	25	12.5 (17.4)	0.518
2	43	16.3 (22.7)	15	21.8 (29.2)	28	13.4 (18.2)	0.339
1	43	19.0 (25.8)	15	27.4 (31.5)	28	14.5 (21.5)	0.040*

MED = morphine equivalent doses; SD = standard deviation.

* Statistically significant, $p < 0.05$.

Table III

Linear Mixed Model Results for Change in MED (mg/kg/day) (N=43) and Pain Score (N=36)

Variable	Time Period	Overall Day Effect P	Pairwise Comparisons		
			Comparison	β (SE)	P
MED	Last 2 weeks of life	<0.001 *	Day 1 vs. Day 14	10.05 (2.43)	<0.001 *
			Day 1 vs. Day 7	4.91 (2.19)	0.025 *
			Day 7 vs. Day 14	5.14 (2.47)	0.038 *
	Last week of life	0.149	Day 1 vs. Day 7	4.92 (2.22)	0.027 *
Pain Score	Last 2 weeks of life	<0.001 *	Day 1 vs. Day 14	1.21 (0.79)	0.128
			Day 1 vs. Day 7	-0.57 (0.78)	0.469
			Day 7 vs. Day 14	1.78 (0.72)	0.014 *
	Last week of life	0.418	Day 1 vs. Day 7	-0.95 (0.73)	0.199

MED = morphine equivalent doses; SE = standard error.

* Statistically significant, $p < 0.05$.

Table IV

Comparison of Opioid Doses at the End of Life – Pediatric Studies

Author Year Reference	N	Context	Opioid route and modality	MED Mean (mg/kg/hr)	MED Median (mg/kg/hr)	MED Range (mg/kg/hr)	MED Maximum (mg/kg/hr)	Other Info
Miser 1980 [16]	N=8	Children (3-16 years) in terminal stages of malignancy	Continuous IV infusion		0.04-0.07	0.025-2.6		Duration of infusion 1-16 days Common but mild side effects
Miser 1983 [17]	N=17	Children (<23 years) with severe pain due to malignant neoplasm	Continuous SQ infusion		0.06	0.025-1.79		Adequate pain control No major side effects
Collins, Berde 1995 [20]	N=1	4 month old infant with rhabdoid tumor metastatic to periaqueductal gray	Continuous IV infusion				Escalation from 0.04 initially to 493 at death	Required addition of midazolam and pentobarbital over last 2 days
Collins, Grier 1995 [18]	N=199 reviewed 12 with massive opioid infusion	Children (<21 years) with terminal malignancy who required massive opioid infusions during terminal phase	Continuous IV infusion				3.8-518	11 of 12 patients had spread of tumor to nerve or spinal cord compression
Sirkia 1998 [21]	N=70 40 patients received IV opioid infusion	Children (<18 years) with cancer in terminal care 60% at home, 29% in hospital	Continuous IV infusion	0.8 at start of infusion, increased to 4.9 at time of death		0.2-55		Difference in MED by tumor type: 0.72-2 brain tumors, 0.9-1.2 leukemia, 0.9-1.5 solid tumors
Drake 2003 [22]	N=30 18 with cancer	Children (<19 years) who died in hospital Includes ventilated patients (66%)	PO/IV Infusions and on demand	7.82		1.03 -101.8		MED increased by 30% during last week of life
Siden 2003 [19]	N=42 32 with cancer	Children (<19 years) who died in inpatient pediatric hospice	PO/IV Infusions and on demand	4.86	0.085	0.001-73.9		Max dose on the day prior to death 7% of patients with apnea
Schiessl 2008 [23]	N=8	Children (<18 years) with terminal malignancy over last week of life	PCA		0.66 on day -62.21 on the last day of life	0.32-18.76		Median daily pain score was low (range 0-3) and did not change with PCA therapy
Our Study	N=43	Children (<24 years) with malignancy who died at pediatric cancer hospital No intubated patients	PCA	10.7 on day 14 19.0 on day 1	4.5 on day 14 9.7 on day 1	0.1-116.9	158.2 (day 5)	Mean MED increased over last 2 weeks in the overall group, by age groups, and by diagnosis groups Pain scores increased over same time, maximum on the day before death

MED=morphine equiva ent dose, IV=intravenous, PO=oral, PCA=patient controlled anesthesia, SQ=subcutaneous, TD=transdermal, PR=rectal