Methylnaltrexone for Opioid-Induced Constipation in Children and Adolescents and Young Adults with Progressive Incurable Cancer at the End of Life

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Abstract

Background: Opioid-induced constipation (OIC) is common among children and adolescents and young adults (AYA) with progressive incurable cancer. Although methylnaltrexone is a successful treatment for OIC in adult cancer patients, no case series has established its safety and efficacy in pediatric cancer patients.

Objectives: The aim of the study was to describe the safety and efficacy of methylnaltrexone use for OIC in children and AYA with progressive incurable cancer at the end of life in the inpatient and outpatient settings.

Methods: We conducted a retrospective review of medical records of children and AYA with progressive incurable cancer who received methylnaltrexone at our institution from May 2008 to June 2013. Pharmacy data were reviewed for each patient and a chart review was performed for documentation of laxation and side effects.

Results: Of the 9 patients (age range: 17 months to 21 years) with progressive incurable cancer who developed OIC, 7 (78%) had laxation after methylnaltrexone administration (0.15 mg/kg/dose). Of these 7 patients, 5 (71%) had laxation with the first dose, and 5 (71%) who responded had a continued response to repeated doses. The longest a patient regularly received methylnaltrexone was 9 months. Of 5 patients with intraabdominal disease, 4 (80%) had laxation. There were no negative side effects in any of the patients. Also, there was no increase in pain either qualitatively or by pain score.

Conclusions: Methylnaltrexone appears to be safe and efficacious in treating OIC in children and AYA with progressive incurable cancer. Methylnaltrexone was tolerated in both the inpatient and outpatient settings and with repeated dosing.

Introduction

CONSTIPATION is a frequently occurring and distressing side effect in patients with progressive incurable cancer at the end of life.¹ The use of opioids for pain management can cause opioid-induced constipation (OIC) in many patients. Although methylnaltrexone is a known and effective treatment option for adults with OIC,^{1,2} its safety and efficacy have not been established in pediatric patients.³

Most regimens to prevent and treat OIC are enteral preparations that become less tolerable as patients clinically decline.⁴ Methylnaltrexone can be administered subcutaneously, thereby providing an alternative route of administration for treating OIC. Methylnaltrexone induces laxation by competing with peripheral μ -opioid receptors, and its selectivity ensures that the central pain-relieving effects of opioids are not compromised.^{5,6}

To our knowledge, there is no case series of the use of methylnaltrexone in pediatric oncology patients with progressive incurable cancer. In this study, we describe the use of methylnaltrexone in this patient population in both the inpatient and outpatient settings.

Methods

A retrospective analysis was conducted on all children and adolescents and young adults (AYA) with progressive incurable cancer who received methylnaltrexone between May 2008 and June 2013 at St. Jude Children's Research Hospital in Tennessee. The study was approved by the Institutional Review Board. Data from children and AYA younger than 22 years of age who had received methylnaltrexone and were deceased were included in the study. Pharmacy data were reviewed for each patient and a chart review was performed.

TABLE 1. RESPONSE TO METHYLNALTREXONE TREATMENT IN CHILDREN WITH PROGRESSIVE INCURABLE CANCER AT THE END OF LIFE (N=9)

Age	Sex	Diagnosis	Location		Response to MNTX	Response to first dose	Intraabdominal disease	Functional status: ambulatory	Duration of use
			Home	Hospital					
17 mos	F	AML		Y	Y	Y	N	N	5 days
5 yrs	F	Wilms tumor	Y	Y	Y	Y	Y	Y	1 mo
9 yrs	F	Medulloblastoma		Y	Y	Y	N	Y	Once
12 yrs	F	Metastatic osteosarcoma	Y		Y	N	N	N	2 mo
14 yrs	M	Synovial sarcoma		Y	N	N/A	Y	N	2 wks
15 yrs	F	Metastatic osteosarcoma	Y	Y	Y	N	Y	Y	9 mo
18 yrs	M	Aggressive small round blue cell neoplasm		Y	Y	Y	Y	Y	Once
18 yrs	M	Ewing sarcoma		Y	Y	Y	Y	Y	4 mo
21 yrs	M	Rhabdomyosarcoma		Y	N	N/A	N	N	2 wks

AML, acute myeloid leukemia; MNTX, methylaltrexone; mos, months; N, no; N/A, not applicable; wks, weeks; yrs, years; Y, yes.

Data were collected from a review of medical records via a data extraction tool evaluating age, sex, diagnosis, location of administration, response to methylaltrexone, response to first dose, presence of intraabdominal disease, functional status, duration of use, and dose. Notes from the institutional palliative care team were reviewed for documentation of laxation for outpatients in the home setting.

All 9 patients (median age: 14 years, range: 17 months to 21 years; Table 1) who met the inclusion criteria had documented OIC, and the administration of enteral preparations and/or suppositories had been unsuccessful in treating OIC before methylaltrexone was initiated. Methylaltrexone was administered subcutaneously at 0.15 mg/kg/dose.

Methylaltrexone administration produced laxation in 7 (78%) patients within 1 hour of administration. Of these 7 patients, 5 (71%) had laxation with the first dose and 5 patients (71%) had a continued response to repeated doses. The longest a patient regularly received methylaltrexone was 9 months. Of 5 children and AYA with known intraabdominal disease, 4 (80%) had successful laxation. There was not a prospective system in place for tracking symptoms before and after administration. All initial doses were administered under direct supervision, and no nurse or physician documented distress, cramping, or new symptoms around the time of administration. Additionally, there was no charted increase in pain either qualitatively or by pain score.

The 2 patients with delayed responses achieved a sustained response to subsequent dosing after the second and fourth doses. Of the 9 children and AYA, 6 (67%) received methylaltrexone at the hospital, 2 (22%) received the medication at the hospital and in the home setting, and 1 (11%) received the medication only in the home setting. Both patients who did not respond to methylaltrexone received two doses of the drug. Both these patients had significant comorbidities and were in the terminal stage of their illness.

Discussion

A case report and recent case series reported that methylaltrexone is a safe and efficacious treatment of OIC in pediatric oncology patients who do not respond to enteral regimens or have acute complications secondary to their constipation.^{3,7} Our data demonstrate that methylaltrexone

appears to be both safe and effective to use in children and AYA with incurable cancer in both inpatient and outpatient settings as well as longitudinally with repeated dosing. Furthermore, 4 of our patients even received a successful dose through the last week of life.

More than one dose of methylaltrexone may be necessary to initiate laxation. In our study one patient who did not pass stools for 2 months responded to the fourth dose and all subsequent doses of methylaltrexone.² Similarly, a study on adults with advanced illness found a significant increase in response rate after two or more doses of methylaltrexone.² Despite the paucity of data on the need for more than one initial dose, we recommend repeating several doses if the patient does not respond to enteral regimens. Once laxation is achieved, enteral regimens should be resumed when possible,⁴ but methylaltrexone can be used at regular intervals if needed. In our series, one patient responded to methylaltrexone for up to 9 months. None of the patients experienced increased pain or negative side effects through the time period of methylaltrexone administration. Methylaltrexone can be used at home to deliver doses as needed in conjunction with enteral regimens or as a single agent. In our series, many parents were taught to administer methylaltrexone as needed. The ease of subcutaneous delivery at home makes methylaltrexone administration possible even for patients at the end of life.

Mechanical gastrointestinal obstruction is a contraindication to the use of methylaltrexone;^{2,8} therefore some may think that intraabdominal disease is a presumed relative contraindication. We found that methylaltrexone produced laxation in 4 of 5 (80%) patients with known intraabdominal disease. Although the risks of methylaltrexone use must be considered, we recommend a trial of methylaltrexone in patients who experience substantial pain and suffering from OIC, even for those having intraabdominal disease. The patient who did not respond to methylaltrexone had significant intraabdominal metastasis with near complete intestinal obstruction. However, this patient had no negative side effects from the medication.

Limitations of our study include the retrospective nature as well as the small size of our cohort. The retrospective nature of this study mandates reliance on medical record review and appropriate documentation. There was inadequate documentation of side effects for the 3 (33%) patients who were administered methylaltrexone in the home setting. Because only

2 of 9 (22%) patients in our series received methylnaltrexone without laxation, we have insufficient data to predict patients who might not respond to methylnaltrexone. Our institutional palliative care team is familiar with methylnaltrexone administration and was comfortable prescribing it for all 9 patients. Therefore, it is unclear how many patients might have benefited from its administration during our study period, but our institution's palliative care team prescribes this medication.

In conclusion, this cohort demonstrates the apparent safety of methylnaltrexone administration in children and AYA with cancer. Methylnaltrexone can be a safe and efficacious option for use in children and AYA with progressive incurable cancer at the end of life in the inpatient and outpatient settings as well as with repeated dosing. However, prospective studies are needed to confirm the efficacy of methylnaltrexone for treating OIC in this patient population.

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Author Disclosure Statement

No competing financial interests exist.

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