Evidence-Based Criteria Supporting Early Discharge for Pediatric Patients With Osteosarcoma Receiving High-Dose Methotrexate: A Retrospective Chart Review

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Purpose: The purpose of this study is to describe the outcomes following the implementation of an early discharge protocol for pediatric patients with osteosarcoma receiving high-dose methotrexate (MTX) to determine if the protocol safely decreased length of stay without increased toxicity. **Methods**: This was a retrospective descriptive cohort design. Participants included children, 5 to 25 years of age, diagnosed with osteosarcoma, who received methotrexate between December 2017 and July 2019. A total of 141 doses across fifteen individual patients were included in the cohort. Data were abstracted from the electronic health record and analyzed using descriptive statistics. **Results:** The majority of administrations (n = 94, 67%) met early discharge criteria without an increase in toxicity or hospital readmission. **Conclusion:** Pediatric patients receiving high-dose MTX for osteosarcoma can be safely discharged from the hospital when serum MTX level < 0.4 µmol/L with the implementation of education, hydration goals, frequent lab monitoring, and close follow-up. More than half of patients on this study were able to be discharged from the hospital sooner than prior protocol. More importantly, this retrospective chart review highlighted the ability to maintain safe administration without increasing toxicity.

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High-dose methotrexate (MTX) is a commonly used chemotherapeutic agent for multiple types of pediatric malignancies and has remained one of the gold standards of chemotherapies in treatment for osteosarcoma for the past few decades. Methotrexate was first used for osteosarcoma in the early 1970s when despite radical resections of primary tumors, 5-year survival was only around 20%. This was most likely due to micrometastasis found in the lungs (Mir et al., 2008). In the mid to late 1970s, MTX (12 g/m^2/dose), with the addition of doxorubicin given preoperatively, was shown to greatly increase survival rate, with 75% of patients having no evidence of disease 30 to 52 months after completing chemotherapy (Mir et al., 2008). Since this time, chemotherapy regimens that include high-dose MTX have become the standard of care for all pediatric patients receiving osteosarcoma therapy.

Despite the benefits of high-dose MTX in osteosarcoma therapy, it is not without risk for toxicity, the greatest risk being to the kidneys. Nephrotoxicity can be life-threatening, related to increased systemic exposure and thus potentiating the risk of other MTX toxicities (Widemann et al., 2004). Greater than 95% of high-dose MTX is excreted unchanged in the urine, with all cases of acute kidney injury (AKI) occurring during the infusion of the drug. This is thought to be due to the precipitation of MTX within urine in the renal tubules. Since the solubility of MTX is limited in acidic solutions (i.e., urine), urine alkalization and hydration via IV fluids is required until MTX levels are at least < 10 µmol/L. Hydration and urine alkalization do not alter renal blood flow or glomerular filtration rate, nor do they increase MTX excretion, but merely are required to enhance MTX solubility in the urine.

Other risks of toxicity include mucositis, hepatotoxicity, neurotoxicity, skin reactions, and even anaphylaxis requiring desensitization (Scott et al., 2013). Given all of these risks for toxicities related to the administration of high-dose MTX, it has been commonplace for the drug to be given in an inpatient setting with supportive care until excretion. This excretion level is often institution specific since there is no osteosarcoma protocol defining an acceptable level. Acceptable MTX levels that signify excretion range anywhere from < 0.05–0.1 µmol/L based on institution (Binder et al., 2019). However, despite the risk of all MTX-associated toxicities related to its administration, many institutions have explored how to decrease inpatient stays given the lengthy average therapy for osteosarcoma while at the same time continuing to safely administer the medication with less toxicity. At this time, there is no evidence-based consensus on an appropriate level for discharge.

The purpose of this study is to describe the outcomes following the implementation of an early discharge protocol for pediatric patients with osteosarcoma receiving high-dose MTX to determine if the protocol decreased length of stay without increased toxicity.

METHODS

This study was reviewed by the Children's Hospital of Philadelphia (CHOP) institutional review board and was determined to be exempt from oversight.

Setting

CHOP is a large quaternary care center that includes a cancer center. CHOP's cancer center team is responsible for the care of children with cancer, including diagnosis, treatment, survivorship, and long-term follow-up. The solid tumor team at CHOP is responsible for the care of children with osteosarcoma. When children with osteosarcoma are treated with MTX, they are admitted to CHOP's inpatient oncology unit and monitored closely until time at which adequate excretion is determined.

Previous Discharge Criteria. Prior to developing standards for early discharge in pediatric osteosarcoma patients receiving MTX, it is important to understand previous discharge criteria for this patient population implemented at CHOP.

When being admitted for high-dose MTX, patients were immediately started on sodium bicarbonate intravenous (IV) fluids, first as a 750 mL/m^2 bolus and then as a continuous infusion at 100 mL/m^2/hour to run concurrently with MTX. Patients were maintained on these fluids (and rates were adjusted based on serum creatinine) until MTX level was < 0.1 µmol/L and were only disconnected briefly for hygienic purposes, if at all. Methotrex-

ate levels and serum creatinine were first monitored at the completion of MTX infusion, 24 hours after completion, and then daily until levels were < 0.1 µmol/L, at which time the patient was then eligible for discharge. Leucovorin rescues of 15 mg/m²/dose were started at hour 24 after the start of MTX and then continued every 6 hours until MTX level was < 0.1 µmol/L. Leucovorin rescues were given in tablet form with a maximum dose of 25 mg due to decreased absorption when given in higher doses. IV doses of leucovorin were only used in cases where body surface area was > 2 m² or in patients who had a history of delayed MTX excretion requiring more intensive supportive care with IV administration. Urinalysis was completed every 8 hours to monitor urine pH, and 0.5 mEq/kg/dose sodium bicarbonate 8.4% boluses were given over 30 minutes to maintain the pH between 7 to 8 to prevent renal dysfunction.

Implementation of the Early Discharge Criteria. In December 2017, the team at CHOP transitioned from the previously described discharge criteria to a new, early discharge criteria protocol.

Patients with osteosarcoma who were receiving MTX at a dose of 12 g/m² over 4 hours are offered early discharge if at hour 24 post MTX dosing their MTX level is < 15 µmol/L, and then following at 48 hours post dosing, their MTX level is < 1 µmol/L. Additional criteria for early discharge includes (1) MTX level, pre-discharge, < 0.4 µmol/L achieved, (2) nausea well controlled, (3) tolerating 75% of maintenance fluids, and (4) tolerating medications taken orally. In addition, families must be able to commit to a return clinic visit within 72 hours from time of discharge for a repeat creatinine level, an MTX level, and physical exam with a provider to check hydration status and rule out any toxicity experienced since time of discharge. Patients who have a history of grade 3 toxicity per Common Terminology Criteria for Adverse Events (CTCAE) guidelines or above due to delayed clearance or decrease in renal clearance during admission are not eligible for early discharge. Patients with Down syndrome were excluded given the risk for increased toxicities at baseline.

If a child meets all criteria for the new early discharge protocol, the oncology team implemented standards for monitoring potential toxicity and patient/family education at home. At the time of discharge, an electronic message is sent to the oncology triage nurse in the oncology outpatient clinic. This message alerts the triage nurse to call each family of those discharged on the early discharge protocol daily, until appropriate excretion, defined as an MTX level < 0.1 µmol/L, is seen in clinic. In addition to the daily follow-up by the oncology triage nurse, families are asked to call the oncology triage nurse for any of the following reasons: if their child (1) was unable to meet the calculated fluid intake, (2) experienced > 3 episodes of emesis, (3) experienced < 3 voids within 24 hours, (4) was unable to tolerate oral antiemetics, and/or (5) was unable to tolerate oral leucovorin.

At the time of the follow-up clinic visit, if the child's MTX level is not < 0.1 µmol/L, patients continue leucovorin and are seen within 72 hours for another visit. Each follow-up visit includes a serum creatinine level, an MTX level, as well as a full exam by a provider. If either the serum creatinine or MTX levels increased by > 25%, the patient is readmitted for IV fluid hydration and supportive care. However, even when a patient reaches the 0.4 µmol/L MTX level, if they were unable to meet the other criteria (MTX levels at specified time periods, stable serum creatinine, tolerate 75% maintenance fluids or supportive medications orally, follow-up clinic visit), they remain as an inpatient until their MTX level is < 0.1 µmol/L for safety concerns.

Early Discharge Criteria, Clinician Procedures. At CHOP, the inpatient nurse practitioners (NP) are the front-line clinicians for patients receiving MTX to ensure a consistent group of providers who are experts in managing MTX levels and excretion. Although decreased length of stay benefits patients and health systems, there was an increased need for resources and role clarity for our clinicians to successfully implement the early discharge criteria protocol. The inpatient NP team would sit down with each patient and family and thoroughly explain the protocol as well as provide written instructions prior to discharge.

During daily inpatient rounds, the solid tumor team discusses the individual MTX levels and titrates IV fluids accordingly. Once the patient's MTX level is < 10 µmol/L, sodium bicarbonate is discontinued, and the MTX infusion

rate is changed to IV plus oral dosing for maintenance. The NPs are responsible for prescribing leucovorin tablets for home and trialing the oral intake goals with patients and families. The patient's antiemetics are also changed from IV to oral to ensure tolerance prior to discharge. The role of the outpatient providers, specifically the NPs, includes increased clinic visits for follow-up MTX levels, serum creatinine, and physical exams. The outpatient NPs are also available to triage any questions or concerns during the daily screening phone calls performed by the oncology triage nurse.

The solid tumor nurse navigator plays a crucial role in the process as well. They serve as a liaison between the patient/family and the oncology outpatient providers. In order to expedite follow-up clinic visits, patients are able to leave once they are evaluated by a provider and serum creatinine results within normal limits. Given the delay in MTX level processing, once the MTX level results are available and after discussion with the outpatient NP, the nurse navigator contacts the family to notify them of the MTX level and relay the plan. If the MTX level is < 0.1 µmol/L, families are advised to discontinue leucovorin and resume bactrim prophylaxis for *Pneumocystis jiroveci* pneumonia after adequate excretion, which is held during MTX given the drug interaction. If the MTX level is > 0.1 µmol/L, a follow-up visit for repeat MTX level, serum creatinine, and clinic visit is scheduled with the family. The outpatient solid tumor nurse navigator is a tremendous help in the communication and reinforcement of education with families in the implementation of our early discharge criteria protocol.

Description of Participants

The cohort for this study includes all inpatient encounters of patients, aged five to twenty-five years, with osteosarcoma treated at CHOP receiving MTX between December 2017 and July 2019.

Design

This is a retrospective descriptive cohort study. Following institutional review board approval, the first author reviewed the study's inclusion and exclusion criteria and generated the listing of eligible inpatient encounters. The first author then worked with the study's principal investigator and data coordinator to ensure accuracy. Next, the first and last authors developed a data dictionary and trained the study's research assistants to extract data elements from the patients' electronic health records. The data elements of interest included demographic data as well as clinical data associated with each MTX treatment encounter: patients' MTX and creatinine levels, date/time of discharge, discharge to home on leucovorin, and repeat MTX and creatinine levels in the oncology clinic. For those patients who were discharged with an MTX level < 0.4 µmol/L (early discharge), the research team reviewed the medical records for readmission prior to appropriate outpatient clearance, as well as any phone encounter notes and/or follow-up oncology clinic notes, for any documentation of toxicity.

RESULTS

After implementation of the early discharge protocol for patients with osteosarcoma receiving MTX, data were reviewed for 15 patients who received 6 to 12 doses of MTX each during their therapy. This included 141 administrations of MTX given to the 15 patients with osteosarcoma between December 2017 and July 2019.

Of the 15 patients in the cohort, five patients (33.3%) had comorbidities. Three of the patients developed osteosarcoma at the site of radiation from a prior oncologic diagnosis. One patient had received prior chemotherapy for a diagnosis of adrenal cortical carcinoma. And one of the patients was diagnosed with Rothmund-Thomson syndrome during the early stages of chemotherapy for osteosarcoma.

Of the four patients who had a prior oncologic diagnosis, two had received dose reductions after the first dose of MTX due to renal toxicity and prolonged drug excretion. These two patients went on to receive 8 g/m^2 in all subsequent cycles. Two of the patients with a prior oncologic diagnosis tolerated the full dose (12 g/m^2) for the duration of therapy. The patient with Rothmund-Thomson syndrome had received full-dose MTX for the first dose prior to genetic testing results. This patient also had delayed excretion and grade 2 mucositis after both full doses of MTX. Due to the prior toxicity and concern for MTX sensitivity in patients

with Rothmund-Thomson syndrome, all further doses of MTX were dose reduced to 8 g/m² (Hicks et al., 2007).

Historically, patients with leukemia who receive 5 mg/m² are hospitalized for at least 54 hours (Ranney et al., 2020). Given that patients with osteosarcoma receive 12 g/m², the average duration of hospitalization is longer than that of leukemia patients.

Analysis of our data for patients with osteosarcoma showed an average time of discharge of 2.93 days, which is approximately 70 hours after implementation of early discharge criteria (Figure 1).

Of the 141 administrations of MTX, 94 of the patients met early discharge criteria and were discharged when MTX level reached < 0.4 µmol/L. Of the patients who were discharged early, nine of them had a documented toxicity during follow-up at the oncology clinic visit. None of the patients with a documented toxicity required readmission to the hospital. Four patients reported a sore throat at the clinic visit. All four patients were able to tolerate oral hydration and take oral leucovorin which, per the CTCAE guidelines, met criteria for grade 1 to 2 adverse events for oral mucositis. Two patients were seen in the emergency room post discharge for fever and neither had a documented infection. Two patients reported mild abdominal pain post discharge but did not require pain medications and were tolerating oral intake. One patient reported a new rash post discharge that resolved without intervention.

For the patients who did not meet early discharge criteria, the majority were due to MTX levels above the allowed range for early discharge and not due to the inability to tolerate oral fluids or medications. Serum creatinine was analyzed at end of infusion, hours 24 and 48 for those who were not discharged early, and none of them had an increase in serum creatinine by more than 0.2 mg/dL. Of the 47 patients who did not meet early discharge criteria, 29 of them had a 24-hour MTX level that was greater than 15 µmol/L.

DISCUSSION

The majority of administrations (67%; n = 94) met early discharge criteria; therefore, patients were discharged earlier. No patients had an increased toxicity that required readmission to the hospital. After review of the data, pediatric patients re-

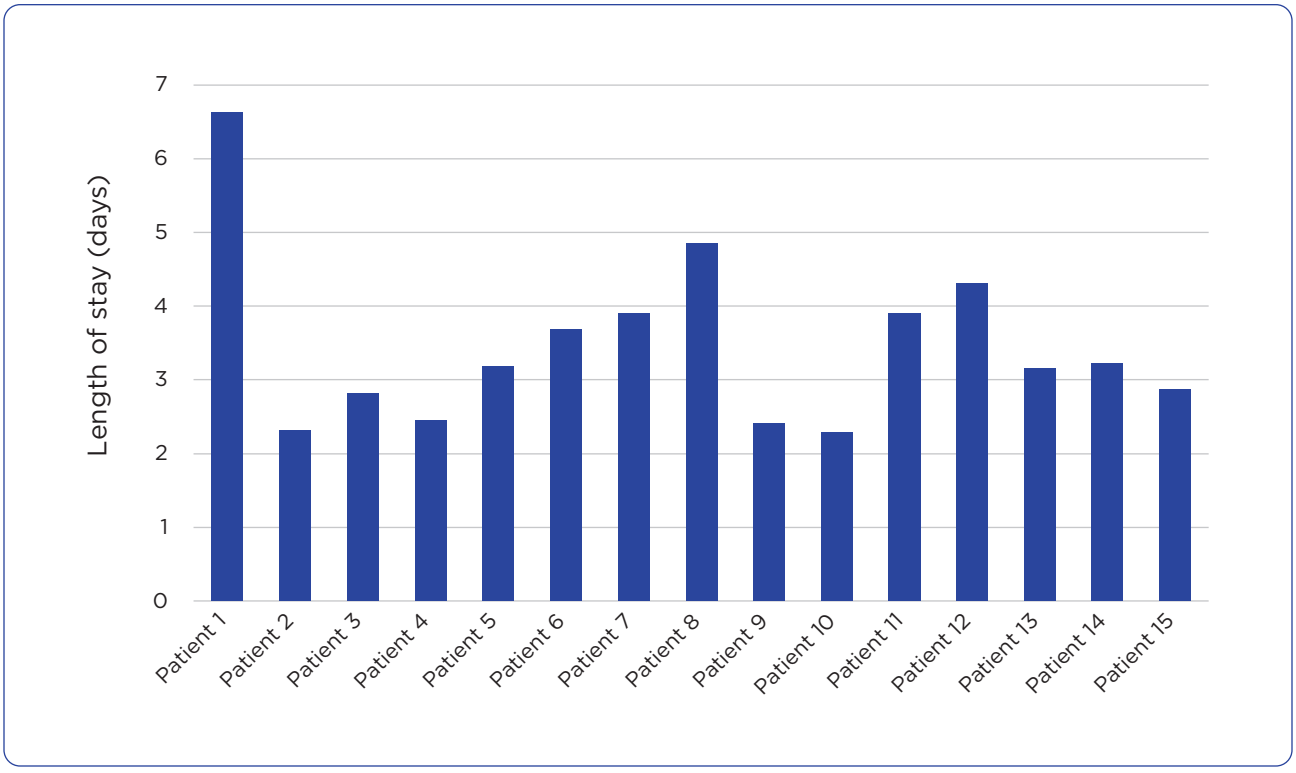

Figure 1. Mean length of stay for methotrexate administration per patient.

ceiving high-dose MTX for osteosarcoma may be safely discharged from the hospital if the specific laboratory criterion is met in combination with the implementation of hydration goal, education, close follow-up, and frequent lab monitoring.

There has been much research published discussing the risks of prolonged and sometimes unnecessary hospitalizations. In a cluster, parallel group, randomized trial performed at a large hospital in Northern Italy, it was found that when applying more physician accountability, such as identifying patient populations where care could be transitioned to the community or outpatient setting sooner and avoid unnecessary days in the hospital, the rate of potential adverse effects, wasted resources, and health-care dollars significantly decreased and allowed for more efficient use of hospital beds (Caminiti et al., 2013).

In addition to potentially decreasing health-care costs and waste, quality of life has been shown to greatly increase with decreased hospitalization. A cancer diagnosis can increase levels of stress for both individuals and their family members related to prognosis, treatment, and continued hospitalizations. Prolonged hospitalizations have been linked with increased deconditioning and impact both physical and social functioning. With decreased length of stay, it has been shown that the impact on these factors is much less, thus significantly improving quality of life (Alaloul et al., 2019). Since the majority of patients with osteosarcoma are adolescents with multiple family members involved in care, it can be inferred that decreasing length of stay for most will overall improve patient quality of life.

The early discharge protocol was developed based on the clinical experience of the solid tumor team at CHOP in caring for patients with osteosarcoma and evaluating excretion curves of methotrexate. Given the lack of consistency in defining MTX excretion across institutions who care for osteosarcoma patients, the hope of this research is that other institutions may be able to adopt this protocol to allow for the safe administration of the chemotherapy and provide the option for early discharge with close follow-up. This will allow for consistency in patient care, work to improve patient/family quality of life, and in turn, decrease unnecessary hospital days.

Limitations

Given this was a retrospective study, there was also no baseline length-of-stay data. While it was known that length of stay was longer prior to implementation of early discharge protocol, there is no average length of stay available for comparison. In addition, given that this was a retrospective study, there were no quality-of-life data collected from patients and families to assess the impact of decreased length of stay. Given comorbidities are more common in the older adult population, it is unknown if this protocol would be safe for these patients.

CONCLUSION

Patients receiving high-dose MTX for osteosarcoma can be discharged from the hospital safely if specific criteria are met and when serum MTX level < 0.4 μmol/L. However, safe early discharge from high-dose MTX is only feasible if the patient is able to take at least 75% of maintenance goal and medications by mouth and comply with follow-up visits. The success of this change also requires a multidisciplinary approach for increased outpatient visits, increased support for the patient and family, the implementation of screening calls, and patient/family education.

In future osteosarcoma studies, researchers should focus on the efficacy of MTX treatment, improved patient satisfaction based on decreased length of stay, and maximal safety based on toxicity levels.

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Disclosure

The authors have no conflicts of interests to disclose.

References

Alaloul, F., Myers, J., Masterson, K. M., Dicicco, J., Collins, M. P., Hogan, F.,...Logsdon, M. C. (2019). Patient experience factors and health-related quality of life in hospitalized

individuals. (2019). *Oncology Nursing Forum*, 46(2), 238–247. https://doi.org/10.1188/19.onf.238-247

Binder, A., Burdette, S., Galanis, P., Birchmeier, K., Handley, N., & Piddoubny, M. (2019). Implementing an early discharge initiative for patients receiving high-dose MTX. *Journal of Clinical Oncology, 37*(27_suppl), 90. https://doi.org/10.1200/JCO.2019.37.27_suppl.90

Caminiti, C., Meschi, T., Braglia, L., Diodati, F., Iezzi, E., Marcomini, B.,...Borghi, L. (2013). Reducing unnecessary hospital days to improve quality of care through physician accountability: A cluster randomised trial. *BMC Health Services Research*, *13*(1), 14. https://doi.org/10.1186/1472-6963-13-14

Hicks, M. J., Roth, J. R., Kozinetz, C. A., & Wang, L. L. (2007). Clinicopathologic features of osteosarcoma in patients with Rothmund-Thomson Syndrome. *Journal of Clinical Oncology*, *25*(4), 370–375. https://doi.org/10.1200/jco.2006.08.4558

Mir, O., Ropert, S., & Goldwasser, F. (2008). Neoadjuvant chemotherapy with high-dose methotrexate in osteosarcoma. *Lancet Oncology*, *9*(12), 1198. https://doi.org/10.1016/s1470-2045(08)70309-7

Ranney, L., Hooke, M. C., & Robbins, K. (2020). Letting kids be kids: A quality improvement project to deliver supportive care at home after high-dose methotrexate in pediatric patients with acute lymphoblastic leukemia. *Journal of Pediatric Oncology Nursing*, *37*(3), 212–220. https://doi.org/10.1177/1043454220907549

Scott, J. R., Ward, D. A., Crews, K. R., Panetta, J. C., & Navid, F. (2013). Hypersensitivity reaction to high-dose methotrexate and successful rechallenge in a pediatric patient with osteosarcoma. *Pediatric Blood & Cancer*, *61*(2), 373–375. https://doi.org/10.1002/pbc.24741

Widemann, B. C., Balis, F. M., Kempf-Bielack, B., Bielack, S., Pratt, C. B., Ferrari, S.,...Adamson, P. C. (2004). High-dose methotrexate-induced nephrotoxicity in patients with osteosarcoma. *Cancer*, *100*(10), 2222–2232. https://doi.org/10.1002/cncr.20255