OUTPATIENT HIGH-DOSE METHOTREXATE FOR ADOLESCENT AND YOUNG ADULT OSTEOSARCOMA PATIENTS

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Introduction

Osteosarcoma is a primary malignant tumor of the bone. It is the most common primary bone malignancy in children and adolescents. Nationwide, approximately 400 children and young adults under 20 are diagnosed with Osteosarcoma every year, with most diagnoses occurring during the adolescent growth spurt. This comprises approximately 2-3% of childhood malignancies, and 56% of all bone cancers in patients under the age of 20. The median age at diagnosis at our center is 14.

At Atrium Health Levine Children's, our Osteosarcoma patients are treated as per COG AOST0331, MAP arm. This therapy is a rigorous 29-week protocol comprised of alternating cycles of cisplatin/doxorubicin and high-dose methotrexate (HD MTX), requiring a minimum of 17 hospitalizations, including limb salvage surgery. Admissions are back-to-back and may be prolonged due to delayed clearance of methotrexate.

AYA patients are at high risk of emotional distress due to these prolonged inpatient stays. This may put them at risk of decreased compliance with therapy, which may decrease their chance for cure of their Osteosarcoma.

Goals

To evaluate the feasibility of outpatient high-dose methotrexate administration for adolescents and young adults with osteosarcoma.

Feasibility will be determined by the number of weeks that patients' Methotrexate levels are ≤0.15µmol/L on/before hour 72, any toxicity requiring hospitalization, and patient satisfaction.

Methods

Most patients receive their first two Methotrexate infusions on the inpatient unit, to assess for delayed clearance or any other significant toxicities. During the first hospitalizations, patients that are ten years old and up along with their parents, are offered to receive subsequent cycles of chemotherapy outpatient.

Beginning in 2013, our department contracted with an external vendor for home infusion pumps. The vendor offers 24-hour oncology nursing support for the pumps. An order set was developed by the provider team that met the pump constraints for maximum fluid allowed per day. Patients are given an outpatient family order set to complement the chemotherapy orders, instructing them on oral pre-hydration and alkalization. Prescriptions are sent to the pharmacy of choice and patients must have oral leucovorin in-hand prior to the start of chemotherapy. Patient must meet urine parameters and infusion must start by noon, or patient must transfer to the inpatient unit for infusion. In this event, patients may be discharged home following completion of the chemotherapy infusion. Patients receive a maximum volume of 3L beginning at hour 4/completion of infusion. Outpatient HD MTX is typically administered on Mondays or Tuesdays, to coincide with our clinic's weekday schedule.

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Patient/Family Orders for Outpatient High-Dose Methotrexate

Diet: Regular. Avoid foods/drinks that have a high amount of Vitamin C.
Activity: As tolerated.
Routine Medications: Hold Septra, Proton Pump Inhibitors (Prilosec, Prevacid, Protonix, Nexium), and Vitamin C

Pre-Chemotherapy Physical Exam: Your exam is scheduled for _____ at _____ am/pm.
Labs will be drawn at this visit, so make sure to have EMLA cream on your port or arm.

Antiemetics: Place Sancuso (granisetron) patch at bedtime the night before your outpatient chemotherapy. This may stay on for up to one week (7 days).
Pre-hydration:
The day prior to your outpatient Methotrexate, you must drink 2-3 liters (64-96 ounces) of fluid (water, Gatorade, or Crystal Light).
On the morning of your outpatient Methotrexate, you must drink 1 liter of fluid before coming in to clinic.
Alkalinization: You should take 2 tablets (1300 mg) of Sodium Bicarbonate every hour before coming to clinic (i.e. 6am, 7am, and 8am).
Chemotherapy Appointment: You must arrive to clinic at 8am on _____. Please come prepared to give a urine sample. *If your urine specific gravity and/or pH are not <1.010 and ≥7, respectively, you will need to receive IV pre-hydration before your Methotrexate infusion can begin.*
Methotrexate: _____ grams (12grams/m^2; max 20 grams) IV over 4 hours. *This must begin no later than 12pm in order to receive outpatient therapy.*
Post-hydration Day 1: Upon completion of your Methotrexate infusion, a Methotrexate level and chemistry panel will be obtained, and your post-hydration fluids will be started. At that time, if you are able to take oral fluids, you will be discharged home from the infusion room.
Post-hydration Days 2-5: You will return to clinic daily at _____ am/pm for a new bag of IV fluids and labs. On day 2, exactly 24 hours after your Methotrexate infusion started, you will begin taking Leucovorin _____ mg by mouth every 6 hours (at 6am, 12pm, 6pm, and 12am). You will continue on IV fluids and Leucovorin until your Methotrexate level is <0.1.

If you have any problems with your home IV pump, please call the support center at 1-800-315-3287.
An Oncology Nurse is available 24 hours a day, 7 days a week.

_____
Nurse Navigator Date/Time

Patient Name:
Date of Birth:
Medical Record #:

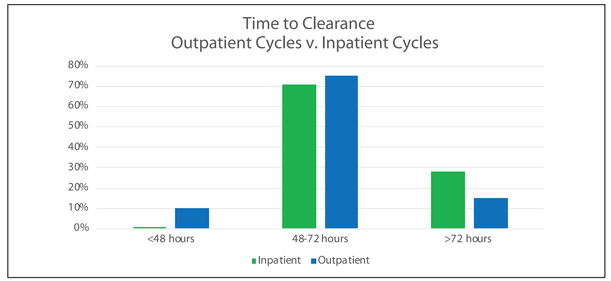
Patients return to the clinic at 24 hours following the start of their Methotrexate infusion. A plasma Methotrexate level is obtained and the first dose of leucovorin is administered IV. Patients must wait for the CMP and Methotrexate results before discharge home that day. Patients with an hour 24 Methotrexate level of >10µmol/L are hospitalized for increased hydration. Patients with hour 24 Methotrexate level of <10µmol/L are discharged home with an additional 3L of fluids and return daily until their Methotrexate level is ≤0.15µmol/L. Oral leucovorin is administered every 6 hours until clearance.

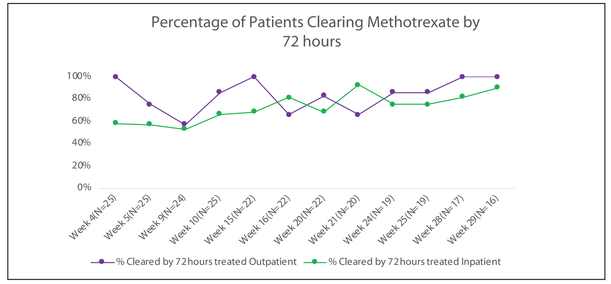
Results/Outcomes

Of 25 patients diagnosed with Osteosarcoma at our center since 2013, 23 were offered the opportunity to receive outpatient HD MTX. One patient was not offered outpatient therapy due to age of 5 at diagnosis, and one patient due to also being affected by Sickle Cell Disease. Eleven patients chose to attempt outpatient HD MTX for at least one cycle. Among patients who declined outpatient HD MTX, the most common reason was transportation/distance from the clinic (n=5). Other patients declined due to history of delayed clearance (n=3), anxiety (n=1), history of severe nausea (n=1), family/works schedules (n=1) and early progression of disease (n=1).

A total of 69 cycles were administered outpatient. In 10% of cycles, the patient cleared their MTX within 48 hours, 75% were cleared in 72 hours, and 14% required longer than 72 hours to clear. This compares to 187 cycles administered inpatient, in which 1% of cycles were cleared in 48 hours, 71% cleared by 72 hours, and 28% required longer than 72 hours to clear.

Median time to clearance was 72 hours for both inpatient and outpatient cycles.





Of 69 cycles administered outpatient, three patients required a total of five admissions for elevated 24 hour MTX levels. Two of three patients successfully completed subsequent cycles of outpatient HD MTX. One patient had a repeatedly high 24 hour level and elevated serum creatinine with his subsequent cycle, and ultimately changed therapy.

Overall, patients have been pleased with the outpatient chemotherapy experience. Of 11 patients who attempted outpatient chemo, 9 completed > 2 cycles. One patient's therapy was terminated early due to infectious/prosthetic complications.

Patient comments:

"I come to the infusion room and get my chemo for four hours. And then they hook me up to a handy-dandy backpack with a big bag of fluids like salt water and potassium. So I get to go home with the back pack and sleep in my bed." – *Alex, age 11*

"We are extremely lucky to live in a city with a phenomenal children's hospital, but nothing compares to being in one's own home. Spending time at home instead of 3 to 4 days in a hospital benefited our entire family both physically and mentally. While we search for less debilitating treatments for these childhood cancers, and outpatient option gives families some sense of normalcy.
– *Tracey, mother of 14 yr old*

"Being able to do outpatient chemo allowed me to sleep in my own bed, and continue to live a normal life while getting treatment. I could keep up with the classes in my senior year of high school, and graduate with my class. The entire process was easier for me with the comforts of my own home." – *Michael, age 17*

"Going home each night truly made a difference in Michael's treatment. He ate and drank better, and was more mobile when we were at home, compared to being inpatient. This seemed to help him better tolerate the medications he was given, and clear his methotrexate levels in a timely manner. The backpack was easy to maneuver and use each week. His medical team felt like family to us - we looked forward to going in to check his levels and get a new bag of fluids. Being at home at night enabled him to relax, with us taking care of him - which helped his whole attitude throughout his treatment." – *Sharyn, mother of 17 yr old*

Conclusion

Osteosarcoma requires many hospitalizations for planned chemotherapy. We have found that it is feasible to administer the HD MTX cycles in our outpatient department. Patients receiving outpatient HD MTX have similar rates of clearance at 72 hours as patients treated inpatient. 7% of outpatient cycles required admission for elevated 24 hour MTX level. All but one patient was successfully re-challenged with outpatient chemotherapy. Patients and families express satisfaction with the outpatient chemotherapy experience.

Resources

1. https://infusystem.com
2. Ottaviani G., Jaffe N. (2009) The Epidemiology of Osteosarcoma. In: Jaffe N., Bruland O., Bielack S. (eds) Pediatric and Adolescent Osteosarcoma. Cancer Treatment and Research, vol 152. Springer, Boston, MA

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