Safety Analysis of High-Dose Methotrexate in Pediatric Non-Hodgkin Lymphomas

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Abstract

High-dose methotrexate (HD-MTX) with rigorous supportive care is essential to the treatment of pediatric non-Hodgkin lymphomas (NHL). We describe the safety and tolerability of HD-MTX in patients with NHL treated at our center. In our cohort of 46 patients, the majority had at least one course of delayed clearance and/or creatinine elevation. Additionally, more than one-third of patients experienced an episode of grade [?]3 mucositis. Creatinine elevations and delayed clearance were independently associated with subsequent grade [?]3 mucositis. We advocate for greater availability of methotrexate monitoring to allow dose escalation of this essential modality around the world.

Introduction

Most children diagnosed with non-Hodgkin lymphoma (NHL) in high-income countries are expected to achieve long-term survival; however, children in lower income countries are diagnosed with NHL at a disproportionally higher rate and do not experience the same chance for cure. [1-10] This disparity is related to many factors, including late disease detection and challenges in delivering high-intensity treatment, such as methotrexate.[3] High-dose methotrexate (HD-MTX; 1-8 g/m^2) is an essential component of pediatric mature B-cell and T-cell NHL treatment.[11] The use of HD-MTX in lower income countries has been challenging due to treatment-related mortality at doses of 1-2 g/m^2, yet even higher doses are needed to adequately treat NHL. This discrepancy may reflect differences in healthcare infrastructure and supportive care interventions which permit safe administration of HD-MTX, such as real-time monitoring of methotrexate levels.[3] Some centers have administered HD-MTX in sub-Saharan Africa with aggressive supportive care in the absence of methotrexate monitoring, though with significant treatment-related toxicity and mortality.[1] The purpose of this study was to describe the real-world clinical safety of HD-MTX in patients with NHL where aggressive supportive care was readily available. Our overarching goal is to provide a greater understanding of the safety of HD-MTX in NHL, to inform potential treatment approaches in limited resource settings.

Methods

This retrospective chart review evaluated pediatric patients with mature B/T-cell NHL who received intravenous HD-MTX (3 g/m^2/dose intravenously over 3 hours) from October 1, 2010 through June 30, 2020 at Texas Children's Hospital. Patients were excluded from data analysis if they received an empiric

methotrexate dose reduction. All data were abstracted from the electronic health record, including diagnosis, race/ethnicity, age, height and weight at diagnosis; dose and timing of HD-MTX administration; relevant laboratory details (i.e., serum creatinine, methotrexate levels, urine pH and specific gravity); select supportive care interventions (i.e., leucovorin, hydration, alkalization, glucarpidase, concomitant medications); tumor lysis syndrome; and vital status. Body surface area and body mass index were calculated from extracted variables. The primary outcome was delayed methotrexate clearance, defined by a methotrexate level above the protocol-defined clearance threshold at hour 48. Secondary outcomes included the time to clearance, frequency of serum creatinine elevations (i.e., an increase [?]25% after start of methotrexate), and incidence of Common Terminology Criteria for Adverse Events (version 5.0) grade [?]3 mucositis. Planned exploratory analysis included evaluation of risk factors associated with delayed clearance of methotrexate, serum creatinine elevations, and mucositis.

The frequency of each methotrexate-associated toxicity was summarized by the number of methotrexate doses resulting in each toxicity and number of patients who experienced the toxicity following any HD-MTX. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the associations between clinical characteristics and the development of each outcome (delayed clearance, creatinine elevations, and mucositis) were calculated using multivariable mixed-effects logistic regression to account for repeated measures following each methotrexate infusion within each patient. A mixed-effects linear regression model was constructed to evaluate associations with time to methotrexate clearance. A step-wise selection process was used to identify a parsimonious model including age, race/ethnicity, and other clinical features associated (p-value<0.2) with one or more of the outcomes in unadjusted models. All analyses were conducted using Stata SE version 15.1 (College Station, TX) at a two-sided significance level of 0.05. This study was approved by Institutional Review Board at Baylor College of Medicine.

Results

Patient population

During the study period, 196 HD-MTX doses were administered to 46 unique patients. Overall, patients included in the analysis were 39% non-Latino White, 33% Latino, and 24% non-Latino Black (Table 1). The mean age of the cohort was 10.5 years at diagnosis, and a majority patients were male (n=34; 74%). The most common oncologic diagnosis was anaplastic large cell lymphoma (ALCL; n=25, 54%), followed by 21 patients (46%) with mature B-NHL, and one patient with peripheral T-cell lymphoma, NOS. The median number of HD-MTX doses per patient was 4 (range: 1 to 6). All patients were treated on or according to one of the following protocols: ALCL99, ANHL12P1, ANHL01P1, and ANHL1131.[8, 10, 12, 13] All patients received protocol-defined supportive care as previously described,[8, 10, 12, 13] including intravenous hydration with alkalinized intravenous fluids, urine pH and output goals, scheduled leucovorin rescue, serum creatinine trending, and methotrexate serum level monitoring at hours 24, 48 and at least every 24 hours until methotrexate level <0.1 or 0.15 μM/L (per protocol). Supportive care interventions for methotrexate clearance were adjusted to achieve therapeutic goals per institutional practice or clinical trial protocol. Patients were counseled on good oral care and given a salt and soda mouthwash for mucositis prevention. Forty-one patients were alive at the time of data extraction (89%). No patient died due to methotrexate-related toxicity.

Toxicities

Methotrexate cleared on time in 76.5% of doses (Table 2). The 46 doses which resulted in delayed clearance occurred in 26 patients (56.5%). Of these, methotrexate cleared by hour 72 in 26 doses, with 20 doses clearing beyond hour 72 (range: 84 to 256 hours). Grade [?]3 mucositis occurred following 25 doses of HD-MTX (13% of all doses administered) in 18 patients (39.1%). Serum creatinine elevations occurred during 48 HD-MTX doses (24%) in 27 patients (58.7%). Creatinine elevations were transient and returned to baseline in all patients, due to early recognition and appropriate increases in hydration. Creatinine elevations were

significantly associated (p<0.001) with an increased likelihood of delayed clearance (OR=4.44, 95% CI: 1.82-10.84) after accounting for clinical factors. Additionally, creatinine elevations (OR=4.36, 95% CI: 1.44-13.25) and delayed clearance (OR=6.24, 95% CI: 2.17-17.95) were independently associated with subsequent grade [?]3 mucositis. No patient required glucarpidase for methotrexate toxicity or delayed clearance. There was no observed association between race/ethnicity and time to clearance, serum creatinine elevations, or mucositis. There was an observed association (p<0.05) of self-reported Latino ethnicity and shorter time to clearance, as well as a potentially increased time to clearance in patients receiving R-CYM cycles in ANHL01P1 and ANHL1131, and an increased risk of serum creatinine elevations observed during methotrexate in patients receiving courses of R-COPADM in ANHL01P1 and ANHL1131.

Discussion

We describe the clinical safety of HD-MTX in a cohort of children and adolescents with NHL treated with routine clinical care at a large tertiary center. We found that about a quarter of HD-MTX doses resulted in delayed clearance, though overall more than half of all patients experienced this during treatment. Similarly, about a quarter of all doses were associated with methotrexate-related serum creatinine elevations, again impacting more than half of all patients. Although 18% of doses were complicated by grade [?]3 mucositis, this impacted nearly 40% of patients in our cohort. Importantly, creatinine elevations and delayed clearance were independently associated with subsequent grade [?]3 mucositis, signifying the importance of early recognition and intervention in patients receiving HD-MTX. Our data are limited by the retrospective, single-center study design and relatively small sample size. In our practice, we can rapidly respond to methotrexate levels and serum creatinine elevations by adjusting intravenous fluids and/or modifying leucovorin rescue, potentially preventing therapeutic morbidity and mortality, though this takes considerable resources (staffing, laboratory capability, and clinical expertise). We strongly advocate for expanded access to methotrexate therapeutic monitoring globally, such that children in limited resource settings, who are most prominently impacted by NHL are given equitable access to this essential modality.

Conflict of Interest statement:

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