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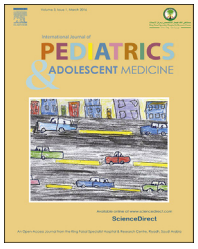

Original Research Article

The frequency of hepatotoxicity and myelotoxicity in leukemic children with different high doses of methotrexate

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Abstract *Objective:* Methotrexate (MTX) is a chemotherapeutic agent that functions as a folic acid antagonist. The frequency of high dose methotrexate (HDMTX)-associated toxicity is variable. In this study, we investigated the frequency of myelosuppression and hepatotoxicity 7 days after HDMTX infusion.

Methods: This study included children diagnosed with acute lymphoblastic leukemia (ALL) between January 2010 and April 2015. The patient blood counts and biochemical parameters measured before and after 7 days of HDMTX infusion were retrospectively recorded. We assessed HDMTX infusions for 48 children. The number of patients and drug doses included the following: 17 children receiving 1 g/m^2 (68 infusions), 14 children receiving 2 g/m^2 (56 infusions), and 17 children receiving 5 g/m^2 (68 infusions). The classification of toxicity was made based on the Common Terminology Criteria for Adverse Events (CTCAE) 2010 criteria. Myelosuppression was defined as a hemoglobin level <10 g/L and absolute neutrophil count $<1 \times 10^9$/L or platelet count $<75 \times 10^9$/L. The presence of transaminase levels ≥ 5 times the upper limit was considered to be hepatotoxicity grade ≥ 3. The MTX levels at 42 h in patients with and without toxicity were compared to evaluate the correlation between MTX levels, hematologic parameters and transaminase levels.

Results: Myelotoxicity was observed in 35.2%, 37.5%, and 33.8% of the infusions and hepatotoxicity grade ≥ 3 was detected in 13.2%, 12.5% and 11.7% of the infusions in patients receiving 1, 2 and 5 g/m^2 HDMTX after 7 days, respectively. There was no statistically significant difference between MTX levels at 42 h in patients with and without toxicity ($P > .05$, for all). There was no correlation between hematologic parameters and transaminase levels and MTX levels at 42 h.

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Conclusion: Hematologic toxicity was the most common toxicity observed. The data indicate the hematologic toxicity increased after repeated cycles in patients receiving 5 g/m^2. However, the hepatic toxicity decreased with additional cycles. Our results show the level of MTX at 42 h is not effective to identify toxicity.

1. Introduction

Methotrexate inhibits dihydrofolate reductase and was initially developed as an anti-cancer treatment in the 1940s [1]. The most commonly described side-effects of high dose methotrexate (HDMTX) therapy are myelosuppression, oral mucositis, and acute liver toxicity with transient elevation of transaminase levels [1]. These adverse effects increase the risk of infection, which can delay the scheduled therapy. There is a difference between methotrexate (MTX) associated myelosuppression and toxicity. MTX-associated toxicity is related to several factors including drug dose, the duration of administration, patient risk factors, and genetic factors [2,3]. In addition, the criteria used to assess toxicity are variable. For example, a study showed the most common toxicity was hematologic toxicity and 64–87% of the patients developed grade 3 and higher toxicity [3,4]. The incidence of transient high levels of transaminase was reported as 64% [5]. There are currently no data regarding the use of HDMTX pharmacokinetic and toxicity information to predict hepatic and hematologic toxicity in children with acute lymphoblastic leukemia. Csordas et al [6] determined there is no correlation between MTX level and hematologic toxicity. However, Rask et al [4] reported there is a relationship between elevated serum MTX levels and hematologic toxicity.

In this study, we aimed to determine the hepatic and hematologic toxicity frequency and assessed whether there is a significant relationship between treatment toxicity and MTX_{42} levels in children taking different doses of HDMTX.

2. Materials and methods

This study included 48 children diagnosed with ALL at Eskişehir Osmangazi University Faculty of Medicine, Pediatric Hematology/Oncology Department between January 2010 and April 2015. The age, gender, leukemia immune phenotype, and the administered HDMTX doses were retrospectively recorded from the file records. The patient hemoglobin (Hb), absolute neutrophil count (ANC), platelet (PLT) count and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were recorded before MTX administration and on the 7th day following drug infusion.

The patients were stratified into three risk groups. The first risk group was defined using the following criteria: (1) Standard risk (SR) patients have an initial leukocyte count $< 20 \times 10^9$/L and age $\geq$1 year or <6 years and absolute blast count in the peripheral blood on day 8 after 7 days of prednisolone treatment $<1 \times 10^9$/L and M1 (<5% blasts) or M2 ($\geq$5% to< 25% blasts) marrow on day 15, and M1 marrow on day 33 (all criteria must be fulfilled). The second group (2) was the high risk (HR) group and is defined as at least one of the following: absolute blast count in the peripheral blood on day 8 after 7 days of prednisolone treatment $>1 \times 10^9$/L, M3 marrow on day 15, M2 or M3 marrow on day 33, t (9; 22) (BCR-ABL), or t (4; 11) (MLL-AF4), or hypodiploidy $\leq$ 45. The third group (3) was the Intermediate risk (IR) grouped and was defined as the patients who were classified as neither SR nor HR. The HR patients were not included in the study because their consolidation treatment is different.

All patients received 4 HDMTX infusions at 2-week intervals on days 8, 22, 36, and 50 of the consolidation phase. The patients also received oral 6-mercaptopurine (6MP) at a dose of 25 mg/m^2/day continuously during the consolidation phase of chemotherapy in addition to HDMTX. Any concurrent treatment with trimoxazole was paused in all patients 2 days before and 3 days after the HDTMX infusion. We excluded patients whose absolute neutrophil count was $<1 \times 10^9$/L with a platelet count $<75 \times 10^9$/L or had liver function tests above the upper limits before the HDMTX infusion.

The patients received 3 different doses of HDMTX. The preB ALL SR patients received 2 g/m^2, which is in accordance with the ALL-IC BFM 2009 protocol. The preB ALL IR and T ALL SR/IR patients received 5 g/m^2 of HDTMX. According to BFM TRALL 2000 protocol, preB ALL SR/IR patients received 1 g/m^2 of HDTMX. As per BFM TRALL 2000 protocol the 1 g/m^2 was given within 36 h and as per the ALLIC BFM 2009 protocol the doses of 2 and 5 g/m^2 were administered via 24-h of infusion. Alkalization was used to maintain the urine pH $\geq$ 7 from −4 h through +72 h after the start of the MTX infusion. The urine was tested by dipstick. Briefly, a bolus infusion of 2 mmol/kg $NaHCO_3$ with 2 ml/kg distilled water was delivered over 1 h. Thereafter, 500 ml 0.45% NaCl/5% dextrose +40 mmol $NaHCO_3$ + 10 ml KCl 7.45% hydration fluid was administered during 4 h. The HDMTX infusion was started only when a urine pH was greater than 7. The bolus infusion was repeated if the urine pH was less than 7. All patients received a loading dose of methotrexate as 1/10 of the total MTX dose over 30 min. The remaining 9/10 dose was given over the following 23 h 30 min or 35 h 30 min for children treated with 2 g/m^2, 5 g/m^2 and 1 g/m^2, respectively. We provided a total 3000 ml/m^2 parallel hydration with 0.45% NaCl/5% dextrose containing $NaHCO_3$ (180 mmol/m^2/24 h) + KCl 7.45% (90 ml/m^2/24 h) during the 72 h or 48 h to children treated with 2 g/m^2, 5 g/m^2 and 1 g/m^2, respectively.

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