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Re-challenge with High Dose Methotrexate vs. Reduced Dose After Methotrexate Toxicity in Pediatric Osteosarcoma: Case Report

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***Abstract*-- Introduction:** Methotrexate (MTX), a classic antifolate, is one of the most widely used and well-studied anticancer agents. High-dose methotrexate (HD-MTX) with folinic acid (leucovorin) rescue is one of the standard therapies for osteosarcoma. High-dose methotrexate (HDMTX) can exert significant toxicity and requires complex pharmacokinetic monitoring and leucovorin rescue. The side effect profile of MTX varies markedly according to the dose. Regimens containing MTX are classified as high, intermediate, or low-dose. High-dose methotrexate (HD-MTX; 12 g/m2) is a part of the golden standard therapy for pediatric osteosarcoma (OS). Risk factors associated with MTX toxicity in children with OS are not well defined. **Case Presentation:** We report here a case of pediatric osteosarcoma with nephrotoxicity associated with delayed MTX excretion who was successfully managed using supportive measures that encouraged us to re-challenge with a full dose of MTX then we reduced the dose to 50% to attain the final critical decision about continuation or changing the regimen of treatment for the patient. Our patient developed moderate renal complications during therapy that improved with supportive care, so we challenged with more cycles of a high dose MTX, but the patient developed serious renal complications. A reduced dose of MTX with 50% was given successfully without any renal impairment. **Conclusion:** Methotrexate toxicity that might not occur during the initial courses of high-dose MTX is not a predictive of the tolerability of further courses and re-challenging with HDMTX is risky, but reduced dose methotrexate is a good option rather than changing the regimen, with good tolerability and rapid clearance of HDMTX. HDMTX-induced renal impairment occurs in a low percentage of patients with osteosarcoma and can be managed successfully by maximum supportive care. MTX clearance can be affected by gender and age.

Keywords: Methotrexate toxicity, Osteosarcoma, Management

1. Introduction

High-dose methotrexate (HDMTX) with folinic acid (leucovorin) rescue is an important chemotherapy that is considered as a cornerstone in the regimen used to treat osteosarcoma [1]. The five-year survival rate in osteosarcoma patients treated with neoadjuvant therapy HDMTX (8–12 g/m2) was 65–75%, and HDMTX is the most effective single agent with a response rate of approximately 30% [2]. The administration of MTX doses 1000 mg/m2 or higher combined with leucovorin (LV) rescue is defined as high-dose methotrexate (HDMTX) [3]. Careful monitoring of drug clearance and extended supportive care to prevent adverse complications are essentially needed [4]. Hydration, alkalinization, and leucovorin rescue are essential for routine clinical administration and in spite of that, delayed excretion of methotrexate (MTX) can occur causing oral mucositis, increased liver enzymes levels, neurotoxicity, gastrointestinal reactions, and hematologic toxicity [3, 5]. Individual monitoring of the methotrexate (MTX) serum levels enables appropriate alterations of the leucovorin dosage helping to avoid potential life-threatening toxicities [5]. Two main therapeutic strategies have been proposed to decrease the risk of severe complications in such cases. First, carboxypeptidase G2 (CPDG2) is used to rapidly hydrolyze MTX to non-active and non-toxic metabolites. Second, aminophylline has been successfully administered to patients with acute neurotoxicity related to MTX [6].

2. Case Presentation

We present a case of a 13 years-old girl, diagnosed with non-metastatic osteosarcoma of the right proximal tibia. Initially before starting chemotherapy, all her blood work up and organ functions including GFR were within normal limits. The patient started the chemotherapy protocol EURAMOS 1 which includes a total of 12 cycles of HDMTX alternating with 4 cycles of platinum/ anthracycline, and 2 cycles of anthracycline without platinum chemotherapy. High dose methotrexate (HDMTX) was defined by a dose of 12 g/m2 administered intravenously over 4 hours, while being associated with hydration using 3 L/m2 of D5% + 0.45% saline containing 40 mmol/L NaHCO3 and 20 mmol/L of KCL that starts 6 hours before the beginning of HDMTX and continues till the safe level of MTX is obtained. Moreover, urine pH was always maintained >7. The patients received Platinum/ Anthracycline; Cisplatin (60mg/m2) day 1, Doxorubicin (37.5mg/m2/day) days 1 and 2. Doxorubicin was

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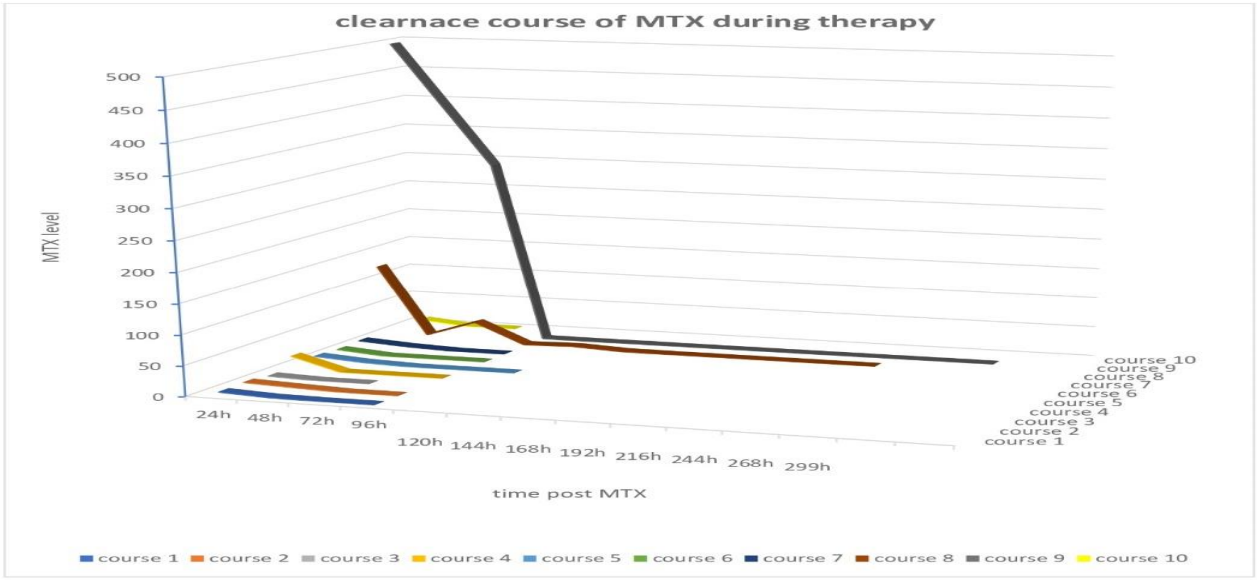

Figure 1. Clearance course of methotrexate during therapy.

solely used without Platinum (37.5mg/m2/day) in days 1 and 2.

As neoadjuvant chemotherapy, the patient received 4 cycles of HDMTX and 2 cycles of Platinum/ Anthracycline. Local control was done with limb salvage (right proximal tibia) resection surgery. The histopathology report reported residual spindle cells with an extensive treatment effect of approximately 75% necrosis. As adjuvant chemotherapy, she received 3 cycles of HDMTX, the 7 cycles of HDMTX went uneventfully with normal and rapid MTX clearance (figure 1).

Furthermore, the eighth cycle of HDMTX was administered but the 24-hours MTX level was 128 µmol/L and serum creatinine raised up to 98 µmol/L, while baseline creatinine was ranging around 30 µmol/L. Accordingly as per protocol, it was considered as severe toxicity (grade III). Hydration was increased to 200 ml/m2/hr and leucovorin was escalated to 150 mg/m2 every 3 hours instead of 15 mg/m2 every 6 hours. The patient was followed up clinically and did not experience any oral mucositis, vomiting or leukopenia. Over the following days MTX levels were decreasing very gradually and slowly reaching to a safe level <0.1 µmol/L after 9 days of leucovorin rescue, while creatinine levels normalized after the same duration. It is worth mentioning that Glucarpidase was not used as it was not available at that time.

Despite the alarming sign of increasing MTX levels following the eighth cycle, the ninth cycle was given as a challenge in full dose of HDMTX, but also showed shouting MTX grade III toxicity as the 24-hours MTX level was 500 µmol/L and creatinine was elevated reaching to 107 µmol/L. There was no history of using any concomitant nephrotoxic medications. Again, the patients received proper hydration and the dose of leucovorin was increased while following up on the patient till MTX safe levels which were achieved 15 days after leucovorin rescue and creatinine was reduced to normal.

Due to the previously mentioned toxicity, the tenth cycle of HDMTX was given with a 50% reduction (6 g/m2) and it passed uneventfully with 24-hours a MTX level of 8 µmol/L and creatinine of 52 µmol/L. Furthermore, MTX safe levels (0.09 µmol/L) were achieved over 72 hours as demonstrated in **figure 1.** In the light of these data, the plan was to continue the remaining doses of HDMTX with a 50% reduction of the standard dose.

3. Discussion

HDMTX-induced renal impairment occurs in approximately 1.8% of patients with osteosarcoma who are treated on common protocols with maximum supportive care [3]. There are risk factors that can be taken into consideration to expect delayed MTX clearance. The incidence of severe delayed excretion of MTX is associated with gender, age, and serum concentrations at 24 hours [1].

In our case, the patient received 7 courses of HDMTX without any associated toxicity. Afterwards in the eighth cycle, she started to have a delayed excretion of MTX as an alarming sign of renal impairment. Nevertheless, the ninth cycle was given as full dose of HDMTX because the patient was classified to have a poor prognosis and we did not want to lose chemotherapy and the omission of MTX can greatly affect the survival. Therefore, we re-challenged with full dose of HDMTX during the ninth course hoping to pass without major complications. However, the patient developed serious complications with shouting levels of MTX associated with renal impairment and low urine output, as well as grade III oral mucositis. So, the decision was to challenge with a reduced dose of MTX as a trial before changing the regimen. The patient received the ten courses of HDMTX with rapid clearance of MTX within 3 days and without toxicities related to MTX.

The patient was successfully managed using supportive measures. However, the factors that predisposed the patient to delayed MTX excretion were unclear in this case. Recent reported findings demonstrated an association between age or gender and treatment toxicity [7]. Moreover, there is a strong

association between race/ethnicity and adverse treatment outcomes suggesting an intrinsic genetic disposition to MTX therapy [7-9].

In most of the cases, after administration of MTX, when the renal function is normal, more than 90% of the administered MTX combines with albumin and is excreted in the urine within 12 hours [5, 10]. The serum levels of MTX are supposed to reflect the drug concentration in tumor cells, and if leucovorin is administered in high dosages, there is a possibility that tumor cells might be rescued [5, 11]. Leucovorin alone may not prevent the development of life-threatening toxicities and in some instances. Moreover, treatment with Leucovorin every 6 hours can be associated with cardiac arrhythmias resulting from hypercalcemia [6]. Demonstrated effective methods to prevent or reduce MTX toxicity include hydration, Leucovorin rescue, urinary alkalinization, and therapeutic monitoring [7].

4. Conclusion

MTX toxicity that might not occur during the initial courses of high-dose MTX is not predictive of the tolerability in further courses. Re-challenging with HDMTX is risky and may cause serious and life-threatening toxicity. However, reduced dose methotrexate is a good option rather than changing the regimen, with good tolerability and rapid clearance of HDMTX.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions: All authors contributed to the case report conception, design and data collection. The manuscript was written by WI and AAM then reviewed and supervised by YE and NA. All authors read and approved the final manuscript.

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