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Reversible Impaired Methotrexate Clearance After Platinum-Based Chemotherapy for Osteosarcoma

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Abstract: The authors present a case of an 18-year-old man with metastasized osteosarcoma, admitted for methotrexate (MTX) treatment combined with cisplatin and doxorubicin. During the first cycle, severe MTX toxicity was observed with increased MTX serum levels and delayed MTX clearance requiring rescue treatment with intensified leucovorin. In the following cycles, cisplatin and doxorubicin were discontinued, and MTX dose was reduced. The elimination half-life slowly improved over the following cycles suggesting a reversible cause responsible for reduced MTX clearance and toxicity during the first cycle. Cisplatin is well-known for its nephrotoxic effects and can induce reversible tubular injury. Previous treatment with cisplatin may well have been responsible for decreased MTX clearance, and combination treatment should be used with adequate monitoring of MTX levels. Other factors that may have contributed, such as urine alkalization, gene polymorphisms, and other drug–drug interactions are discussed.

Key Words: methotrexate, osteosarcoma, therapeutic drug monitoring

CLINICIAN
An 18-year-old man was admitted for the treatment of high-grade osteosarcoma of the right femur with pulmonary metastases. He was previously treated with neoadjuvant chemotherapy consisting of cisplatin plus doxorubicin with poor response (>10% vital tumor cells at resection). Methotrexate (MTX) was added to the adjuvant treatment, at a dose of 12 g/m2 intravenously in 6 hours on days 21 and 28, with doxorubicin and cisplatin on days 1–3, in a 5-weekly regimen. Hydration, urine alkalization, and leucovorin rescue were given according to local protocol. Serum MTX levels were 4.99, 2.94, and 1.16 μmol/L at 48, 72, and 96 hours, respectively, after dose (Fig. 1). A decrease in renal function was observed at 72–96 hours (eGFR decreasing from 130 to 96 mL/min/1.73 m2). In addition, MTX was complicated by severe mucositis for which intravenous antibiotics and morphine were started and mild hepatotoxicity (ASAT and ALAT 4 × ULN). Given the high serum MTX levels and toxicity of the treatment, could this patient be a slow metabolizer of MTX and would an increase in the leucovorin dose be valuable?

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The 48-hour MTX concentration of 4.99 μmol/L exceeds the 1 μmol/L threshold for toxicity at 48 hours.1 Together with a calculated increased terminal elimination half-life of 30 hours (reference value 8–12 hours),2,3 this indicates that the patient is suffering from reduced MTX clearance and is at risk for toxicity. For effective rescue from MTX toxicity, high intracellular leucovorin concentrations are required. Because both MTX and leucovorin enter cells by the reduced folate carrier, this competition results in low intracellular leucovorin concentrations in situations of reduced MTX clearance, and leucovorin dose should be increased. Furthermore, hydration and urine alkalization should be continued.

Reduced MTX clearance can have multiple causes, among which drug–drug interactions, impaired renal clearance, third space accumulation, and genetic polymorphisms. Of the possible drug–drug interactions, piperacillin/tazobactam, which was started at 48 hours, has been reported to reduce MTX clearance and induce MTX toxicity.4 Piperacillin is a suspected nephrotoxin5,6 and an inhibitor of OAT1/3.7 MTX is 90% excreted unchanged in urine, and transport is mainly dependent on OAT1 and OAT3.8 As a result, piperacillin may have contributed to delayed MTX elimination. However, since high MTX concentrations and toxicity were already present at the start of piperacillin treatment, other factors must be involved. With an eGFR decrease from 130 to 96 mL/min/1.73 m2, renal function was still within the normal range making it less likely to be a direct cause for reduced MTX clearance. If the patient has a “third space fluid” such as pleural fluid or ascites, MTX will accumulate in this compartment with subsequent slow redistribution resulting in a prolonged elimination half-life.9 Another potential factor is MTX intratubular crystallization, for example, due to urine pH < 7, which was observed once in the first 24 hours despite proper urine alkalization (see Figure 1, Supplemental Digital Content 1, http://links.lww.com/TDM/A348). Finally, also genetic polymorphisms in
Transporters and enzyme genes can alter MTX clearance, although there is currently no consensus on clinical impact.

**Clinician**

There were no clinical signs of a third space in which MTX could have accumulated. Leucovorin was increased to 100 mg intravenously every 3 hours. The patient recovered slowly, renal function normalized (to 133 mL/min/1.73 m²), and liver enzymes improved to 1.73, 0.56, and 0.26 μmol/L at 24, 48, and 72 hours after dose (elimination half-life 22 hours, Fig. 1). The patient had no complaints, renal function remained stable, and liver enzymes did not deteriorate. It was decided to discontinue cisplatin and doxorubicin given the lack of benefit in the neoadjuvant setting and signs of progressive disease at a repeated CT scan. MTX was continued in a 2-weekly schedule. With regard to current MTX levels and half-life, would you advise to increase the dose?

**TDM Consultant**

The mechanism responsible for the reduced elimination half-life in the first MTX course was not entirely clear and therefore could still be present. Together with the toxicity of the first MTX course, this involves a risk for severe toxicity when the full MTX dose is given again. Although MTX dose reductions are not generally recommended, an arbitrary dose reduction of 50% is advisable for the second course to avoid further MTX toxicity. To ensure that the reduced MTX dose reaches an effective concentration (peak value > 700 μmol/L), 11 MTX concentration measurement at the end of infusion is recommended.

**Clinician**

The patient received the second dose of MTX at a dose of 6 g/m². Peak MTX level at the end of administration was 226 μmol/L. Serum MTX levels were 1.73, 0.56, and 0.26 μmol/L at 24, 48, and 72 hours after dose (elimination half-life 22 hours, Fig. 1). The patient had no complaints, renal function remained stable, and liver enzymes did not deteriorate. It was decided to discontinue cisplatin and doxorubicin given the lack of benefit in the neoadjuvant setting and signs of progressive disease at a repeated CT scan. MTX was continued in a 2-weekly schedule. With regard to current MTX levels and half-life, would you advise to increase the dose?

**TDM Consultant**

The peak MTX serum concentration was well below the target peak concentration, supporting a dose increase. Furthermore, the lack of toxicity, the stable renal function, and the improved MTX clearance indicate that the dose can be increased to 75%. The improvement of the MTX clearance is of interest because this indicates a reversible etiology of the observed toxicity during the first cycle. Genetic polymorphisms can therefore be considered very unlikely. One reversible factor that could have reduced MTX clearance is recent therapy with cisplatin-based chemotherapy, especially when the cumulative cisplatin dose is > 200 mg/m².12 Our patient had received a cumulative dose of 400 mg/m² cisplatin before the initiation of MTX treatment, and the last cisplatin dose was administered 20 days before the first MTX dose. Cisplatin is well-known for its nephrotoxic effects, can induce reversible tubular injury, and is slowly eliminated.13 Although cisplatin is also substrate for OAT1 and OAT3, there is no evidence for an inhibitory effect of cisplatin on OAT1 and OAT3.14

**Clinician**

The MTX dose was increased to 9 g/m². The peak serum MTX level was 617 μmol/L. MTX levels were 3.62, 1.01, and 0.74 μmol/L at 24, 48, and 72 hours after dose with an MTX elimination half-life of 18 hours. The patient had no complaints, renal function remained stable, but liver enzymes increased slightly (ASAT >2 × ULN and ALAT >3 × ULN).
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The peak MTX serum concentration of 617 \mu mol/L is close to the target concentration of 700 \mu mol/L, however, has increased by a factor of 2.7 after a dose increase from 50% to 75%. The nonlinear rise in peak MTX serum concentration, together with the slight increase in liver enzymes, creates prudence in further dose escalation. Using MwPharm as population pharmacokinetic modeling software,\textsuperscript{15} the next dose recommendation was based on modeling the patients’ data from the previous 3 MTX doses. The scenario of an increase to an 85% dose (10.2 g/m\textsuperscript{2}) predicted an adequate peak MTX serum concentration of \textgt;700 \mu mol/L.

CONCLUSIONS

Although based on pharmacokinetic modeling, it was advised to increase the MTX dose to 85%, liver enzymes remained increased \textgt;2 \times ULN, and therefore, MTX was not escalated. During the remaining 2 cycles, the half-life normalized to 10–15 hours and peak MTX serum concentration reached 606 and 661 \mu mol/L. Given the reversibility of the reduced MTX clearance, we consider the earlier treatment with cisplatin-based chemotherapy as one of the most-likely factors that may have contributed to MTX toxicity observed during the first cycle. Other factors that may have contributed are reduced renal clearance due to co-administration of piperacillin-tazobactam, and inadequate urine pH alkalization.

Treatment combinations such as cisplatin, doxorubicin, and MTX are widely used in the perioperative setting in osteosarcoma.\textsuperscript{15} Given\textsuperscript{16} the possibility of increased MTX exposure, combination with cisplatin-based chemotherapy should be used with caution. Strict monitoring of MTX concentrations is indicated with a first MTX measurement not later than 24 hours from start of MTX infusion and, if necessary, adjustment of leucovorin doses. In cases of MTX toxicity, individualized MTX dosing based on therapeutic drug monitoring is an option to improve the individual benefit–risk ratio.

In our patient, there was unfortunately insufficient response to MTX to allow curative surgical treatment.

REFERENCES