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Successful management of acute renal failure after high-dose methotrexate in a patient with relapsed osteosarcoma

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Summary

Background: The incidence of reported acute renal failure (ARF) due to methotrexate is about 1.8%. Although standard of care of this condition includes hyperhidration and leucovorin rescue, hemodialysis may be considered in some cases.

Case Report: We present the case of a 13-year-old girl with a relapsed osteosarcoma three months after the end of first treatment. Three pulmonary nodes were removed and after she received intravenous methotrexate (12 g/m^2) she developed a severe ARF, seizures and pancytopenia. The patient underwent to hemodialysis and folinic acid rescue. She recovered and is in complete remission with normal renal function 60 months after the end of the treatment.

Conclusions: Although the indication of hemodialysis is not a consensus, we suggest this procedure should be indicated to treat severe ARF due to methotrexate when Carboxypeptidase G2 is not readily available.

Key words: **osteosarcoma • methotrexate – adverse effects • acute renal failure (ARF) • hemodialysis**

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Background

High-dose methotrexate (MTX) is frequently included in the treatment of osteosarcoma [1]. Following intravenous high dosages, approximately 50 to 60% of this drug is bound to plasma proteins and more than 50% of MTX is excreted unchanged in the urine [2].

The most common side effects of MTX are mucositis of varying degrees and liver toxicity. Leukopenia, thrombocytopenia, severe mucositis, diarrhea, skin rash or renal dysfunction are not usually observed if prevention based on hydration and urine alkalization are adequately administrated [2, 3].

The reported incidence of acute renal failure (ARF) due to MTX is about 1.8% [4]. The mechanism of renal damage seems to be the intratubular precipitation of crystals produced by MTX and the consequence is usually a persistence of high serum levels of the drug [5].

The aim of this report is to describe the management of a patient who developed ARF following high dose MTX administration.

Case Report

A 13-years-old girl with a localized osteosarcoma of the tibia was treated with the combination of adriamycin and cisplatin (120 mg/m2 x 6 courses) and surgical resection of the primary tumor. There was no relevant toxicity during this period of chemotherapy. Three months after the end of the treatment, three pulmonary nodes were removed and the histological analysis identified a relapse. We decided to administrate high dose MTX. The serum creatinine at the start of therapy was 0.8 μmol/L. She received the first dose of 12 g/m^2 IV over 6 hours after appropriate prehydration and alcalinization. The urinary pH was 7.0 at the time of MTX infusion. The posthydration consisted of 125ml/m^2/h of continuous fluid infusion.

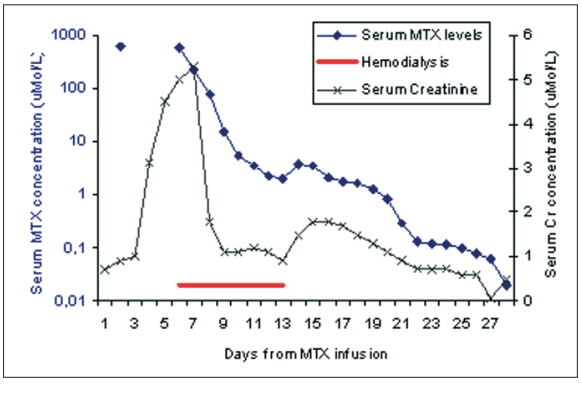

Figure 1. Initial and subsequent MTX and creatinine serum values.

Twelve hours after beginning the chemotherapy infusion the patient developed sobs and vomiting. The serum creatinine and MTX serum levels 24 hours after the initiation of the drug infusion were 3.1 μmol/L and 590 μmol/L, respectively. Serum electrolytes were normal. Aggressive hydration and urine alkalization was sustained and the leucovorin dose was increased from 60 to 240 mg/m^2/day in 6 divided doses.

Three days after the high-dose MTX infusion, the patient presented a prolonged tonic-clonic seizure requiring mechanical ventilatory support. The serum creatinine increased to 5 μmol/L and the MTX levels was 570 μmol/L at hour 80 instead the hydration and urine pH was 7.5. The urine output during this time was normal. The patient was then submitted to a continuous hemodialysis for 8 days and the serum concentration of the drug decreased to 230, 80, 15 and 5,5 μmol/L at one, two, three, and four days, respectively, after this procedure. The initial and subsequent MTX and creatinine serum values are illustrated on Figure 1. The leucovorin rescue was continued during hemodialysis.

Only mild mucositis was noted five days after MTX beginning but persistent severe pancytopenia developed, as illustrated on Figure 2. Leukocyte counts less than 500 x 10^6/μL lasted for 12 days (from day 6 to day 18), despite the use of G-CSF. The lowest platelet level was 6,000 x 10^6/μL requiring platelets transfusions. The hemoglobin levels also decreased to levels of 6.6 g/dL and the patient received two red blood cell transfusions. Broad antibiotics were necessary for 13 days due to fever and neutropenia but no infectious agent was isolated in the culture. The hemodialysis was discontinued on day 12 from the MTX infusion, when the MTX level was 2 μmol/L. She had a slowly but complete recovery of the blood counts and renal function. The patient was discharged from the hospital 29 days after the MTX infusion, with normal creatinine levels.

One month after the MTX infusion the patient started to receive five additional cycles of chemotherapy

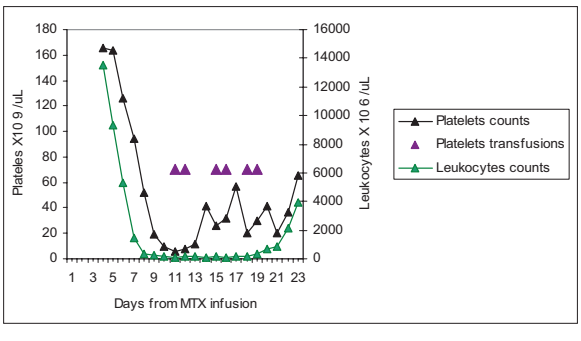

Figure 2. Leukocytes and platelets counts and platelets transfusions.

consisting of cyclophosphamide (1.2g/m2/day x 1 day) and Etoposide (165mg/m2/day x 3 days). There were no unexpected toxicities associated to these drugs.

This patient is, at the present, in complete remission, with normal creatinine clearance, 60 months after the last chemotherapy cycle.

Discussion

MTX is an antimetabolite drug that acts blocking the enzyme dihydrofolate reductase, which inhibits the conversion of folic acid to tetrahydrofolic acid which results in the arrest of DNA, RNA, and protein synthesis [2, 6]. The toxicities are related to the concentration of the drug and the duration of the exposure. The toxic reactions to high-dose MTX can be prevented with aggressive hydration and administration of leucovorin. Plasma MTX levels bellow 1 μM/L at 48-hour after the drug infusion is usually associated to moderate and manageable drug toxicities in most patients [2, 6].

Many institutions are using front-line regimens without MTX. This is particularly common in institutions with no access to MTX levels. Since front line chemotherapy usually includes cisplatin some degree of renal damage is expected. High-dose MTX is used in salvage chemotherapy but even when the serum creatinine is normal, MTX clearance is frequently delayed after cisplatin [6-8]. In this situation its administration should be carefully planned, otherwise, patients develop significant toxicity early in the treatment.

The renal function of the patient reported assessed by creatinine clearance before the drug infusion was normal, so it was prescribed the conventional dose of 12 g/m^2. Aggressive hydration and urinary alkalinization was implemented before and during the MTX infusion, however the patient presented an ARF, an unusual adverse effect after high-dose MTX.

High-dose leucovorin and also hemodialysis are recommended by some authors as a treatment strategy for these patients [3, 9]. Carboxypeptidase G2 (CPDG2), a recombinant bacterial enzyme that metabolizes MTX, has become a standard drug for the treatment of ARF induced by MTX. CPDG2 is tolerated well, appears to be relatively safe in pediatric patients undergoing HD MTX and the decrease in plasma MTX concentration is reported to be more rapid and consistent than that with dialysis-based methods [4, 10-12].

The initial management of our patient included high-dose leucovorin rescue, but due to her critical clinical condition we decided to begin hemodialysis. A continuous decrease in serum MTX and creatinine levels was observed. We considered administrating CPDG2, but unfortunately this drug is not available in our country and at that time it takes a long period to import it.

Widemann et al, after a meta-analysis, recommends CPDG2 as a first choice for patients with severe HDMTX-induced renal dysfunction with sustained plasma MTX levels >10 μM/L beyond 42 to 48 hours after the start of the MTX infusion [4, 13]. We entirely agree with their recommendation, but considering a previous report from Saland et al [9] and the effectiveness of hemodialysis observed in our patient, we suggest that this therapy should be indicated when CPDG2 is not readily available.

Conclusions

In conclusion, severe renal toxicity to MTX is an uncommon but life-regimen-related toxicity in children undergoing HDMTX. Identification of patients at risk, prompt diagnosis and institution of appropriate and medical therapy including CPDG2 reduce both morbidity and mortality. However this drug is not available commercially but can be obtained from the manufacturer on a cost recovery basis calling the clinical research company (AAI Pharma) designated to manage the treatment protocol that has been approved by the US Food and Drug Administration. Their 24-hour AAI-Pharma telephone contact number is +1-866-918-1731. The drug is usually shipped overnight [14]. We also suggest that is important to consider the risks and benefits of administer high dose MTX in patients previously exposed to cisplatin based regimen, even when the renal function tests are normal.

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