Clinical Case Study

Difficulty Measuring Methotrexate in a Patient with High-Dose Methotrexate–Induced Nephrotoxicity

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[3] Nonstandard abbreviations: HDMTX, high-dose methotrexate; MTX, methotrexate; $CPDG_2$, carboxypeptidase G_2

CASE

An 18-year-old male presented with pain and swelling in his left leg that he noted after playing football. An x-ray of the affected leg showed a destructive lesion that prompted a concern for malignancy. Subsequent tests, including magnetic resonance imaging, a bone scan, and a needle biopsy of the lesion, confirmed nonmetastatic osteosarcoma in the left proximal tibia. The patient was started on a standard regimen of chemotherapy. He received 4 cycles of high-dose methotrexate (HDMTX)[3] with leucovorin rescue and 2 cycles of cisplatin and doxorubicin, which he tolerated well. Each HDMTX course involved the intravenous administration of 20 g methotrexate (MTX) over 4 h. The patient experienced delayed MTX clearance after the first cycle but showed typical clearance after the subsequent 3 cycles. He then underwent a planned radical resection of the tumor with allograft placement. After the patient recovered from surgery, chemotherapy resumed, and the patient received 2 additional cycles of cisplatin and doxorubicin and 1 additional cycle of HDMTX. His treatment was interrupted when he had to undergo surgery for a wound infection in the affected leg. After recovery from the second surgery, the patient received a sixth HDMTX cycle. After this cycle, the patient developed acute nephrotoxicity, which was manifested by marked renal dysfunction and delayed MTX clearance. His plasma creatinine concentration increased from 0.8 mg/dL (8 mg/L) at the start of the cycle to 6.8 mg/dL (68 mg/L) after he received HDMTX. Plasma MTX concentrations were 1700 μmol/L at 24 h after infusion, 450 μmol/L at 48 h, and 350 μmol/L at 72 h. The patient was treated with aggressive hydration, diuresis, and 1500 mg leucovorin intravenously every 6 h for several days. These measures did not reduce MTX below the toxic concentration, however, and the decision was made to give the patient glucarpidase [carboxypeptidase G_2 ($CPDG_2$); BTG International] 4 days after he received the HDMTX infusion.

The laboratory experienced difficulty in reporting subsequent plasma MTX concentrations because of discrepancies in the Abbott TDx immunoassays of the MTX concentrations in serially diluted samples. For example, the plasma MTX concentration for a sample obtained after $CPDG_2$ administration and diluted with 9 volumes of diluent was 9.6 μmol/L, whereas the measured concentration was 50 μmol/L for the same sample diluted with 99 volumes of diluent.

Because MTX could not be measured accurately and because of concern for ongoing MTX toxicity, a second $CPDG_2$ dose was administered to the patient 2 days after the

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first. Five days later, the discrepancy in MTX measurements disappeared, and the laboratory was able to report subsequent plasma MTX concentrations, which were <4.5 μmol/L. Because MTX and creatinine concentrations were decreasing steadily, the decision was made to complete intravenous hydration at 170 mL/h and leucovorin rescue with 250 mg administered intravenously every 6 h at home until the MTX concentration was <0.1 μmol/L.

Questions to Consider
• What is the incidence of MTX-induced nephrotoxicity, and how is it treated?
• What is the mechanism of $CPDG_2$ action, and what is its clinical utility?
• How is MTX measured, and what is the source of the discrepancy in the patient's MTX measurements?

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the December 2010 issue of *Clinical Chemistry*. To view the case and comments online, go to http://www.clinchem.org/content/vol56/issue12 and follow the link to the Clinical Case Study and Commentaries.

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