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Severe nephrotoxicity during high-dose methotrexate administration in an adolescent with acute lymphoblastic leukemia

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ABSTRACT

High-dose methotrexate is an effective and safe therapy. It is included in the treatment regimens of various hematologic and oncologic diseases. The acute and severe toxicity of this chemotherapeutic agent is unusual. Nephrotoxicity occurs in about 2-12% of patients, associated with a slow clearance of the drug. It is usually reversible but requires an early approach.

The objective was to describe the case of a patient diagnosed with lymphoblastic leukemia who presented with acute kidney injury after the administration of high doses of methotrexate.

Keywords: *leukemia; methotrexate; acute kidney injury; drug-related side effects and adverse reactions.*

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INTRODUCTION

High doses of methotrexate are an effective and safe therapy. It is part of the treatment of several oncologic diseases.[1] With proper care, severe toxicity of this agent is rare.[1] Nephrotoxicity occurs in 2-12% of patients, associated with slow drug clearance.[1] Renal involvement is usually reversible but requires an early approach.[1]

The objective is to present the case of a patient with acute lymphoblastic leukemia (ALL) who presented with acute kidney injury after administration of high doses of methotrexate.

CLINICAL CASE

A 13-year-old adolescent diagnosed with high-risk BALL due to a slow initial response to treatment, in complete remission at the time of presenting this adverse event, receiving treatment according to ALLIC-BFM 2009 protocol.[2]

The patient started the consolidation phase with high-risk blocks (HR-1 block), with normal kidney function before the chemotherapy block, which included high doses of methotrexate. Hyperhydration and alkalinization fluids were indicated. A 5 g/m² methotrexate infusion was started and administered over a 24-hour period, ensuring balance of fluid input and output. Thirty-six hours post-infusion, the patient presented with swelling in both eyelids, hands, and feet. She was in fair general condition, tachycardic, tachypneic, and hypertensive, with crackles in the left lower lung field. The patient had a positive fluid balance of 2000 mL over 24 hours, with a diuretic infusion rate of 81 mL/m²/h, A 16.8% weight gain was observed, all unequivocal signs of volume overload. Laboratory showed creatinine: 2.07 mg/dl (glomerular filtration rate: 38 ml/m^2 /1.73 m^2), with a subsequent maximum value of 3.16 mg/dl. Urea: 73 mg/dl, with a peak value of 125 mg/dl, and methotrexate determination: 35 µmol/L (hour +36). Renal ultrasound was normal; chest X-ray showed a cardiothoracic index of 0,58. A diagnosis of acute kidney injury secondary to methotrexate toxicity was made. To manage this condition, alkalinization therapy and electrolyte correction were initiated. Additionally, a hemodialysis catheter was placed, and renal replacement therapy was initiated. Leucovorin was prescribed at 75 mg/m^2 every 6 hours, and the the infusion of HR-1 block was suspended. Three hemodialysis sessions were required. Methotrexate concentrations remained elevated until hour +315, so the administration of leucovorin calcium was extended. The patient's evolution was favorable, with normalization of kidney function and urine analysis, although she received amlodipine daily. She continued receiving high-risk blocks, with adjustment of the dose and sequence of methotrexate, with the usual toxicity for this type of treatment (cytopenias, oral mucositis). Currently, she is in the maintenance phase of treatment, 13 months after achieving complete remission and 14 months after her initial diagnosis.

DISCUSSION

Methotrexate is used in the treatment of various hematological and oncological diseases.[1] When administered appropriately, it is typically well-tolerated. In uncommon cases, severe toxicities can arise, resulting in increased morbidity and delayed chemotherapy regimen.[1]

Methotrexate doses exceeding the threshold of 500 mg/m² are classified as high-dose.[1,3,4] It is classified as an antimetabolite agent and acts in the S phase of the cell cycle.[1,3] It interferes with folic acid metabolism, competitively inhibiting the enzyme tetrahydrofolate reductase, which is necessary for synthesizing nucleic acid precursors.[1,3]

The toxicity of the drug depends on the concentration and time of exposure.[5]

Thus, prolonged exposure to low concentrations of methotrexate may lead to increased hematologic or gastrointestinal toxicity.[5] On the other hand, exposure to higher concentrations in a short time may increase the risk of kidney toxicity.[5]

It is 50% bound to plasma proteins.[3,4,6] Therefore, concomitant administration of drugs that competitively displace methotrexate from protein binding sites can elevate the free drug concentration, thereby augmenting the risk of toxicity. Examples of this interaction are sulfonamides, salicylates, and diphenylhydantoin.[1]

Regarding its distribution, if the patient presents a third space, this may act as a deposition site, leading to delayed drug release and a prolonged increase in plasma concentrations.[1] The generation of a third space in our patient probably occurred due to a decrease glomerular filtration rate, which slowed plasma methotrexate elimination.

Renal excretion occurs by glomerular filtration and tubular secretion.[3,6] Diminished renal excretion can result in elevated methotrexate plasma concentrations, thereby increasing the risk of myelosuppression and mucositis.[1,4-6]

Reduced kidney blood flow, administration of nephrotoxic drugs, acidic urinary pH, use of drugs that compete with methotrexate for tubular secretion, and pre-existing nephropathy may contribute to this situation.[1,5,6]

Methotrexate-associated nephrotoxicity may be observed in 2-12% of patients.[2,5]

The proposed pathophysiological mechanisms are precipitation of methotrexate crystals or their metabolites in the tubular lumen, vasoconstriction of the afferent arteriole, and direct damage to tubular cells.[1,4-6] It usually presents as a non-oliguric acute kidney injury, with elevation in plasma creatinine concentration during or after infusion as the most frequent sign.[5,6] Despite its specificity, this parameter is late.[6,7] The earliest element for detecting methotrexate-induced toxicity is, precisely, the plasma concentration of the drug.[6]

Slow elimination of methotrexate is a complication that is difficult to foresee since it can occur randomly and not be repeated later. For this reason, studying enzymes related to methotrexate metabolism is not helpful in a case such as the one we present since the problem in this patient was not the drug's metabolization but a defect in its elimination.

It is important to note that, before administering methotrexate at high doses, hematologic and laboratory parameters (predominantly kidney and liver function) should be reviewed,[6] and the prescription of hyperhydration and alkalinization fluids is implemented to induce diuresis before, during, and after methotrexate infusion.[1,5,6] Consideration should be given to replenishment of concurrent losses.[1] Alkalinizing the urine increases the solubility of methotrexate by 10-fold, reducing the risk of it precipitating in the kidney tubules.[2,6] Additionally, administration of leucovorin adjusted to methotrexate determinations is indispensable.[1,5,6] It represents a source of tetrahydrofolate. It competes with methotrexate for cell entry and polyglutamate formation.[6] For this reason, leucovorin salvage should begin within 24 hours of the initiation of methotrexate infusion.[1,6]

Once acute kidney injury is established, strategies should be employed to favor the elimination of accumulated methotrexate, as well as to reduce the toxicity exerted by it:[5,6] I) If possible, maintain urinary alkalinization;[4-6] II) Indicate renal replacement therapy promptly;[5] III) Optimize doses of leucovorin to antagonize competitive inhibition of tetrahydrofolate reductase;[4,6] IV) If available, indicate carboxypeptidase.[4-6,8] It represents a recombinant enzyme that catalyzes the conversion of methotrexate to 2,4-diamino-N10-methylpteroic acid and glutamate, both inactive metabolites that are eliminated in the biliary tract.[4-6] Carboxypeptidase has a precise indication in patients with impaired kidney function and high plasma methotrexate concentrations (greater than 1 µmol/L).[4,5] However, the availability of this tool may be limited.[4,8]

Methotrexate is dialyzable due to its low molecular weight and moderate binding to plasma proteins. Intermittent hemodialysis is effective, although, according to the literature, kidney replacement therapies do not offer significant benefits since they only eliminate intravascular methotrexate and remove folinic acid. In the case of our patient, the decision to start hemodialysis was based on the patient's fluid overload and electrolyte imbalances, which did not improve with standard treatments.[8]

Acute kidney injury induced by high doses of methotrexate is unusual and reversible.[6] Most patients will have a favorable outcome if appropriate measures are taken early. Most patients who receive prompt and appropriate treatment for methotrexate toxicity have a good prognosis and can safely receive high-dose methotrexate in the future, as seen in this case. ■

REFERENCES

1. Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and managing toxicities of high-dose methotrexate. *Oncologist*. 2016;21(12):1471–82.
2. Campbell M, Kiss C, Zimmermann M, Riccheri C, Kowalczyk J, Felice MS, et al. Childhood acute lymphoblastic leukemia: Results of the randomized acute lymphoblastic leukemia intercontinental-Berlin-Frankfurt-Münster 2009 trial. *J Clin Oncol*. 2023;41(19):3499–511.
3. Chabner BA, Bertino J, Cleary J, Ortiz T, Lane A, Supko J, Ryan D. Fármacos citotóxicos. En Brunton LL, Chabner BA, Knollmann BC. eds. Goodman & Gilman: Las bases farmacológicas de la terapéutica. 12° ed. México: McGraw Hill Interamericana Editores; 2012:pág.1677-1730.
4. Hamed KM, Dighriri IM, Baomar AF, Alharthy BT, Alenazi FE, Alali GH, et al. Overview of methotrexate toxicity: A comprehensive literature review. *Cureus* 2022;14(9):e29518.
5. Widemann BC, Adamson PC. Understanding and managing methotrexate nephrotoxicity. *Oncologist*. 2016;11(6):694–703.
6. Ramsey LB, Balis FM, O'Brien MM, Schmiegelow K, Pauley JL, Bleyer A, et al. Consensus guideline for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance. Oncologist. 2018;23(1):52–61.
7. Skärby T, Jönsson P, Hjorth L, Behrentz M, Björk O, Forestier E, et al. High-dose methotrexate: on the relationship of methotrexate elimination time vs renal function and serum

methotrexate levels in 1164 courses in 264 Swedish children with acute lymphoblastic leukaemia (ALL). *Cancer Chemother Pharmacol.* 2003;51(4):311–20.

8. Ghannoum M, Roberts DM, Goldfarb DS, Heldrup J, Anseeuw K, Galvao TF, et al. Extracorporeal treatment for methotrexate poisoning: systematic review and recommendations from the EXTRIP Workgroup. *Clin J Am Soc Nephrol.* 2022;17(4):602-22.