CASE REPORT

The utility of online haemodiafiltration in methotrexate poisoning

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SUMMARY

We report a case of a 56-year-old woman with a high-grade diffuse large B-cell lymphoma who unexpectedly developed toxic plasma levels of methotrexate (MTX) following the first cycle of rituximab-cyclophosphamide, hydroxydanorubicin, oncovin, prednisolone (R-CHOP) with a high-dose MTX chemotherapy protocol. She also developed non-oliguric acute kidney injury secondary to MTX nephrotoxicity. We elected to treat her with online haemodiafiltration (HDF) and this proved to be efficient with a dramatic response. Rapid clearance of MTX to therapeutic levels was possible within three sessions. Prompt therapy with high-volume online-HDF is an effective choice for rapid MTX clearance and swift reversal of MTX nephrotoxicity.

BACKGROUND

Methotrexate (MTX) is an antimetabolite drug with an established role in the treatment of rheumatoid arthritis and is an important component of several treatment protocols for haematological malignancies. MTX interferes with folate metabolism, which is essential for purine and thymidine synthesis. Rapidly dividing malignant cells need larger amounts of folate. Development of MTX toxicity is dose dependent and the dose varies with the use of different regimens, which can be high, intermediate or low-dose protocols. Following high-dose MTX infusion, almost 50–90% is excreted unchanged in the urine which occurs in the first 12–24 h postinfusion in patients with a normal renal function.¹ In order to hasten clearance of the drug, vigorous intravenous hydration and alkalinisation of the urine is advised. In the setting of renal impairment, this regime may fail. There are a few reports of MTX removal by means of haemodialysis (HD) and haemoperfusion.^{2–4} However, little is known about MTX removal by haemodiafiltration (HDF). We report a case of a patient who developed unexpectedly high MTX levels after the first cycle of an R-CHOP high-dose MTX protocol, and we opted to treat the patient with high-volume online-HDF, which effectively cleared the drug within three sessions. We continued the treatment for a total of 12 sessions until full renal recovery. A toxic concentration of MTX is defined as greater than 5–10 µmol/L at 24 h, 0.9–1 µmol/L at 46 h and 0.1 µmol/L at 72 h after infusion of the MTX.⁵

CASE PRESENTATION

A 56-year-old woman reported symptoms of pain at the right hip joint 2 weeks prior to admission. MRI of the hip joint was performed in a small community hospital and revealed fluid collection in the gluteal region; therefore, she underwent incision and drainage. However, the patient had persistent pain for which a pelvic MRI was performed and it revealed a right gluteal mass measuring around 5 cm with an area of central necrosis. She was referred to our institute for further management. On presentation, she reported pain in the right hip, headache and weakness in the right arm. She looked depressed but was conscious, oriented and alert with a pain score of 8–9/10, and her vitals were stable and within normal limits. Physical examination was unremarkable except for tenderness elicited in the right gluteal region with a palpable underlying mass and tender right thigh. Her medical history was only significant for hypothyroidism for which she was on replacement. She gave a positive history of significant weight loss over the past few months. Family history was negative for malignancy.

INVESTIGATIONS

CT of the brain revealed multiple enhancing lesions with surrounding vasogenic oedema likely to be of a malignant nature. CT of the chest, abdomen and pelvis showed a left upper lobe lesion, with left mediastinal nodal involvement and multiple bilateral lung metastases. There was a large right gluteal mass in keeping with soft tissue metastasis. Skin biopsy from the right thigh lesion revealed a high-grade diffuse large B-cell lymphoma. Her serum creatinine was 60 µmol/L prior to treatment. There was a sharp rise in serum creatinine to 153 µmol/L after the first dose of R-CHOP with high-dose MTX chemotherapy protocol. Urine output was around 700 mL/24 h. Renal ultrasound demonstrated a right kidney measuring 11.2 and a left 10.9 cm with normal renal cortical thickness. No focal lesion was seen and there was no evidence of hydronephrosis. She received the first cycle of R-CHOP with high-dose MTX (dose was 3.5 g/m² body surface area—4.9 g) on 10 September 2013. The treatment was complicated with severe mucositis, febrile neutropaenia, sepsis, pneumonia and acute kidney injury (AKI). On routine assessment 24 h after administration of MTX, the serum MTX level was unexpectedly high, measuring 99.94 µmol/L. The MTX level was measured by

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spectrophotometric analysis using the cobas c 311 analyser (Roche, Germany).

DIFFERENTIAL DIAGNOSIS

AKI secondary to:

1. MTX nephrotoxicity: The Naranjo algorithm⁶ yielded a score of 9. It is used for determining the likelihood of whether an adverse drug reaction (ADR) is actually due to the drug concerned. Points are added when answering positively to previous conclusive reports on this reaction; the adverse events follow the administration of the drug; improve on drug withdrawal and reappear on readministration. Additional points are awarded when the drug is detected at toxic levels in the blood and when the ADR is more severe at higher doses with objective evidence documenting the episode. Points are not lost when answering negatively to alternative causes of the adverse reaction. A score of 9 in our patient suggests that the ADR as a result of MTX is definite.
2. Pre-renal azotaemia: The fractional excretion of sodium (FENa) was >1%, making pre-renal azotaemia unlikely. Additionally, the patient was not dehydrated and did not receive any diuretic therapy that could invalidate the interpretation of FENa.
3. Contrast-induced nephropathy (CIN): Using the risk score of CIN⁷ the total score for this patient was 3. At that score, the risk of CIN was 7.5% and the risk of dialysis was 0.04%, making the diagnosis of CIN a low probability.
4. Sepsis-induced AKI—blood cultures were positive for *Pseudomonas aeruginosa* around the time of AKI making this diagnosis a possibility, this organism was pan-sensitive and was effectively treated.
5. Lymphomatous infiltration of the kidney: This is possible in a patient with haematological malignancy, but was less likely in our patient given the normal renal sonographic appearance. Although a normal renal ultrasound does not rule it out, a renal biopsy is useful in this situation.
6. Tumour lysis syndrome (TLS): This is ruled out with normal serum calcium, phosphate, potassium and uric acid levels together with absent classical clinical features. The patient did not meet the criteria for laboratory or clinical TLS using the Cairo-Bishop definition.⁸

The onset of a rise in serum creatinine from baseline together with the onset of the suspected cause of a renal insult should

concur. AKI is often a result of a combination of multiple causes. It is worth noting that the diagnosis of MTX nephrotoxicity is based on statistical probability and the exclusion of other possibilities rather than a specific diagnostic test.

TREATMENT

In our patient who was haemodynamically stable, we elected to treat her with high substitution volume online HDF in an attempt to rapidly correct the toxic levels. She was dialysed through a non-tunnelled right internal jugular catheter. Online HDF treatment sessions were carried out on Fresenius Medical Care (FMC) 5008 dialysis machines. The dialyser used was the FMC Helixone high-flux dialyser of the FX class (FX 80). Online HDF was performed postdilution in the autosubstitution mode. Dialysate and substitution fluid were ultrapure and generated in-house. Each session was for 4 h with high bicarbonate dialysate of 40 mmol/L, dialysate flow of 1000 mL/min and the substitution volume ranged between 15 and 20 L per session. In the reported case where continuous venovenous HDF (CVVHDF) was used for MTX toxicity, treatment time was longer than intermittent online-HDF.⁹ However, we had a higher blood flow rate and a high-flux dialyser that compensated for shorter treatment duration.

OUTCOME AND FOLLOW-UP

The patient underwent a total of 12 successive sessions with rapid correction of MTX to acceptable therapeutic levels achieved in just 3 sessions (figure 1) without rebound elevation in the MTX level. The MTX levels reported in the graph are measured pre-HDF. Our patient developed more severe AKI and her urine output had progressively declined. Although plasma concentration of MTX was low without rebound after the fifth to sixth online-HDF session, the patient continued to receive a total of 12 sessions by which time she had sufficient renal function to be off dialytic treatment. Thereafter, the patient received her second cycle of R-CHOP high-dose MTX chemotherapy protocol with 15% dose reduction 4 weeks from the first cycle, which was well tolerated; measurement of MTX levels after the subsequent cycles of chemotherapy confirmed therapeutic levels. She received the subsequent third, fourth and fifth cycles in full dose which was also uneventful except that she required pegfilgrastim for a low white cell count. Follow-up positron emission tomography-CT after the third cycle confirmed an appropriate clinical response to therapy. MRI of the

Figure 1 Graph of serum methotrexate level ($\mu\text{mol/L}$) over time since the initiation of high- volume online haemodiafiltration.

brain also showed resolution of cerebral lesions. She had a full renal recovery.

DISCUSSION

MTX is not nephrotoxic at low doses; however, high-dose MTX can affect renal function by two mechanisms. MTX can precipitate in the renal tubules and confer direct tubular toxicity and the risk increases in the setting of acidic urine as two of its metabolites are poorly soluble in low pH. MTX can also cause afferent arteriolar constriction or mesangial cell constriction that can cause a transient decline in the glomerular filtration rate after each dose; this effect can be aggravated when additional nephrotoxic drugs are coadministered.¹⁰ The recommended treatment is in the form of adequate hydration and urinary alkalisation in patients with normal renal function for high-dose MTX regimens. Considering the expanding indications for high-dose MTX treatment protocols, methods of MTX removal in case of unexpected toxic levels are of interest. Current regimens with high-dose MTX (12 g/m² per dose) are used in treatment of several malignancies such as osteogenic sarcoma and high-grade non-Hodgkin's lymphoma. AKI due to MTX nephrotoxicity may lead to persistent high MTX levels and manifest clinically with hepatotoxicity, nausea, vomiting and mucositis.¹¹ Jaffe *et al*¹¹ reported an incidence of nephrotoxicity of 1.1% per treatment and 14.6% per patient with fatal results in two of six cases. Current protocols advocate adequate hydration to maintain high urine output in order to decrease tubular fluid MTX concentrations in addition to urine alkalisation to keep urinary pH above 7.0. An alkaline medium prevents MTX precipitation. Therapeutic drug monitoring has decreased the incidence of MTX nephrotoxicity with early identification and prompt management. Despite these precautions, the risk of renal impairment after high-dose MTX is still approximately 2%.¹² The utility of HD in MTX toxicity has been reported previously, but with variable degrees.^{3 13} It has been shown that acute intermittent high-flux HD is an effective method of clearing high MTX levels in chronic dialysis patients on high-dose MTX treatment.³ Some have used a combination of HD and charcoal haemoperfusion.^{4 14} Others have advocated the use of HD with serum exchange,¹⁵ haemodialysis with plasma perfusion¹⁶ and haemofiltration with plasma perfusion over an anion-exchange resin.¹⁷ In the setting of oliguric AKI with toxic levels of MTX, the therapy of choice is intravenous administration of glucarpidase (a recombinant bacterial enzyme carboxypeptidase G2) that has been shown to rapidly clear plasma MTX levels by 98% in such a setting. Although well tolerated, the overall results are still unsatisfactory in adults and elderly patients.¹⁸ However, this is not available in our institution, and given the toxic levels we did not have time to acquire it. HD offers a clearance of 38–40 mL/min; however, it has been reported that CVVHDF offers a clearance of 64.4 mL/min, which is far greater given the situation where rapid drug clearance is mandated.⁹ In our patient, immediate initiation of online-HDF was fundamental in effective clearance of the toxic MTX levels. Daily sessions of online-HDF were prescribed to avoid the rebound elevation of plasma MTX levels which has been observed in previous reports.^{14–16} We used a high-bicarbonate bath of 40 mmol/L to promote alkalisation of urine, together with adequate intravenous hydration, intravenous sodium bicarbonate, for rapid clearance of the drug. Once a toxic serum level of MTX is confirmed in patients with normal renal function, we recommend immediate management that comprises urinary alkalisation with intravenous sodium bicarbonate, vigorous intravenous hydration (dextrose 5% (D5W)

with 100–150 mEq of sodium bicarbonate per litre, administered by continuous infusion at 125–150 mL/h and high-dose folinic acid (25 mg/m²) within 24–48 h after MTX administration—used to reduce gastrointestinal epithelial cell and bone marrow toxicity. In case of toxic MTX levels that occur in the setting of renal impairment as in our patient where rapid clearance is mandated, intravenous administration of glucarpidase has been shown to rapidly clear plasma MTX levels by 98%.¹⁸ In a situation where glucarpidase is not available or is insufficient, we advocate the use of high-volume online HDF in place of intermittent HD as it offers greater clearance. This case highlights the rapid and effective clearance of plasma MTX using high-volume online HDF in a patient diagnosed with high-grade diffuse Large B-cell lymphoma with AKI secondary to MTX nephrotoxicity following R-CHOP high-dose MTX therapy.

Learning points

- ▶ Therapeutic drug monitoring should be initiated 12–24 h postmethotrexate (MTX) infusion.
- ▶ MTX in low doses is not nephrotoxic. When it is used in high doses, renal injury is caused by two mechanisms:
 - Through intratubular precipitation and direct tubular toxicity that is exacerbated in acidic urine.
 - Afferent arteriolar constriction or mesangial cell constriction that can cause a transient decline in the glomerular filtration rate.
- ▶ Standard treatment for toxic levels of MTX involves vigorous intravenous hydration and urinary alkalisation with intravenous sodium bicarbonate. Folinic acid (leucovorin) is administered within 24–36 h after MTX is used to prevent MTX-induced host toxicity without diminishing antitumour activity.¹⁹
- ▶ Online haemodiafiltration with a high substitution volume is an effective mode of rapid clearance of MTX in patients with toxic levels and renal impairment.

Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 Kamen B. Folate and antifolate pharmacology. *Semin Oncol* 1997;24(5 Suppl 18): S18–30–S18–39.
- 2 Saland JM, Leavey PJ, Bash RO, *et al*. Effective removal of methotrexate by high-flux hemodialysis. *Pediatr Nephrol* 2002;17:825–9.
- 3 Wall SM, Johansen MJ, Molony DA, *et al*. Effective clearance of methotrexate using high-flux hemodialysis membranes. *Am J Kidney Dis* 1996;28:846–54.
- 4 Relling MV, Stapleton FB, Ochs J, *et al*. Removal of methotrexate, leucovorin, and their metabolites by combined hemodialysis and hemoperfusion. *Cancer* 1988;62:884–8.
- 5 Evans WE, Pratt CB, Taylor RH, *et al*. Pharmacokinetic monitoring of high-dose methotrexate. Early recognition of high-risk patients. *Cancer Chemother Pharmacol* 1979;3:161–6.
- 6 Naranjo CA, Busto U, Sellers EM, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–45.
- 7 Mehran R, Aymong ED, Nikolsky E, *et al*. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004;44:1393–9.
- 8 Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol* 2004;127:3–11.

- 9 Vilay AM, Mueller BA, Haines H, *et al.* Treatment of methotrexate intoxication with various modalities of continuous extracorporeal therapy and glucarpidase. *Pharmacotherapy* 2010;30:111.
- 10 Widemann BC, Adamson PC. Understanding and managing methotrexate nephrotoxicity. *Oncologist* 2006;11:694–703.
- 11 Frei E III, Jaffe NJ, Pitman S. Letter: limitations of methotrexate and citrovorum-factor treatments. *N Engl J Med* 1975;292:107–8.
- 12 Widemann BC, Balis FM, Kempf-Bielack B, *et al.* High-dose methotrexate-induced nephrotoxicity in patients with osteosarcoma. *Cancer* 2004;100:2222–32.
- 13 Thomson AH, Daly M, Knevil J, *et al.* Methotrexate removal during haemodialysis in a patient with advanced laryngeal carcinoma. *Cancer Chemother Pharmacol* 1996;38:566–70.
- 14 Grimes DJ, Bowles MR, Buttsworth JA, *et al.* Survival after unexpected high serum methotrexate concentrations in a patient with osteogenic sarcoma. *Drug Saf* 1990;5:447–54.
- 15 Thierry FX, Vernier I, Dueymes JM, *et al.* Acute renal failure after high-dose methotrexate therapy. Role of hemodialysis and plasma exchange in methotrexate removal. *Nephron* 1989;51:416–17.
- 16 Kawabata K, Makino H, Nagake Y, *et al.* A case of methotrexate-induced acute renal failure successfully treated with plasma perfusion and sequential hemodialysis. *Nephron* 1995;71:233–4.
- 17 Greil J, Wyss PA, Ludwig K, *et al.* Continuous plasma resin perfusion for detoxification of methotrexate. *Eur J Pediatr* 1997;156:533–6.
- 18 Schwartz S, Borner K, Muller K, *et al.* Glucarpidase (carboxypeptidase g2) intervention in adult and elderly cancer patients with renal dysfunction and delayed methotrexate elimination after high-dose methotrexate therapy. *Oncologist* 2007;12:1299–308.
- 19 Goldin A, Venditti JM, Kline I, *et al.* Eradication of leukaemic cells (L1210) by methotrexate and methotrexate plus citrovorum factor. *Nature* 1966;212:1548–50.

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