Acute Renal Failure Post High Dose Methotrexate Infusion Successfully Managed with High Dose Folinic Acid and High Flux Dialysis

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Abstract High dose methotrexate infusion has become the standard of care in pediatric and adult acute lymphoblastic leukemia management. Adequate hydration, alkalinization of urine and optimal folinic acid rescue are the key factors in the prevention of toxicity. The development of acute renal failure after high dose methotrexate infusion is very rare, albeit a few cases have been reported in literature. Various options have been available in addition to high dose folinic acid rescue, such as ultra filtration dialysis, continuous extracorporeal therapy, thymidine and Glucarpidase infusion to directly counter act excess methotrexate. In a developing country with limited reserves, managing a patient who develops acute renal failure immediately after high dose methotrexate is a nightmare without Glucarpidase. We report here a case that has been managed successfully with intensive supportive measures alone.

Introduction

High dose methotrexate (HDMTX) should be administered with appropriate attention to hydration and diligent monitoring of the decay curve. The contra indications to administration of HDMTX are infection and pathologic accumulation of fluid (ascites and pleural effusions) where Methotrexate (MTX) may sequester and result in a prolonged delay in excretion. MTX levels in excess of an institute's specific designated values at specified times portend potential toxicity and should be treated immediately by increasing intravenous hydration and augmenting the dose of leucovorin.

Normal methotrexate elimination should be approximately 10 μM at 24 h after administration, 1 μM at 48 h, and less than 0.2 μM at 72 h. The BFM group recommends high dose folinic acid rescue, even if the serum methotrexate level is more than 0.2 $\mu\text{mol/l}$ at 54 h of administration. (2×10^{-7} M) [1] and the recommended folinic acid rescue to be given is mentioned in Table 1. Methotrexate toxicity has to be counteracted as medical emergency as it may be lethal [2].

There are three major mechanisms of nephrotoxicity related with MTX. First one is that induced by allergic reaction, which usually appears as interstitial nephritis. In this case MTX is contraindicated. Second mechanism is direct pharmacological toxicity against renal tubules. The third is precipitation of MTX, which plugs the renal tubules. The latter two are consequently dose dependent and are usually associated with high-dose chemotherapy [3].

Case Report

A 20 year old male diagnosed to have Acute Lymphoblastic Leukemia (Pre T) had been started on BFM 95 Pediatric protocol and had gone into Complete Remission post induction. He was admitted for high dose methotrexate as per schedule. He received 2 g/m^2 of high dose methotrexate during the first cycle. (In our institution, we use Pediatric protocol in patients up to 25 years of age, but reduce the dose of methotrexate during the first cycle to assess tolerability). The usual protocol for high dose methotrexate such as alkalinization, hydration etc. were followed as per the protocol. Just after 36 h of starting methotrexate infusion he had started to have vomiting and had slow onset facial puffiness and pedal edema. Evaluation revealed the patient to be in acute renal failure with

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Table 1 Folinic acid dosing according to methotrexate levels

Methotrexate level	Folinic acid dose (mg/m ² q6 h)
5×10^{-7} M	15
1×10^{-6} M	100
$>2 \times 10^{-6}$ M	200

Table 2 Methotrexate levels at different time points

Hours post MTX infusion	Level of MTX (μmol/l)
36	40
60	24
86	12
110	6
134	4
158	2.8
182	1.6
228	0.8

creatinine of 8.3 mg/dl, but he was still passing adequate amounts of urine. He was started on high filtration dialysis for 4 h daily and calcium leucovorin rescue was started with a dose of 200 mg/m² every 3 h. There are different guidelines available for rescuing patients with leukovorin and we decided to administer the maximum recommended dose possible. The levels of methotrexate measured at different time intervals are given in Table 2.

Considering the seriousness of the situation, we tried to procure carboxypeptidase, but could not get it in time. However, we persisted with high flux dialysis and high dose leukovorin rescue. G-CSF was given right from the time renal failure was recognized till neutrophil recovery. Creatinine level improved to 1.5 mg/dl on day 10. Even though there was a drop in the White cell count, the nadir was $1.0 \times 10^9/l$ on day 7 and Absolute Neutrophil Count of $>1.0 \times 10^9/l$ was reached on Day 13. The patient by then had ultimately received a total dose of 14.4 g (14,400 mg) of calcium leucovorin.

We ruled out the possibilities of autosomal polycystic kidney [4] and Methyl tetrahydrofolate reductase (MTHFR) mutation in this patient [5], as both of them are known to predispose to reduced methotrexate clearance. The most common polymorphism of MTHFR gene is C677T. Homozygotes and heterozygotes for this variant have 30 and 60% of the normal MTHFR activity respectively, causing impaired remethylation of homocysteine to methionine and subsequent hyperhomocysteinemia. This mutation predisposes individuals to adverse effects from drugs with antifolate effects such as MTX, even at low doses.

Discussion

The development of renal failure during HDMTX constitutes a medical emergency. MTX is cell cycle specific for the S phase. It acts by inhibiting the conversion of dihydrofolate to tetrahydrofolate and prevents the transfer of 1- carbon donors. This surceases the folate pool, thwarts the formation of purine and thymidine and ultimately disrupts DNA replication.

Carboxypeptidase G1 is a bacterial enzyme, first reported by Abelson et al. [6]. It inactivates MTX by removal of its terminal glutamate residue and destroys circulating MTX. MTX and leucovorin share a common carrier, called the reduced folate carrier, for entry into cells. This transport mechanism is present in normal cells but not in resistant cancer cells. High-dose MTX enters normal cells via the carrier mechanism and by virtue of its high extracellular concentration, enters also resistant malignant cells through diffusion over time (concentration time). Leucovorin also enters normal cells via the carrier mechanism, but unlike MTX, is prohibited from entry into malignant cells because of its relatively low extracellular serum concentration and the absence of a carrier mechanism. It rescues normal cells while malignant cells, in the absence of intracellular leucovorin, self-destruct [7].

More than 90% of MTX is cleared by the kidneys. MTX is poorly soluble at acidic pH, and its metabolites, 7-OH-MTX and DAMPA, are six- to ten-fold less soluble than MTX, respectively. An increase in the urine pH from 6.0 to 7.0 results in a five- to eightfold greater solubility of MTX and its metabolites, a finding that underlies the recommendation of intravenous hydration (2.5–3.5 l of fluid per m² per 24 h, beginning 12 h before MTX infusion and continuing for 24–48 h) and urine alkalinization (40–50 mEq sodium bicarbonate per liter of infused fluid) prior to, during, and after the administration of HDMTX. Shorter durations of HDMTX infusions with resultant higher plasma and urinary MTX concentrations may carry an increased risk for renal dysfunction. Several drugs have been associated with increased toxicity when co administered with MTX. The most significant interactions involve agents that interfere with MTX excretion, primarily by competing for renal tubular secretion, such as probenecid, salicylates, sulfisoxazole, penicillins, and non steroidal anti-inflammatory agents [8].

HDMTX-induced renal dysfunction continues to occur in approximately 1.8% of patients with osteosarcoma who are treated on clinical protocols with optimal supportive care in the largest report of 3,887 patients reported by Brigitte et al. [9]. Nephrotoxicity was either Grade 2 or 3 significant enough to be reported and 23 patients (0.6%) developed Grade 3 or 4 toxicity. Three patients received Glucarpidase, 1 patient was treated with hemoperfusion, 1

patient was treated with plasmapheresis, 2 patients received Glucarpidase and underwent high-flux hemodialysis or hemodialysis, and 17 patients were treated with supportive measures that included alkalization, hydration and leukovarin rescue only. There were 3 deaths attributable to HDMTX-induced renal dysfunction. This group recommends early usage of Carboxypeptidase to circumvent methotrexate toxicity, even though around 35% of this cohort were salvaged with supportive measures which we adopted in our setting [9]. (Leukovorin rescue, hydration and continuing alkalization).

The exact mechanism of renal failure in this patient is not clear, even though early onset vomiting with consequent suboptimal hydration and alkalization would have added additional insult. However, we did not attempt to re-challenge this patient with a repeat dose of high dose methotrexate as allergic interstitial nephritis cannot be ruled out with certainty.

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