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Case Report Open Access

The Clinical Importance of Drug Monitoring: Methotrexate-Induced Acute Renal Failure

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Abstract

Plasma concentrations of methotrexate (MTX) represent the best predictive value of its toxicity. Monitoring of the MTX is a common practice that allows identifying patients with acute toxicity and adjusting the dose of folinic acid, and establishing immediate corrective actions. However, the main adverse effects that must be found after a patient treated with this drug are myelosuppression, mucositis of the entire gastrointestinal tract, renal failure and in some cases neurological alterations.

Keywords: Acute Lymphoblastic Leukemia; Creatinine; Mucositis; Hemodialysis

Introduction

Plasma concentration of methotrexate (MTX) is a common practice which enables identifying patients with acute toxicity. Since the 60s has begun to report on rare adverse effects such as acute renal failure in relation to the MTX in pediatric and adult patients. In the last decade have been reported cases of intoxication by MTX at high doses in pediatric oncology patients with nephrotoxicity. However, in the group of adults there has been less cases, we report a new case in adults.

Case

A 36-year-old man with a diagnosis of Acute Lymphoblastic Leukemia (LAL) subtype L2 of the FAB classification without cytogenetic abnormalities (2006) with late medullary relapse (2012), that is currently in second remission and receiving a consolidation cycle treatment according to PETHEMA LAL-AR-2003 as a step prior to allogeneic bone marrow transplantation from unrelated donor. As part of its consolidation treatment receives an unique total dose of 5 g in continuous infusion of 24 hours, which correlates to the recommended dose in the protocol, which is of 3 g/m^2, with analytical parameters prior normal (Creatinine: 1.2 mg/dl). During the first 48 hours the patient presents gastrointestinal symptoms (Abdominal pain, diarrhea, vomiting, and mucositis). Two days post-MTX infusion and with the adequate rescue of folinic acid, the first plasma control levels of MTX was determinate above the toxic detection range (>0.08 μM) of immunofluorescence technique (TDX Abbot). After this plasmatic control, there are two new controls to the 72 and 96 hours, persisting high plasma levels. It is evident others adverse effects such as myelosuppression and after 10 days post infusion, corresponding to the fourth determination of plasma MTX, it was observed a acute renal failure (creatinine: 4 mg/dl). Therefore, it has been carry out a daily monitoring of plasma levels of MTX revealing the persistence of toxic levels of the drug by a decrease in creatinine clearance and delaying the elimination of the MTX, and the patient has to be treated with ultrafiltration hemodialysis.

Discussion

Through daily monitoring of plasma levels of MTX shows the effectiveness of drug clearance by hemodialysis, however MTX levels (Pre-dialysis) remain detectable in the blood despite clinical and laboratory improvement (serum creatinine) of the patient (Figure 1). Also, consider the time of exposure to high plasma drug levels, this increase toxicity [4]. In the literature, the exposure to plasma concentrations above 0.05 μM (MTX) at 48 hours post infusion was associated with increased toxicity. In this case there have been several adverse effects that are caused by MTX from mucositis (very common), myelosuppression (common) and renal failure (rare) that are correlated with the high dose administered

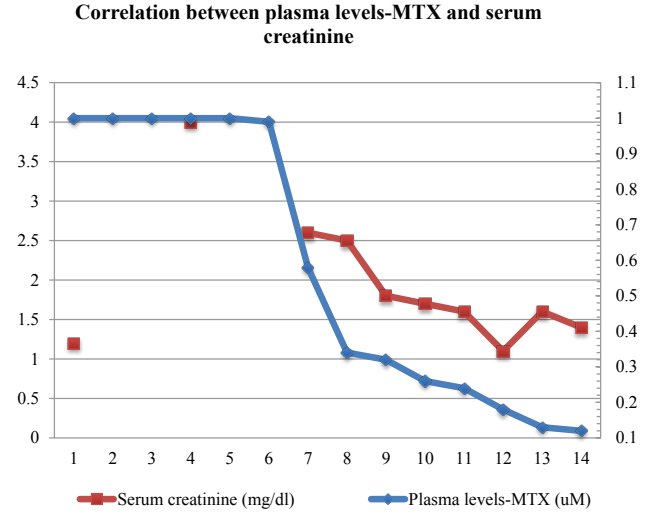

Figure 1: Dialy monitoring of plasma levels-MTX and serum creatinine after the acude renal failure was detected by laboratory anormalities.

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and the persistence of high plasma levels of MTX registered by daily monitoring. This provided a guidance to the clinician physician to rely on the elimination kinetics of the drug and thus make appropriate treatment decisions. Renal failure is a rare adverse effect caused by MTX, and very few cases reported in the literature, with a frequency of 1:10,000 and are believed to be after several days of high plasma levels of MTX increased drug toxicity and rare side effects occur. In this case we applied the Naranjo causality scale classified as probable (Numeric value=8 pts). There is not clearly established in the literature, which is the renal damage that this drug can cause, but it is assumed the reversibility of the process due to gradual eliminating MTX and improving serum creatinine levels. However, three mechanisms has been proposed by MTX can damage the kidneys. The first, which causes allergenic reaction interstitial nephritis, the second, a direct pharmacological effect against the renal tubules and the third, the precipitation of crystals of MTX that obstructs the renal tubules [5]. In addition, there are other concomitant situations such as receiving proton pump inhibitor (PPI) therapy, might contribute with elevate and prolonged serum level of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. It has also been reported that treatment with high-dose MTX can cause serious toxicity and prolonged the hospitalization due to the life threating.

Conclusion

Despite adequate clinical management of toxicity such as hydration and urinary alkalization, the routine monitoring of plasma levels of MTX plays an important role. Therefore, it is still necessary to monitor acute toxicity of MTX given the wide intra-variability and inter-variability in drug elimination between different patients and even in the same patient at different cycles. Furthermore, to notify any clinical adverse event is important because it contribute with the safety of the patients and increase the knowledge of well-known drug such as MTX.

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