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Brief Communication

High dose methotrexate and extended hours high-flux hemodialysis for the treatment of primary central nervous system lymphoma in a patient with end stage renal disease

Howard Mutsando[1], Magid Fahim[2], Devinder S Gill[1], Carmel M Hawley[2,3], David W Johnson[2,3], Maher K Gandhi[1,4], Paula V Marlton[1,4], Helen G Mar Fan[1,4], Peter N Mollee[1,4]

[1]Haematology Department, Princess Alexandra Hospital, Brisbane, Australia; [2]Department of Nephrology, Princess Alexandra Hospital, Brisbane, Australia; [3]Centre for Kidney Disease Research, University of Queensland, Brisbane, Australia; [4]University of Queensland School of Medicine, Brisbane, Australia

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Abstract: This report discusses the case of a 52 year old female with post-transplant lymphoproliferative disorder, confined to the central nervous system, which was managed with high dose methotrexate (HDMTX) in the context of end stage renal disease. The patient received two doses of HDMTX followed by extended hours high-flux hemodialysis, plasma methotrexate concentration monitoring and leucovorin rescue. The hemodialysis technique used was effective in clearing plasma methotrexate and allowed delivery of HDMTX to achieve complete remission with limited and reversible direct methotrexate-related toxicity. Dialysis-dependent renal failure does not preclude the use of HDMTX when required for curative therapy of malignancy.

Keywords: High dose methotrexate, end stage renal disease, dialysis, primary central nervous system lymphoma, post-transplant lymphoproliferative disorder

Introduction

Methotrexate (MTX) is an antimetabolite with activity against a wide variety of malignancies. High dose MTX (HDMTX), defined as a MTX dose greater than 500 mg/m^2, is used in the treatment of lymphoid malignancies and osteosarcomas. MTX is excreted 90% unchanged in the urine. The safe use of HDMTX requires adequate elimination of drug, monitoring of MTX concentrations and the use of a leucovorin rescue. End stage renal disease (ESRD) has been viewed as a contraindication to MTX therapy due to an increased incidence of serious adverse events [1, 2].

Materials and methods

Submission of this case report was approved by the human research ethics committee (reference number HREC/11/QPAH/478). It discusses the case of a 52 year old female with post-transplant lymphoproliferative disorder (PTLD), primary central nervous system lymphoma (PCNSL), which was managed with HDMTX in the context of ESRD. She had previously undergone a heart-lung transplant for severe pulmonary hypertension due to recurrent pulmonary emboli complicating essential thrombocythemia. Post-transplant, she developed calcineurin inhibitor induced ESRD and was commenced on hemodialysis. She also required a jejunostomy feeding tube and experienced chronic diarrhoea following a transplant-related vagal injury. Five years post-transplant, the patient presented with a left upper limb monoparesis and partial seizures. An MRI brain revealed several space occupying lesions, biopsy of which was consistent with Epstein-Barr virus positive monomorphic B-cell PTLD (subtype diffuse large B-cell lymphoma). Staging did not reveal any other disease sites. Her ECOG performance status was 2. Immunosuppressive therapy was reduced. Following discussions

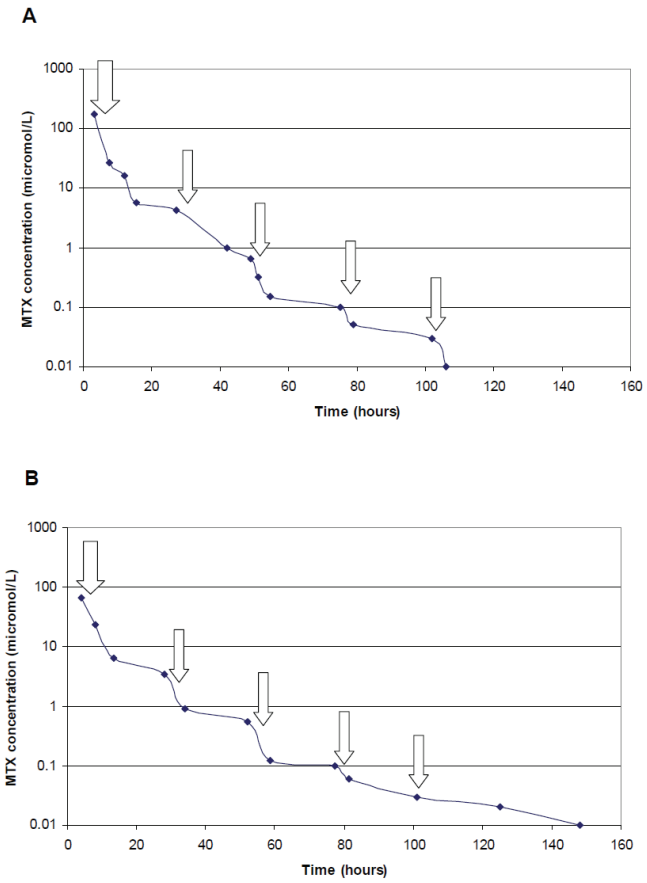

Figure 1. Plasma MTX concentrations following dose 1 (A) and dose 2 (B) of HDMTX in a logarithmic scale. Time 0 indicates the start of the 2 hour MTX infusion. The arrows indicate the high-flux hemodialysis sessions [an extended hours session (7 hours first dose; 9 hours second dose) commencing 1 hour following completion of the MTX infusion, followed by 4 daily 4-6 hour sessions].

between the treating teams and patient, she commenced treatment with a regimen including HDMTX supported by extended hours, high-flux hemodialysis.

Treatment consisted of HDMTX (1g/m^2; total dose 1600mg) administered as an intravenous (IV) infusion over 2 hours every two weeks, followed by extended hours high-flux hemodialysis (**Figure 1**). At each dialysis session a Fresenius FX80 synthetic high-flux membrane (Fresenius Inc., Walnut Creek, CA) was used with a blood flow rate of 250 ml/min and a dialysate flow rate of 500 ml/min. Plasma MTX concentrations were measured using a Fluorescence Polarization Radioimmunoassay (Abbott Laboratories, Abbott Park, IL) according to manufacturer's instructions (**Figure 1**). Leucovorin rescue commenced with a dose of 60mg IV 12 hours after completion of the MTX infusion followed by 50mg IV q6h × 2, then 200mg IV q4h × 12 doses after the first dose of HDMTX and 50mg IV q6h × 15, then 200mg IV q6h × 10 doses after the second dose. In addition to HDMTX, the patient's treatment included dexamethasone, rituximab 375mg/m^2 IV weekly × 8 and intrathecal cytarabine 100mg. Subsequently, when further myelosuppressive chemotherapy was precluded by infection, EBV specific T-cell therapy and whole brain irradiation (30Gy in 10 fractions) was administered [3].

Results

The patient tolerated the first dose of HDMTX well apart from worsening of her pre-existing anemia and mild transient transaminase elevation. Greater toxicity was noted following the second dose. The patient developed neutropenia (neutrophil count nadir 0.29 × 10^9/L) which resolved following two doses of granulocyte colony stimulating factor, transient worsening of pre-existing thrombocytopenia (platelet count nadir 34 × 10^9/L) and ongoing anemia. Her pre-existing diarrhoea worsened necessitating treatment with an octreotide infusion. In addition, she again experienced mild transient transaminase elevation plus nausea and oral mucositis that responded to symptomatic management. She also suffered from a urinary tract infection and an enterococcus fecalis infection of her arteriovenous fistula, which was complicated by aortic valve endocarditis. She was treated with broad spectrum antibiotics and made a complete recovery.

Unfortunately the patient died approximately four months following her second dose of HDMTX from a cytomegalovirus (CMV)-related perforated gastric ulcer. CMV infection had preceded her diagnosis of PTLD. A post mortem examination showed that she was in complete remission with no evidence of lymphoma.

Discussion

This case discusses the use of HDMTX in a patient with ESRD with the support of high-flux hemodialysis, MTX concentration monitoring

and leucovorin rescue. The use of MTX in ESRD is controversial with the literature describing prolonged severe toxicity and increased mortality following low dose MTX [1, 2]. While HDMTX has traditionally been avoided in patients with ESRD, it is documented that patients with delayed MTX excretion due to HDMTX induced acute renal failure (ARF) experience substantial morbidity and mortality [4-6]. However, HDMTX has a critical role in the management of PCNSL with several studies demonstrating the superiority of HDMTX over radiation alone and of chemotherapy regimens containing HDMTX over those which do not [7-12]. Therefore, in order to treat the described patient optimally, HDMTX needed to be included in the regimen. HDMTX is also used in the curative treatment of acute lymphoblastic leukemia, Burkitt's lymphoma and childhood osteosarcoma. Furthermore, while the use of intensive hydration and alkalinisation of the urine has substantially reduced the risk of ARF following HDMTX, it still occasionally occurs [4, 6, 7, 13]. The use of optimal techniques to clear MTX in this scenario is essential to avoid a fatal outcome.

Both standard intermittent hemodialysis and peritoneal dialysis have limited effectiveness in reducing plasma MTX concentrations due to its moderate (50%) plasma protein binding and large volume of distribution (0.76 L/kg), such that rebound increases of MTX concentrations post-dialysis have been reported, particularly following shorter dialysis sessions [6, 14, 15]. The effective use of repeated prolonged hemodialysis and charcoal hemoperfusion in the management of a patient who developed ARF and very high MTX concentrations following HDMTX has been described, with the patient avoiding significant toxicity [13]. High-flux hemodialysis has been successfully used to avoid toxicity in the management of three pediatric patients who developed post-HDMTX ARF, two of whom also received carboxypeptidase G2 (glucarpidase) [16]. Two previous reports have described the effective use of high-flux hemodialysis in patients with pre-existing ESRD. Murashima et al describe the case of a patient with cerebral lymphoma who received HDMTX without significant toxicity with the support of high-flux hemodialysis [17]. In the same patient, the use of continuous multiple exchange peritoneal dialysis achieved lower clearance of MTX, but also prevented toxicity. A report from the M.D. Anderson described the effective clearance of MTX in six patients with high-flux hemodialysis [18].

Alternative approaches to dialysis in the management of high MTX concentrations complicating HDMTX induced ARF have been investigated, the most promising of which is glucarpidase, which rapidly metabolises circulating MTX to an inactive metabolite. Glucarpidase is not commercially available, but has been used on a compassionate basis. Reported case series of these patients indicate that the administration of glucarpidase rapidly reduces MTX concentrations, although does not completely prevent toxicity and deaths still occur, especially if administration is delayed [6, 19]. There have been no reports of its use to facilitate the delivery of HDMTX in patients with pre-existing ESRD.

With the support of high-flux hemodialysis, our patient was able to receive two doses of HDMTX. The toxicities directly attributable to MTX were limited, easily managed and reversible. More toxicity was observed following the second dose than the first. While the frequency and severity of abnormal transaminases relates to number of doses received [20], no such trend has been observed for mucositis or hematological toxicity [21]. Possible reasons for the greater mucositis and hematological toxicity observed following the second dose include the lower dose of leucovorin given in the first 48 hours, longer time to complete clearance of MTX, more severe hypoalbuminemia and the presence of infection [22, 23]. The infectious complications seen in the second cycle preceded, and may have contributed to, the brief episode of neutropenia. They occurred in the context of a patient who had substantial co-morbidities and multiple other risk factors for infection, including post-transplant immunosuppressive therapy, ESRD, dexamethasone, rituximab and the presence of a central venous catheter and ateriovenous fistula. The patient's immunosuppressive state also substantially contributed to her cause of death. It is likely that the use of HDMTX played a role in the achievement of the complete pathologic response observed at autopsy.

This case adds to the limited literature showing that intensive high-flux hemodialysis can effectively clear MTX in patients with ESRD. While these patients may have other co-morbidities which limit their tolerance of aggressive ther-

apy, ESRD is not an absolute contraindication to the use of HDMTX when required for curative therapy of malignancy.

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Address correspondence to: Dr. Peter Mollee, Department of Haematology, Pathology Queensland, Princess Alexandra Hospital, Ipswich Rd, Woolloongabba 4102,Australia Tel: +61 7 32402396; Fax: +61 7 34207042; E-mail: peter_mollee@health.qld.gov.au

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