

BRIEF REPORT

Hypersensitivity Reaction to High-Dose Methotrexate and Successful Rechallenge in a Pediatric Patient With Osteosarcoma

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Hypersensitivity reactions to methotrexate are rare, but have been reported. Methotrexate has shown activity against many malignancies, and omission of methotrexate therapy may increase the risk of cancer-related death in some patients. Therefore, rechallenging patients with methotrexate following hypersensitivity may be beneficial. We report a case of a child with metastatic osteosarcoma

who experienced a hypersensitivity reaction to high-dose methotrexate and was successfully rechallenged with methotrexate using a 6-hour infusion. Using this regimen, adequate peak methotrexate plasma concentrations were achieved and no further hypersensitivity reactions were noted. *Pediatr Blood Cancer* © 2013 Wiley Periodicals, Inc.

Key words: anaphylaxis; hypersensitivity; methotrexate; osteosarcoma; pediatric

INTRODUCTION

Methotrexate is a dihydrofolate reductase inhibitor that is widely used in pediatric oncology for the treatment of both hematologic and non-hematologic malignancy. High-dose methotrexate with leucovorin rescue is commonly used for the treatment of osteosarcoma [1]. The major side effects of high-dose methotrexate include mucositis, nephrotoxicity, hepatotoxicity, neurotoxicity, and pulmonary toxicity. Hypersensitivity reactions to high-dose methotrexate are uncommon, but have been reported [2–14]. Rechallenging pediatric oncology patients with high-dose methotrexate following hypersensitivity reactions has also been reported in the literature [4–6,10,13,14]. In osteosarcoma patients, these case reports have often used extended infusions (e.g., infusion times of up to 27 hours) to desensitize patients to methotrexate [4,14]. Data suggest that attainment of adequate peak methotrexate plasma concentrations (≥ 700 – $1,000 \mu\text{mol/L}$) is important for successful outcomes in osteosarcoma patients [15–18]. Therefore, extended infusions of high-dose methotrexate, which result in lower peak plasma concentrations, are not ideal for the treatment of osteosarcoma. We report a case of a hypersensitivity reaction to methotrexate in a child with metastatic osteosarcoma who was successfully rechallenged with high-dose methotrexate and attained adequate peak methotrexate plasma concentrations using a 6-hour infusion.

CASE REPORT

The patient is a 9-year-old female diagnosed with osteosarcoma of the right humerus with metastases to the lungs and multiple bony sites treated on an institutional front-line osteosarcoma protocol (NCT00667342) to evaluate bevacizumab in combination with chemotherapy consisting of high-dose methotrexate, doxorubicin, cisplatin, ifosfamide and etoposide. High-dose methotrexate was administered at weeks 3, 4, 8, 9, 23, 24, 31, 32, 36, and 37. Her first course of high-dose methotrexate was complicated by delayed excretion and acute kidney injury requiring glucarpidase administration; however, no hypersensitivity reaction was noted. A summary of the pharmacokinetics for this and subsequent high-dose methotrexate courses is depicted in Table I. For her second course of high-dose methotrexate, the dosage was reduced from 12,000 to

8,000 mg/m^2 based on her delayed excretion with course 1 [19]. During the course 2 high-dose methotrexate infusion, she developed respiratory distress, cough, rash, hives, pruritis, and facial and tongue swelling approximately 2.6 hours into the infusion. The patient's methotrexate infusion was stopped, and she was given IV diphenhydramine. At that time, the patient had received approximately 65% of the total dose ($5,213 \text{ mg/m}^2$). Symptoms rapidly improved following diphenhydramine administration; however, the infusion was not restarted. A methotrexate plasma concentration that was obtained 36 minutes after the infusion was discontinued was $579 \mu\text{mol/L}$. She subsequently cleared her second course of methotrexate at hour 72 (i.e., methotrexate plasma concentration $< 0.1 \mu\text{mol/L}$) with no late toxicity noted (Fig. 1).

Following this reaction, the decision was made to rechallenge the patient with high-dose methotrexate based on the extent of her disease and the potential benefit of methotrexate therapy. A plan for rechallenging the patient with methotrexate was developed using the estimated pharmacokinetics from the previous course, with goals of avoiding a hypersensitivity reaction while achieving an end-of-infusion methotrexate plasma concentration of ≥ 700 – $1,000 \mu\text{mol/L}$ so that efficacy could be maintained. The patient's MTX pharmacokinetics were estimated by fitting a first-order two-compartment pharmacokinetic model to the patient's high-dose methotrexate concentration-time data using the MAP estimation algorithm as implemented in ADAPTII (Biomedical Simulations Resource, University of Southern California, Los Angeles, CA) and the prior pharmacokinetic parameter distribution from previous OS

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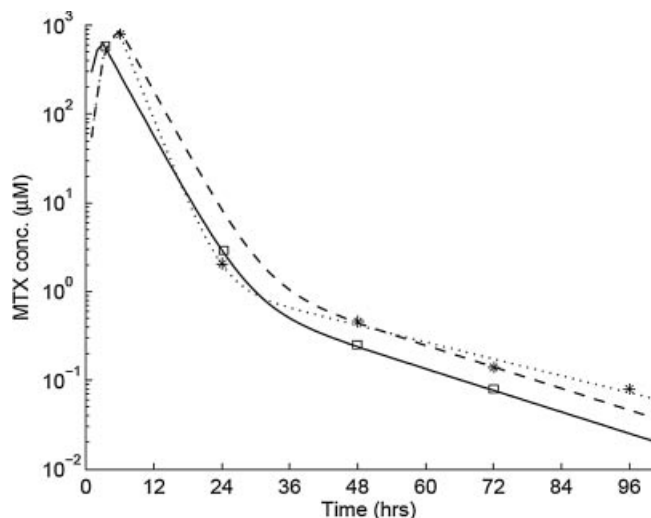


Fig. 1. Pharmacokinetic Simulations of doses 2 and 3 high-dose methotrexate. The solid line and squares are the plasma methotrexate plasma concentration data and fitted curve for course 2 high-dose methotrexate (5.2 g/m^2 over approximately 2.6 hours). The dashed line is the simulated course 3 curve (8 g/m^2 over 6 hours) based on course 2 pharmacokinetics. The dotted line and stars are the actual course 3 fitted curve and data.

studies [16]. Simulations indicated that adequate peak methotrexate plasma concentrations could be attained ($\geq 700\text{--}1,000 \mu\text{mol/L}$) [1,15–18] using a dosage of 8 g/m^2 given as a 6-hour infusion (Fig. 1).

For high-dose methotrexate course 3, the patient was given premedication with dexamethasone 4 mg PO q12h beginning 24 hours prior to admission. She was admitted overnight for prehydration with $\text{D5W} + 10 \text{ mEq/L KCl} + 40 \text{ mEq/L NaHCO}_3$ at $200 \text{ ml/m}^2/\text{hour}$ and received the following immediately prior to initiation of methotrexate: hydrocortisone IV 50 mg/m^2 , diphenhydramine IV 1 mg/kg , and ranitidine IV 1 mg/kg . Epinephrine, methylprednisolone, and diphenhydramine were available at the patient's bedside in case of anaphylaxis.

For course 3, methotrexate 8 g/m^2 infusion (dose rounded to 8.26 g/m^2) was diluted in $1,500 \text{ ml/m}^2$ (increased from the standard

volume of 800 ml/m^2) to a final concentration of 5.4 mg/ml . After premedication, 4% of the total dose was administered over the first hour of the infusion. At hour 1, the infusion rate was increased so that 8% total dose was given over the second hour of the infusion. At hour 2, the patient was redosed with hydrocortisone IV 50 mg/m^2 and the methotrexate infusion was increased to full rate (88% of the total dose over 4 hours). At hour 4, the patient was redosed with diphenhydramine IV 1 mg/kg . Leucovorin rescue $15 \text{ mg/m}^2 \text{ PO q6h} \times 6$ doses was initiated at hour 30 per institutional protocol. Hydration continued at $200 \text{ ml/m}^2/\text{hour}$.

The patient tolerated the high-dose methotrexate course 3 well. Plasma methotrexate concentrations were measured by fluorescent polarization immunoassay (TDx System; Abbott Laboratories, Abbott Park, IL). Her peak methotrexate plasma concentration was $798 \mu\text{mol/L}$ after the extended 6 hours infusion and she cleared methotrexate at hour 96 with no notable toxicity. A rechallenge was also attempted with course 4 using the above approach. The patient's peak methotrexate plasma concentration for course 4 was $809.6 \mu\text{mol/L}$. During this course, she cleared methotrexate at hour 120. The patient experienced grade II mucositis following course 4; however, the mucositis quickly resolved with increased leucovorin rescue and no additional complications were noted.

For courses 5 and 6, high-dose methotrexate was infused over 4 hours. For course 5, she was given 8 g/m^2 , and the dosage for course 6 was increased to 10 g/m^2 . Premedications were given in courses 5 and 6 as with courses 3 and 4. The patient tolerated these courses well, with peak levels of 809.4 and $842.4 \mu\text{mol/L}$, respectively. She cleared courses 5 and 6 methotrexate at hour 72 with no toxicity noted. The patient was subsequently taken off of protocol due to progressive disease.

DISCUSSION

Methotrexate hypersensitivity reactions, although rare, present a challenge for clinicians. Although further high-dose methotrexate therapy may be omitted from chemotherapy regimens in some cases, this omission may increase a patient's risk for cancer-related death [1]. Therefore, a rechallenge with high-dose methotrexate should be considered. Previous reports of methotrexate rechallenge in osteosarcoma have used extended infusions up to 27 hours for desensitization [4,14]. Although these rechallenges have been successful in some cases, there is question whether the efficacy of

TABLE I. Methotrexate Pharmacokinetic Profiles for Courses 1–6 With Model Estimates

MTX course	MTX dose (g/m ²)	Infusion time (hour)	Methotrexate plasma concentrations (μM)				Cl (ml/minute/m ²)	AUC (μM hour) ^a	C _{max} (μM) ^a
			Time						
			Peak	24 hours	48 hours	72 hours			
1	12	4	1,627	61	0.75	0.62	30.99	13,637	1,651
2	5.2	2.6	578.6	2.9	0.25	0.08	52.59	3,632	673.7
3	8	6	797.6	2.1	0.46	0.14	65.23	4,640	814.1
4	8	6	809.6	3.6	0.35	0.13	59.67	5,024	827.4
5	8	4	809.4	1.1	0.12	0.03	62.69	4,499	862.4
6	10	4	842.4	1.7	0.15	0.04	79.43	4,775	869.1

MTX, methotrexate; CL, clearance; AUC, area under the methotrexate plasma concentration-time curve; C_{max} , peak methotrexate plasma concentration. ^aCalculations based on pharmacokinetic model estimations.

high-dose methotrexate is decreased by the use of extended infusions [1,15–18]. Furthermore, a significantly extended high-dose methotrexate infusion may increase a patient's risk for methotrexate toxicity [4,20]. Therefore, a shorter infusion is desirable in osteosarcoma patients to maximize efficacy and decrease toxicity of methotrexate. This case report illustrates how an individual patient's available methotrexate pharmacokinetic data were used to select a dosage and an infusion rate that would attain adequate peak plasma concentrations when rechallenging a patient with a prior hypersensitivity reaction. We showed that, based on the pharmacokinetic modeling for our patient, using a 6-hour high-dose methotrexate infusion was feasible, and adequate peak methotrexate plasma concentrations were obtained.

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