

Delayed Renal Excretion of Methotrexate After a Severe Anaphylactic Reaction to Methotrexate in a Child With Osteosarcoma

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Summary: Although methotrexate is an agent widely used in the practice of pediatric oncology, allergic reactions to methotrexate are most unusual. Most of these reactions typically occur after repeated administration. Here, we report a severe anaphylactoid reaction to the first dose of high-dose methotrexate infusion in a child with osteosarcoma who has also experienced a delayed excretion of methotrexate. Clinicians must be aware of the possibility of a systemic, near-fatal anaphylactic reactions with methotrexate and patients who experience severe anaphylactic reactions should be followed carefully because of the possibility of delayed methotrexate excretion.

Key Words: anaphylactic reaction, methotrexate, delayed excretion (*J Pediatr Hematol Oncol* 2009;31:289–291)

Although there are a large number of chemotherapeutic agents used to treat cancer, hypersensitivity reactions are not common except with asparaginase, platinum compounds (cisplatin, carboplatin), epipodophyllotoxins (teniposide, etoposide), and taxanes (paclitaxel).^{1,2} Allergic reactions to methotrexate (MTX) are most unusual.^{3,4} Most of these reactions typically occur after repeated administrations, and only a few cases have developed the reaction after the first dose of MTX. The reactions that have been reported during the first exposure have mostly been seen in patients who have received high-dose methotrexate (HDMTX) infusion.^{5–7}

Here, we report a severe anaphylactic reaction to the first dose of HDMTX infusion in a child with osteosarcoma who has also experienced a delayed excretion of MTX.

CASE REPORT

A 15-year-old girl with osteosarcoma localized at the left distal femur was started on preoperative chemotherapy according to the Children Cancer Group-94 7921 protocol which includes HDMTX, ifosfamide, doxorubicin, and cisplatin. Having received the first course of the ifosfamide and doxorubicin combination without any problem, she was hospitalized for the first HDMTX (12 g/m², 4h) infusion. Before the treatment, blood chemistry

including kidney and liver functions were normal. Three hours after the start of the infusion, she developed fever, severe hypotension, tachycardia, tremor, vomiting, diffuse urticaria, facial swelling, and flushing. She was not taking any other medication except for antiemetic prophylaxis with standard dose of granisetron that had been used before and subsequently leaving MTX as the only suspect compound. The MTX infusion was terminated and treatment with intravenous fluids, epinephrine, dexamethasone, diphenhydramine, dopamine, and dobutamine infusions were started immediately. She was transferred to the intensive care unit. Her blood pressure returned to normal level after 3 hours of antishock treatment and the other findings of hypersensitivity reaction resolved within 12 hours.

Monitoring serum MTX level according to the protocol, the 24th hour of the HDMTX infusion showed a high level of serum MTX (180 µmol/L). The serum creatinine levels increased to twice of the basal values due to a shock-like syndrome associated with reduced renal blood flow and simultaneously, serum ALT levels increased to 2291 U/L. Owing to the delayed MTX clearance and the increased serum creatinine concentration, she required a prolonged course of hyperhydration/alkalinization (17d) and additional doses of folinic acid rescue. Liver and kidney functions returned to normal levels in 2 weeks.

The patient was not rechallenged with MTX because of the severe cardiovascular collapse she developed during the first exposure. She had a history of allergic dermatitis and her brother had allergic rhinitis. We decided that an MTX skin test, even with a preservative-free formulation, could lead to another life-threatening episode because of the previous severe anaphylactic reaction. Although MTX is a major component of chemotherapy regimens used for osteosarcoma treatment, we agreed to omit this agent from the regimen and switched to another combination using doxorubicin and cisplatin which had been demonstrated to be effective in the treatment of osteosarcoma.⁸ After the preoperative chemotherapy protocol, limb-sparing surgery was performed and then she continued postoperative chemotherapy with the same regimen. Owing to the cumulative dose of doxorubicin (405 mg/m²) and the nephrotoxic adverse effect of cisplatin, the chemotherapy protocol was changed to ICE protocol (ifosfamide, etoposide, carboplatin), which had been used for the treatment of refractory osteosarcoma.⁹ The patient is now doing well in complete remission and she is still on postoperative chemotherapy without any further complication.

DISCUSSION

MTX is an antimetabolite agent widely used in the practice of pediatric oncology. Although it has many adverse effects, allergic reactions related to MTX are uncommon. In the English literature, 35 allergic reactions including anaphylaxis, urticaria, angioneurotic edema, acute pneumonitis, cutaneous vasculitis, epidermal toxicity, hemolytic anemia, and hepatitis attributed to MTX have been reported, mostly observed in the patients receiving

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repeated MTX infusions. Although allergic reactions varied in severity, there were no reports of death.

Anaphylaxis is a life-threatening type of allergic reaction. The clinical manifestations of anaphylaxis include urticaria, angioedema, hypotension, and spasm of bronchial, gastrointestinal or uterine musculature. Severe anaphylactic reactions related to MTX have been reported in 15 patients (Table 1). Anaphylactic reaction to MTX was first described by Goldberg et al¹⁰ in 2 patients after repeated courses of HDMTX in conjunction with BCG immunotherapy. Although most cases involve intravenous infusion, anaphylaxis may also develop after intrathecal, intramuscular, or subcutaneous administration.^{3,11–13}

So far, only 4 adult cases have been reported with anaphylaxis to the first dose of MTX. Alkins et al⁵ described an anaphylactic reaction in a 30-year-old patient with osteosarcoma receiving the first HDMTX infusion. Straka et al¹² described a 34-year-old patient with ectopic pregnancy who developed an anaphylactic reaction in the first few minutes after intramuscular administration of 50 mg/m² MTX. In addition, Davis et al¹⁴ reported a 22-year-old man with osteosarcoma who had an anaphylactic reaction during the initiation of the MTX infusion and they also described a desensitization protocol to HDMTX. Similarly, Lluch-Bernal et al¹⁵ reported a 49-year-old woman with breast cancer who had an anaphylactic reaction due to her first MTX infusion and also demonstrated positive intradermal and skin prick tests to MTX.

Our case is the first pediatric patient who developed an anaphylactic reaction during the first infusion of MTX. The patient developed a severe cardiovascular collapse during the reaction. A delay in excretion of MTX was also detected in our patient during routine monitoring of serum drug levels. She did not have any renal dysfunction or any effusion that may lead to delayed MTX excretion. Renal hypoperfusion secondary to anaphylactic reaction may explain this complication together with the elevation of serum creatinine level.

As some of these reactions have appeared after the first dose of the drug, an antigen encountered earlier can lead to a cross reactivity with MTX. Previous chemotherapy with agents other than MTX had been reported as a risk factor for developing anaphylactic reactions to the first dose of MTX (Table 1). This could be a predisposing factor also for our patient.

Although the exact pathogenesis of these reactions is still unknown, an immunologically mediated mechanism has been most frequently suggested.^{4,16,17} Vega et al⁴ pointed out that anaphylactic reaction to MTX is a immunoglobulin E (IgE)-mediated reaction by demonstrating positive MTX skin prick testing in an affected patient whereas control subjects showed negative results. In contrast, the studies investigating in vitro-specific IgE failed to detect IgE antibodies in the serums of these patients. The authors explained this result by the technical difficulties.^{4,10,16} Our patient's reaction was probably IgE-mediated but we could not prove it.

When no alternative therapy is available and the reaction is not life threatening, rechallenge may be considered.^{5,6} A preservative-free MTX skin testing could have been helpful in terms of determining the mechanism, but the fact that most patients with immediate hypersensitivity reactions to MTX developed recurrent symptoms during the rechallenge despite prophylactic premedication was a discouraging factor both for us and for the family.⁵ None of these patients (except 2) with severe anaphylactic reaction received further MTX cycles.^{14,15} Therefore, our patient's treatment was changed to another regimen without MTX that contained other effective agents for osteosarcoma.

In conclusion, anaphylactic reactions to MTX may develop in an initial or subsequent doses of the drug in both adults and children. Clinicians must not only be aware of the commonly encountered toxicities of HDMTX, but also of the risk of systemic, near-fatal anaphylactic reactions, however, this might be rare. The patients who experienced a

TABLE 1. The List of the Previous Patients With Severe Anaphylactic Reactions

Diagnosis	Age (yr)	Dose	Route of Administration	Cycle	Symptoms	Possible Predisposing Factor	Cancer Treatment After Reaction	References
ALL	NM	12 mg	IT	5	Urticaria, angioedema, low BP	R-MTX	No MTX	3
BC	60	75 mg	IV	7	Urticaria, low BP	R-MTX	No MTX	4
OS	30	12g/m ²	IV	1	Urticaria, angioedema	P-CT	No MTX	5
OS	18	250 mg/kg	IV	8	Urticaria, angioedema	P-CT, BCG	No MTX	10
PCNSL	53	12 mg	IT	2	Angioedema, low BP	R-MTX	NM	11
EC	34	50 mg/m ²	I.M.	1	Urticaria, angioedema	absent	No MTX	12
RA	46	25 mg	SC	42	Urticaria, angioedema, low BP	etanercept	No MTX	13
OS	22	24 g	IV	1	Urticaria, angioedema,	P-CT	With MTX	14
BC	49	NM	IV	1	Dyspne, low BP, urticaria	P-CT	With MTX	15
BC	NM	200 mg	IV	12	Dyspne, low BP,	R-MTX	NM	16
OS	NM	300 mg/kg	IV	9	Dyspne, low BP,	R-MTX	NM	16
OS	NM	200 mg/kg	IV	14	Dyspne, low BP,	R-MTX	NM	16
BC	52	60 mg	IV	6	Dyspne, low BP,	R-MTX	No MTX	17
PM	56	0.5g/m ²	NM	Many	Urticaria, dyspne, low BP	R-MTX	NM	18
OS	2	12.5g/m ²	IV	23	Urticaria, angioedema	R-MTX	No MTX	19
OS	39	12g	IV	7	Urticaria, nausea, vomiting	R-MTX	NM	20
OS	34	12g	IV	2	Urticaria, angioedema	R-MTX	NM	20

ALL, acute lymphoblastic leukemia; BCG, BCG vaccine; BC, breast cancer; BP, blood pressure; CT, chemotherapy; EC, ectopic pregnancy; IV, intravenous; IT, intrathecal; NM, not mentioned; OS, osteosarcoma, PCNSL, primary central nervous system lymphoma; PM, polymyositis; P-CT, previous chemotherapy; RA, rheumatoid arthritis; R-MTX, repeated methotrexate; SC, subcutaneous.

severe anaphylactic reaction should be followed carefully for the possibility of delayed MTX excretion.

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