Published in final edited form as:

Pediatr Blood Cancer. 2017 May ; 64(5): . doi:10.1002/pbc.26306.

Methotrexate Hypersensitivity Reactions in Pediatrics: Evaluation and Management

Meredith A. Dilley, M.D.^{1,2}, Joyce P. Lee, Pharm.D., BCPS¹, and Ana Dioun Broyles, M.D.^{1,2}

¹Boston Children's Hospital, Boston, MA

²Harvard Medical School, Boston, MA

Abstract

Reports of hypersensitivity reactions (HSRs) to MTX are limited to single case studies. We retrospectively reviewed HSRs to MTX during a 12-year period in our tertiary care pediatric center. Seven patients were evaluated for HSRs to MTX. Skin testing was positive in one of the 4 patients tested. One patient underwent successful graded challenge to MTX. Seventeen desensitizations to MTX were successfully performed in the other 6 patients. Skin testing, graded challenge, and desensitization were safe and effective procedures in the evaluation and management of patients with HSRs to MTX in our pediatric population.

Keywords

Methotrexate; Drug allergy; Desensitization; Chemotherapy

INTRODUCTION

Methotrexate (MTX) is a folate antimetabolite used to treat various malignancies and autoimmune conditions¹. Hypersensitivity Reactions (HSRs) to MTX are rare and usually occur with re-exposure². HSRs may include urticaria, angioedema, rash, abdominal pain, bronchospasm, dyspnea, and hypotension and severe reactions are reported in <1% of HSR to MTX¹. The mechanism of most immediate HSRs to MTX is suspected to be IgE-mediated, though other mechanisms may also be involved¹. Skin testing and/or graded challenge are diagnostic procedures that may help in characterizing these reactions. Skin testing can help in the initial diagnosis. In cases with negative skin testing and/or mild reactions, graded challenge may be considered. Graded challenge is a diagnostic procedure

Correspondence: Meredith A. Dilley, M.D. 300 Longwood Ave, Fegan 6, Boston, MA, 02115. (617) 355-6117. meredith.dilley@childrens.harvard.edu.

Ana Dioun Broyles, M.D. Boston Children's Hospital, 300 Longwood Ave, Boston, MA, 02115 (617) 355-6117 ana.broyles@childrens.harvard.edu

Conflicts of Interest: None

Conflict of Interest Statement: The authors whose names are listed below attest that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter discussed in this manuscript.

Meredith A. Dilley, M.D.

Joyce P. Lee, Pharm.D.

Ana Dioun Broyles, M.D.

in which incremental doses of a drug are administered in a monitored setting while the patient is being observed; doses are not aimed at inducing tolerance³.

In cases with positive skin testing and/or history of more significant reaction, desensitization should be considered, particularly when alternate therapies are not available and/or the drug to which the patient has reacted is the first line therapeutic agent. Desensitization is the process of inducing temporary immunologic tolerance by administering gradually higher doses of a drug until the final cumulative therapeutic dose is achieved. Reports of MTX HSRs and desensitization in the adult and pediatric populations are limited to case studies⁴⁻¹⁰. We discuss our experience in a pediatric population with HSRs to MTX including skin testing, graded challenge, and desensitization protocols. To our knowledge this is the first case series describing the evaluation and management of HSRs to MTX, and the first report of using a 12-step desensitization protocol for MTX.

METHODS

We performed a retrospective chart review of patients undergoing graded challenge and desensitization to MTX at Boston Children's Hospital between 2002 and 2015. Institutional Review Board approval was obtained.

Skin Testing

Skin testing was performed through our clinic's standard technique, at least 2 to 4 weeks after the initial reaction to reduce the possibility of false-negative results¹¹. Skin prick testing to MTX was done at the concentration of 10mg/mL; intradermal testing was done with 0.1 mg/mL, 1 mg/mL, and 10 mg/mL concentrations which were based on previous reports^{11,12}. Histamine (10 mg/mL) and saline were used as positive and negative controls, respectively. In three patients skin testing was not performed due to the urgent need for drug administration. Based on skin testing results and clinical history, decision was made to perform either graded challenge or desensitization.

Graded Challenge and Desensitization: Procedures, and Protocols

Before considering graded challenge or desensitization, we utilized the Brown Classification Criteria to characterize reaction severity (Table 1)¹³. The results of skin testing when performed also helped determine the choice of procedure. Informed consent was obtained before the procedures which were performed with one-to-one nursing in an intermediate care or intensive care unit setting. Rescue medications (intravenous diphenhydramine, intramuscular epinephrine, nebulized albuterol, methylprednisolone, and normal saline) were available at the bedside.

Pre-medications were based on the well-described frequency of reactions during infusion and/or desensitization to chemotherapeutic agents¹⁴. Pre-medication regimens were aimed at minimizing breakthrough reactions during desensitization and were used in patients with more severe initial reactions^{14,15}. Pretreatment regimens were selected based on patient's history and/or the clinician's preference and were administered one hour prior to the start of the desensitization. If breakthrough reactions occurred during desensitization, they were

addressed by one or more of the following: stopping the infusion, treating the reaction, proceeding after lowering the infusion rate, and/or adding steps to the protocol ^{11,16}.

Most patients underwent desensitization using the protocol described in Table 2. It is based on a 12-step desensitization protocol not previously reported for MTX desensitization, though successfully used for some other chemotherapeutic agents ¹². One patient who did not tolerate this 12-step protocol underwent a 16-step protocol which was previously described for other drugs but not MTX ¹⁷.

RESULTS

Characteristics of the patients evaluated are shown in Table 1. Seven patients were evaluated for HSR to high-dose MTX. Skin testing was performed in 4 out of 7 patients and not done in the other 3 due to the urgency for re-administration of MTX. Testing was positive in patient 5 only. Patient 3 had a history of a mild reaction to MTX including hives and pruritus which occurred during concurrent administration of morphine. After negative skin testing, he tolerated a graded challenge to MTX without any reactions ¹⁸. Future MTX infusions were tolerated without incident.

A total of 17 desensitizations to MTX were performed in patients 1–2 and 4–7. Two out of 6 patients received pre-medications before undergoing desensitization, which included one or more of the following: H1 antagonists, H2 antagonists, corticosteroids, and/or acetaminophen.

Most patients underwent desensitization using the protocol described in Table 2. Patient 7 initially underwent 12-step desensitization. When the infusion rate was increased to 80 cc/hour, she developed hives, abdominal pain, and throat swelling. She received intravenous diphenhydramine and intravenous methylprednisone and the rate of infusion was reduced to 60 cc/hour. For subsequent desensitizations, a 16-step protocol, previously described for other drugs but not MTX ¹⁷, was used and tolerated without any reactions. Patients were able to receive planned doses of MTX per their chemotherapy protocol; Patient 4 died before further treatment could be given. No dose adjustments were made for toxicity as the cumulative dose for each desensitization is the same as the final planned dose.

DISCUSSION

To our knowledge, this is the first case series describing skin testing, graded challenge and desensitization to MTX as well as the first report of using 12-step and 16-step desensitization protocols for this drug. In our experience, these procedures are safe and effective in the pediatric population.

In the setting of an immediate HSR to MTX, defining the nature of the HSR and skin testing in appropriate cases may guide the clinician in deciding to perform graded challenge or desensitization. Obtaining a tryptase level immediately following the reaction may be helpful in diagnosing IgE-mediated allergy ¹¹. If tryptase level is elevated and IgE-mediated reaction is suspected, desensitization may be favored over graded challenge. Tryptase levels were not obtained by the physicians taking care of our patients, possibly due to these

physicians not being specialized in allergy and hence not being familiar with the importance of sending this test. While MTX skin testing is reported, there is no extensive data on the validity of skin testing to MTX. In some cases when the use of chemotherapy is urgent, skin testing may not be feasible due to time constraints. In addition, if the patient's HSR occurred recently, the probability of false negative reactions on skin testing are increased ¹¹. In those situations, desensitization may be the only option if treatment with the drug is deemed necessary. Also in patients with negative skin testing who have a history of severe HSR to the drug, desensitization should still be favored over graded challenge. In patients with negative skin testing, based on the clinical history, graded challenge may be considered, as we did for patient 3 in our case series. In patient 3, the clinical history along with negative skin testing led to the decision to perform graded challenge. However in patients with negative skin testing who have a history of severe HSR to the drug, desensitization may still be favored over graded challenge. Although such procedures are most effective in IgE-mediated reactions, desensitization is also used successfully in non IgE-mediated HSRs ¹⁶.

While there are several case reports involving MTX desensitization in pediatric and adult patients ⁵⁻⁹, these reports describe use of prolonged infusions, ranging from 11 to 33 hours, rather than step-wise, 2-fold increase in dose-based 12-step and 16-step desensitization protocols which have also been successfully used for other chemotherapy agents ¹⁷. This 12-step protocol has been adopted as a safe and cost-effective method of administering chemotherapy and has been adopted as the standard at our institution and others ^{12,14}. All of our patients tolerated the desensitization procedures well and were able to receive the benefits of treatment.

In patients with HSRs to MTX, graded challenge or desensitization to this drug may be considered based on the history, skin testing, and availability of alternate therapies. In our experience these procedures are safe and effective in re-administering MTX to pediatric patients with HSRs to MTX who would otherwise have to avoid this medication.

Acknowledgments

Sources of funding: Meredith Dilley is supported by NIHCHD grant: T32HD075727.

Abbreviations

MTX	Methotrexate
HSR	Hypersensitivity reaction

References

1. Ruggiero A, Triarico S, Trombatore G, et al. Incidence, clinical features and management of hypersensitivity reactions to chemotherapeutic drugs in children with cancer. *Eur J Clin Pharmacol*. 2013; 69(10):1739–1746. [PubMed: 23765411]
2. Pugi A, Benemei S, Vietri M, et al. Anaphylaxis during the first course of high-dose methotrexate: a case report and literature review. *J Clin Pharm Ther*. 2012; 37(2):245–248. [PubMed: 21569069]
3. Cernadas JR, Brockow K, Romano A, et al. General considerations on rapid desensitization for drug hypersensitivity - a consensus statement. *Allergy*. 2010; 65(11):1357–1366. [PubMed: 20716314]

4. Kohli A, Ferencz TM, Calderon JG. Readministration of high-dose methotrexate in a patient with suspected immediate hypersensitivity and T-cell acute lymphoblastic lymphoma. *Allergy Asthma Proc.* 2004; 25(4):249–252. [PubMed: 15510585]
5. Oulego-Erroz I, Maneiro-Freire M, Bouzon-Alejandro M, Vazquez-Donsion M, Couselo JM. Anaphylactoid reaction to high-dose methotrexate and successful desensitization. *Pediatr Blood Cancer.* 2010; 55(3):557–559. [PubMed: 20533520]
6. Bouchireb K, Dodille A, Ponvert C, Gouraud F, Dubrel M, Brugieres L. Management and successful desensitization in methotrexate-induced anaphylaxis. *Pediatr Blood Cancer.* 2009; 52(2):295–297. [PubMed: 18855892]
7. Caldeira T, Costa V, Silva I, Oliva T, Norton L. Anaphylactoid reaction to high-dose methotrexate and re-administration after a successful desensitization. *Pediatr Hematol Oncol.* 2008; 25(2):131–134. [PubMed: 18363180]
8. Fernando SL. Successful desensitization to low-dose methotrexate. *Rheumatology (Oxford).* 2013; 52(12):2305–2306. [PubMed: 23681395]
9. Davis KA, Williams P, Walker JC. Successful desensitization to high-dose methotrexate after systemic anaphylaxis. *Ann Allergy Asthma Immunol.* 2003; 90(1):87–89. [PubMed: 12546343]
10. Scott JR, Ward DA, Crews KR, Panetta JC, Navid F. Hypersensitivity reaction to high-dose methotrexate and successful rechallenge in a pediatric patient with osteosarcoma. *Pediatr Blood Cancer.* 2014; 61(2):373–375. [PubMed: 23955991]
11. Hsu Blatman KS, Castells MC. Desensitizations for chemotherapy and monoclonal antibodies: indications and outcomes. *Curr Allergy Asthma Rep.* 2014; 14(8):453. [PubMed: 24994467]
12. Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol.* 2008; 122(3):574–580. [PubMed: 18502492]
13. Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol.* 2004; 114(2):371–376. [PubMed: 15316518]
14. Castells Guitart MC. Rapid drug desensitization for hypersensitivity reactions to chemotherapy and monoclonal antibodies in the 21st century. *J Investig Allergol Clin Immunol.* 2014; 24(2):72–79. quiz 72 p following 79.
15. Hong DI, Dioun AF. Indications, protocols, and outcomes of drug desensitizations for chemotherapy and monoclonal antibodies in adults and children. *J Allergy Clin Immunol Pract.* 2014; 2(1):13–19. quiz 20. [PubMed: 24565764]
16. Brennan PJ, Rodriguez Bouza T, Hsu FI, Sloane DE, Castells MC. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol.* 2009; 124(6):1259–1266. [PubMed: 19910036]
17. del Carmen Sancho M, Breslow R, Sloane D, Castells M. Desensitization for hypersensitivity reactions to medications. *Chem Immunol Allergy.* 2012; 97:217–233. [PubMed: 22613865]
18. MacGinnitie AJ, Walensky LD, Turvey SE, et al. Management of an anaphylactoid reaction to methotrexate with a stepwise graded challenge. *Pediatr Allergy Immunol.* 2003; 14(5):409–411. [PubMed: 14641613]

Table 1

Patient Characteristics

Patient	Age/Sex	Indication	Reaction History *	Reaction severity **	Skin Testing	Desensitization Premedications	No. of desensitizations	Outcome
1	10/M	Osteosarcoma	Near the end of 12gm/m ² infusion, patient developed throat pruritus, diffuse urticaria, orofacial edema. The infusion was stopped, and treatment with epinephrine, diphenhydramine, and hydrocortisone led to resolution of symptoms.	Severe	Negative	None	2	Successful
2	4/M	Metastatic osteosarcoma	Patient developed pruritic rash during MTX infusion. Infusion was stopped.	Mild	Negative	None	3	Successful
3	9/M	ALL	At the beginning of 4mg/m ² infusion, developed hives and pruritus while receiving concomitant morphine infusion. The infusions were discontinued. Diphenhydramine and ranitidine were administered with gradual improvement of symptoms.	Mild	Negative	None	n/a***	Successful
4	6mo/F	Infantile ALL	Following MTX infusion, patient was noted to have erythematous, maculopapular rash. The MTX infusion was stopped. Patient succumbed to illness before skin	Mild	Not done	None	1	Successful

Patient	Age/Sex	Indication	Reaction History*	Reaction severity**	Skin Testing	Desensitization Premedications	No. of desensitizations	Outcome
			testing could be performed.					
5	16/F	Osteosarcoma	Halfway through 12gm/m ² infusion, patient developed generalized urticaria and pruritus. The infusion was stopped. After treatment with diphenhydramine and hydrocortisone, symptoms resolved within 30 minutes.	Mild	Positive	None	5	Successful
6	10/F	Osteogenic Sarcoma	During the middle of second MTX infusion, patient developed flushing and pruritis of face, neck, and upper extremities. Diphenhydramine, acetaminophen, and hydrocortisone were administered with resolution of symptoms.	Mild	Not done	Diphenhydramine, acetaminophen	4	Successful
7	15/F	Relapsed LBCL	During 4th MTX infusion, patient developed rhinorrhea, sneezing, throat pruritis, and urticaria of the face, neck and shoulders. The infusion was stopped. Diphenhydramine, hydrocortisone, and ranitidine were administered; symptoms resolved within 30 minutes. Attempt was made to restart infusion, but symptoms recurred.	Moderate	Not done	12-step: Diphenhydramine, ranitidine, prednisone, 16-step: Prednisone, Montelukast, Aspirin Cetirizine, Ranitidine	2	2 nd Attempt successful

ALL: Acute lymphoblastic leukemia; LBCL: Large B-cell Lymphoma

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

* All reactions occurred upon re-exposure to MTX.
*
* Brown Classification Criteria: Mild (skin and subcutaneous involvement only), Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement); Severe (hypoxia, hypotension, or neurologic involvement)⁸,
*** Graded challenge, successful

Table 2

12-Step Methotrexate Desensitization Protocol Used in Patient 7 *

Full Therapeutic Dose = 16960 mg (8076 mg/m ²)							
Solution	Total Volume (mL)	Drug per bag (mg)	Concentration (mg/mL)				
1	250	169,600	0.678				
2	250	1696,000	6.784				
3	250	16826,525	67.306				
Step	Solution	Rate (mL/hr)	Rate (mg/kg/hr)	Time	Dose per step (mg/m ²)	Cumulative dose (mg/m ²)	
1	1	2	0.015	15	0.1615	0.1615	
2	1	5	0.037	15	0.4038	0.5653	
3	1	10	0.074	15	0.8076	1.3729	
4	1	20	0.149	15	1.6152	2.9881	
5	2	5	0.372	15	4.0381	7.0262	
6	2	10	0.743	15	8.0762	15.1024	
7	2	20	1.486	15	16.1524	31.2548	
8	2	40	2.972	15	32.3048	63.5596	
9	3	10	7.372	15	80.1263	143.6859	
10	3	20	14.744	15	160.2526	303.9385	
11	3	40	29.488	15	320.5052	624.4437	
12	3	80	58.976	174.375	7451.7467	8076.1904	

* Patient weight: 91.3kg. Target dose: 16.96g

** Total time = 339.38 minutes (5.6 hours)