

Case Report

Management of an anaphylactoid reaction to methotrexate with a stepwise graded challenge

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We report the management of a 15-year-old boy with an anaphylactic or anaphylactoid response to his first dose of methotrexate during induction therapy for acute lymphoblastic leukemia (ALL). Because weekly methotrexate therapy is an important component of continuation chemotherapy for pediatric ALL, a stepwise graded challenge was employed to achieve drug tolerance.

**Andrew J. MacGinnitie¹,
Loren D. Walensky^{2,3}, Stuart
E. Turvey¹, Jordan S. Orange¹,
Francisco A. Bonilla¹,
Lewis B. Silverman^{2,3} and
Hans Oettgen¹**

¹Division of Allergy/Immunology, Children's Hospital and ²Division of Hematology/Oncology, Children's Hospital and ³Department of Pediatric Oncology, Dana-Faber Cancer Institute, Harvard Medical School, Boston, MA, USA

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Andrew MacGinnitie, Division of Allergy/Immunology, Fegan 6, Children's Hospital, Boston, MA 02446, USA
Tel.: +1 617 355 5635
Fax: +1 617 730 0528
E-mail: Andrew.macginnitie@TCH.harvard.edu

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Case report

The patient is a 15-year-old male who presented with jaundice and hepatosplenomegaly resulting from leukemic infiltration of his liver. The diagnosis of acute lymphoblastic leukemia (ALL) was confirmed by bone marrow evaluation. The patient began therapy as per established protocols (1, 2). On day two of induction chemotherapy, the patient began an infusion of high dose methotrexate (4 g/m² or 72 g) that was due to be administered over 1 h. Within the first 20 min of infusion, having received approximately 2 g of the drug, the patient developed diffuse urticaria and pruritis. He reported a subjective sensation of throat tightness, although there was no clinical evidence of respiratory distress. No associated hypotension or gastrointestinal symptoms were documented. The infusion was discontinued and 50 mg of diphenhydramine and 50 mg of ranitidine were administered intravenously with gradual symptomatic improvement. No epinephrine was administered.

Intrathecal thiotepea was given instead of intrathecal methotrexate for subsequent therapeutic lumbar punctures (3). The patient achieved complete remission within 4 weeks of beginning therapy.

After 6 months of intensification therapy, the patient was due to begin continuation chemotherapy, including weekly intravenous low dose methotrexate (30 mg/m² or 54 mg per dose) for 18 months. Therefore, the patient initially underwent skin prick followed by intradermal testing to methotrexate at concentrations of 0.1, 1, and 10 mg/cc. No reaction was detected, whereas a normal response to a histamine control was demonstrated. A control subject, tested in parallel, also failed to react to methotrexate. Because methotrexate skin testing is not standardized and weekly desensitization was not feasible, we performed three stepwise graded challenges to methotrexate (see Table 1) in the intensive care unit (ICU) setting. The first challenge consisted of consecutive 5, 50, 500 µg, 5, and 50 mg doses at 30-min intervals, for a total dose equal to the

Table 1. Stepwise graded challenge to methotrexate

	Dose
Starting dose, week no. 1 →	1. 5 µg in 50 ml of NS then
Starting dose, week no. 2 →	2. 50 µg in 50 ml of NS, then
Starting dose, week no. 3 →	3. 500 µg in 50 ml of NS, then
	4. 5 mg in 50 ml of NS, then
	5. 50 mg in 50 ml of NS

planned weekly dose of 30 mg/m². The first increment of 5 µg represented approximately 1/400,000 of the dose which prompted the initial reaction, a dose consistent with desensitization protocols used at our institution, and less than the starting dose recommended in published desensitization protocols (4). In the second week, the challenge commenced with 50 µg of methotrexate, followed by a starting dose of 500 µg in the third week. The patient displayed no adverse reaction to the infusions. He subsequently received the standard weekly doses of methotrexate as a 30-min infusion in the outpatient setting without incident.

Discussion

Methotrexate is commonly used for the treatment of bone and hematologic cancers, as well as rheumatologic conditions. Approximately 20 cases of anaphylactic or anaphylactoid reactions to methotrexate have been reported in the literature (5). While most cases involve intravenous infusion, anaphylaxis to intrathecal administration has also been reported (6). One study demonstrated positive skin testing and specific IgE to methotrexate (7).

Reactions to methotrexate typically occur after repeated administration, but several cases of severe reactions to the first dose of methotrexate have been documented. Alkins et al. (5) described two patients with immediate hypersensitivity to a first infusion of methotrexate. One patient was not re-challenged because of airway involvement, while the second had recurrence of pruritis and urticaria upon re-challenge despite pre-medication with dexamethasone and diphenhydramine. A second report (8) documents one patient who developed urticaria upon initial exposure to methotrexate and was treated with diphenhydramine. The infusion was restarted after a 20-min pause and proceeded uneventfully; all subsequent treatment incorporated antihistamine premedication and there was no recurrence of an allergic response. Of note, all three of these cases involved a reaction to high dose methotrexate.

In the case reported here, our patient reacted immediately upon first exposure to high dose methotrexate. Whether this represented a true IgE-mediated anaphylactic event or an anaphylactoid reaction resulting from non-specific mast cell degranulation is unknown. The negative response to skin testing and the reaction to a first dose both support a non-IgE-mediated mechanism. The symptoms of urticaria and subjective throat tightness beginning during infusion are most consistent with mast cell degranulation, with no evidence of a more delayed reaction due to immune complexes (serum sickness-like reaction) or cell-mediated immunity (Stevens-Johnson/toxic epidermal necrolysis-type reaction).

The severity of the initial reaction coupled with the need for long-term weekly dosing prompted us to perform a series of graded challenges to methotrexate. Each week, the challenge was started at a 10-fold increased dose of methotrexate until it was apparent that there was no further allergic response. The patient has subsequently tolerated weekly methotrexate without incident and without the use of antihistamine pre-medication. Although methotrexate is usually administered as a rapid intravenous push, the patient continues to receive his therapy as an infusion delivered over 30 min in order to minimize the risk of an idiosyncratic anaphylactoid response. Because intrathecal methotrexate results in sustained systemic exposure for days after administration, an adverse reaction would be difficult to manage; therefore an alternative medication was substituted for intrathecal methotrexate.

Because our patient's reaction was probably not IgE mediated, we cannot be sure our approach would be safe in a patient with specific IgE against a medication. However, by starting at a dose much lower than the one that caused the initial reaction and then slowly increasing the starting dose each week the possibility of a systemic anaphylactic reaction is minimized. In cases where IgE against the medication is demonstrated by skin testing, consideration could be given to increasing the weekly starting dose more slowly. Our approach would not be suitable for delayed reactions not consistent with mast cell degranulation.

Many medical regimens involve chronic intermittent therapy, including cancer chemotherapy, anti-inflammatory treatments for rheumatologic illnesses, and intravenous immunoglobulin (IVIG) infusion for immunological and neurological conditions. The management of patients with adverse drug reactions is particularly challenging when long-term therapy is indicated. Here we describe the use of a stepwise graded

challenge as an approach to addressing this clinical problem. Although this strategy required three ICU admissions, it resulted in our patient safely receiving the remainder of his methotrexate therapy in the outpatient setting. The stepwise graded challenge may be useful as a general approach for addressing immediate adverse responses to medicines that require sustained intermittent use.

References

1. SILVERMAN LB, DECLERCK L, GELBER RD, et al. Results of Dana-Farber Cancer Institute Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1981–95). *Leukemia* 2000; 14: 2247–56.
2. SILVERMAN LB, GELBER RD, DALTON VK, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91–01. *Blood* 2001; 97: 1211–8.
3. GUTIN PH, LEVI JA, WIERNIK PH, WALKER MD. Treatment of malignant meningeal disease with intrathecal thioTEPA: a phase II study. *Cancer Treat Rep* 1977; 61: 885–7.
4. NACLEERIO R, MIZRAHI EA, ADKINSON NF JR. Immunologic observations during desensitization and maintenance of clinical tolerance to penicillin. *J Allergy Clin Immunol* 1983; 71: 294–301.
5. ALKINS SA, BYRD JC, MORGAN SK, WARD FT, WEISS RB. Anaphylactoid reactions to methotrexate. *Cancer* 1996; 77: 2123–6.
6. DEVECIOGLU O, BENER B, KARABOCUOGLU M, UNUVAR A, AGAOGLU L. Systemic near-fatal anaphylactic reaction after intrathecal methotrexate administration. *Med Pediatr Oncol* 2000; 34: 151–2.
7. VEGA A, CABANAS R, CONTRERAS J, et al. Anaphylaxis to methotrexate: a possible IgE-mediated mechanism. *J Allergy Clin Immunol* 1994; 94: 268–70.
8. POSTOVSKY S, ELHASID R, BEN-BARAK A, LEVIN K, BEN ARUSH MW. Allergic reaction to high-dose methotrexate. *Med Pediatr Oncol* 2000; 35: 131–2.