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CASE REPORT

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Rapid desensitization to methotrexate: a successful case in acute lymphoblastic leukemia

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Abstract
Methotrexate (MTX) is a folate antimetabolite indicated for the treatment of malignant and autoimmune diseases. It is one of the most effective drugs used for the treatment and maintenance therapy of acute lymphoblastic leukemia (ALL). This paper presents a 13-year-old patient with B-type ALL who experienced a severe hypersensitivity reaction, prompting the implementation of a MTX desensitization protocol. This protocol may serve as a useful reference for future desensitization procedures. This case challenged the medical team in determining how to safely continue with the prescribed therapy. Although cases of MTX desensitization have been published in the literature, most of these are adult patients; only a few were pediatric patients; and even a fewer were patients with ALL. Given the absence of alternative treatment options, MTX desensitization was implemented, leading to a successful continuation of the therapy.

Introduction

Methotrexate (MTX) is a folate antimetabolite widely indicated for the treatment of malignant and autoimmune diseases. It is one of the oldest but most effective drugs used for the treatment and maintenance therapy of acute lymphoblastic leukemia (ALL).[1]

Although the use of MTX is essential in the treatment of ALL, the occurrence of hypersensitivity reactions (HSRs) poses a significant risk to the continuation of the therapy.[2] The manifestations of HSRs are studied with standard dose, high dose, oral, intramuscular, intrathecal, and/or intravenous forms of MTX. The reactions can include pruritus, urticaria, angioedema, wheezing, dyspnea, hypotension,

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and/or loss of consciousness.[2,3] While the incidence of HSRs is unknown, they are considered as rare, with documented cases of anaphylaxis.[3] Skin tests and/or graded challenges are diagnostic procedures that may help in characterizing these reactions.[1] The following concentrations have been used for prick testing (10 mg/mL) and intradermal testing (0.1 mg/mL and 1 mg/mL).[3]

For patients with MTX reactions, the management should be individualized in context of the overall clinical picture after considering risks and benefits of reintroduction.[3] The use of alternative treatments in ALL may lead to suboptimal results or death because of cancer progression. Desensitization allows treatment to be continued, preventing the development of HSRs by inducing temporary tolerance.[4]

We present the case of a 13-year-old male patient with Down's syndrome and B-cell ALL, who underwent rapid desensitization with MTX. He currently continues weekly treatment without developing HSRs.

Case Report

A 13-year-old male patient diagnosed with B-cell ALL was undergoing treatment with vincristine, dexamethasone, MTX, and cytarabine. Two months later, premedication with cetirizine (20 mg orally) and hydrocortisone (200 mg intravenously) was administered and 15 min after the start of the seventh intravenous MTX infusion, the patient developed a facial rash, eyelid angioedema, fever, and a foreign body sensation in the pharynx (globus sensation). The infusion was discontinued, supplemental oxygen was initiated, and intravenous diphenhydramine (300 mg) and hydrocortisone (200 mg) were administered. During the next infusion, 2 weeks later, the patient was premedicated with 300 mg of diphenhydramine and 200 mg of hydrocortisone. However, 10 min after start of the infusion, the patient again developed a facial rash, angioedema, globus sensation, and respiratory distress. On this occasion, intramuscular adrenaline (0.5 mg) was administered, with clinical improvement. MTX administration was considered necessary, and the patient was referred to the Allergy Department for evaluation.

According to the Brown Classification, the patient was classified as having a mixed HSR grade 2. Skin prick testing with MTX (10 mg/mL) and intradermal testing (0.1 mg/mL and 1 mg/mL) were performed. The intradermal test yielded a positive result (wheal 12×12 mm; control 7×7 mm). A drug challenge was deferred, as the second MTX infusion had already elicited an anaphylactic reaction, which was considered a positive challenge with a favorable response to epinephrine administration.

A 12-step desensitization protocol was designed, with premedication consisting of hydrocortisone (200 mg), cetirizine (20 mg), and montelukast (10 mg) (Table 1). Vital signs were continuously monitored throughout the procedure. The patient developed a mild rash 10 min after the start of step 12, which resolved with an additional dose of cetirizine (10 mg). The desensitization was completed with no further complications. Subsequent desensitizations were performed weekly using the same concentration. During the third session, the protocol was shortened to eight steps, which the patient tolerated without manifestations. Therefore, during the fourth desensitization, MTX was administered conventionally, with no recurrence of HSR.

During the fifth administration, a drug challenge was performed. The patient initially received one-tenth (1/10 or 10%) of the total dose, with continuous monitoring of vital signs. After 30 min of observation without adverse events, the total dose (25 mg) was completed; this was also well

Table 1 Rapid desensitization protocol to methotrexate (MTX).

Total dose	25 mg	Dilution concentration (mg/mL)	Total dose of each dilution (mg)
Dilution A (1:100)	0.25 mg	0.001	0.009
Dilution B (1:10)	2.5 mg	0.01	0.18
Dilution C (total dose)	24.8 mg	0.05	24.8
Step	**Solution**	**Infusion (mL/h)**	**Duration (min)**
1	A	2.5	15
2	A	5	15
3	A	10	15
4	A	20	15
5	B	5	15
6	B	10	15
7	B	20	15
8	B	40	15
9	C	10	15
10	C	20	15
11	C	40	15
12	C	80	174.4

Note: The total duration is approximately 5 h, 45 min–6 h.

tolerated. The patient subsequently continued a weekly oral dose of 25 mg at home, with no reactions until the end of the treatment. He is currently in good general health and remains under follow-up of the Hematology Department, with regular evaluations by the Allergy Department.

Discussion

Comparable pediatric cases of MTX desensitization have been described, although they remain uncommon.[5,6] Dilley et al. reported the largest pediatric series to date, including seven children who underwent 17 desensitizations, all of which were successful, highlighting that structured protocols with incremental dosing can safely allow continuation of essential chemotherapy.[1] Similarly, Caldeira et al. and Oulego-Erroz et al. described individual children with ALL or osteosarcoma who developed anaphylactoid reactions to high-dose MTX and were subsequently re-exposed using stepwise desensitization protocols, with good tolerance and no recurrence of hypersensitivity.[7,8] Kohli et al.[9] and Scott et al.[10] also reported successful re-administration of high-dose MTX in adolescents after urticaria or anaphylaxis, using prolonged infusions or fractionated doses to maintain therapeutic drug levels. Overall, the similarities among these cases and ours include the immediate-type presentation, the necessity of continuing MTX for curative intent, and the effectiveness of desensitization to restore tolerance.[9,10] Differences exist mainly in the chosen protocol—rapid multi-step versus prolonged infusion—the use of premedication, and the clinical setting (ALL vs. osteosarcoma). Our case reinforces the feasibility and safety of rapid desensitization in pediatric patients with confirmed MTX hypersensitivity when continuous therapy is essential.

Conclusion

We report a successful MTX desensitization protocol that may be useful as a guide for future desensitization in patients requiring MTX as part of their chemotherapy or treatment plan. We demonstrate that pharmacological desensitization in children can be performed safely and successfully, with a positive impact on survival and the overall prognosis.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

Author Contributions

All authors contributed equally to this article.

Conflicts of Interest

The authors declared that they had no competing interests.

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