

Case Report

ANAPHYLACTOID REACTION TO HIGH-DOSE METHOTREXATE AND RE-ADMINISTRATION AFTER A SUCCESSFUL DESENSITIZATION

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□ *Methotrexate (MTX) is an antimetabolite with a major role in the treatment of acute lymphoblastic leukaemia (ALL). The authors report the management of a 9-year-old boy who developed an anaphylactoid reaction to high-dose MTX infusion, after a first challenge with intrathecal administration, during induction therapy for ALL. A desensitization protocol was followed and MTX tolerance has been successfully achieved, allowing this patient to complete the needed chemotherapy.*

Keywords desensitization protocol, methotrexate hypersensitivity

Methotrexate (MTX) is a commonly used anti-neoplastic drug in the treatment of pediatric cancer. It is used in high-dose intravenous (IV) infusion and as intrathecal (IT) administration in the treatment of acute lymphoblastic leukemia (ALL).

It acts by inhibition of dihydrofolate reductase activity on de novo purine synthesis. MTX is metabolized by polyglutamate synthetase into polyglutamylated MTX (MTXPG) (with five additional glutamates added to the molecule in leukemic lymphoblasts). These extended MTXPG are retained for even longer inside the cell. Increased intracellular levels of active MTXPG metabolites accumulation have been associated with a better clinical outcome [1]. B-cell ALL blasts accumulate more MTXPG than the T-cell ALL blasts, determining their higher sensitivity to MTX. Very high doses of MTX appear to improve the outcome in patients with T-cell ALL [1].

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High-dose MTX (HDMTX) major side effects are mucositis, bone marrow depression, hepatotoxicity, and renal damage. There are few reports of allergic reactions to methotrexate administration in children who have described different management approaches either by excluding MTX from the treatment regimen [2] or re-administrating MTX after antihistamine premedication [3] or a stepwise desensitization protocol [4–6]. Desensitization protocols to other cytotoxic drugs more commonly associated with hypersensitivity reactions, namely carboplatin, have been described [7]. Based on these protocols, a desensitization regimen for high-dose MTX was developed [6], which we successfully adapted and applied.

A 9-year-old boy was admitted to our institution with a 1-month history of weight loss, pallor, and fatigability. Initial CBC and cytomorphology showed hemoglobin 5.3 g/dL, white blood cells 78,000/mm³, platelets of 34,000/mm³, and presence of blasts in peripheral blood. Immunophenotyping demonstrated a T-cell ALL and molecular studies were negative for other abnormalities. There was no CNS or genital involvement.

The patient was treated according the CLG-EORTC ALL randomized phase III study (58951). This includes intrathecal MTX on day 1, along with prednisolone. On day 8 T-cell ALL patients receive intravenous high-dose MTX (5 g/m²) over 24 h. Approximately 30 min after the beginning of the infusion, our patient developed a pruritic, urticarial rash on the face, upper limbs, and trunk. Chemotherapy was immediately stopped and he was treated with clemastine and hydrocortisone, with rapid and complete regression of the rash. Considering the crucial role of MTX in ALL chemotherapy, we decided to pursue the treatment with this drug. Thus, we followed a short desensitization protocol for high-dose MTX, based on the administration of 1/1000 of the total intravenous dose over 90 min, then 1/100 of the dose over 90 min, 1/10 over 6 h, and the remaining dose over 24 h [6]. The patient received premedication with clemastine and hydrocortisone 1 h before the infusion. The first infusion of desensitization protocol took place in the intensive care unit. All other high-dose MTX infusions were administered following the same protocol but in the inpatient pediatric oncology unit. No subsequent manifestations of allergic reaction were documented.

DISCUSSION

Although there are a few case reports in the literature describing allergic reactions during the first MTX administration [3, 8], most anaphylactic reactions to MTX occur after a previous challenge with the drug. It is speculated that the mechanism of MTX hypersensitivity is likely to be a type I IgE-mediated hypersensitivity reaction [9]. Our patient was sensitized after a first exposure to MTX given intrathecally, probably leading to production

of specific IgE antibodies and subsequent mast-cell degranulation on MTX re-administration.

Some previous reports describe desensitization protocols for patients with MTX hypersensitivity [4, 6, 10]. In one patient, MTX subsequent doses were safely given after antihistamine premedication only [3]. Another report describes a premedication regimen starting 5 days before the MTX administration, using oral histamine receptor antagonists H1 and H2 and leukotriene receptor antagonists, oral corticosteroids every 6 h started 13 h before the infusion, and IV corticosteroids and diphenylhydramine 1 h before the gradually increasing doses of MTX infusion [10]. We followed a desensitization regimen, which has the advantage of a one-time administration of premedication of corticosteroid and antihistamine H1 antagonist, and a 3-step MTX infusion with increasing doses, over 33 h [6]. The patient received consecutive increasing doses of MTX (1/1000 and 1/100) over a 1.5-h period, then 1/10 of the dose over 6 h, and, finally, the remaining dose was infused in 24 h. This desensitization protocol was administered before every high-dose MTX infusion until the end of the treatment. Maintenance treatment included weekly low doses (20 mg/m²) of oral methotrexate, where no desensitization was done.

HDMTX significantly reduces central nervous system (CNS)-related relapses, and reinforces systemic therapy reducing non-CNS relapses and improving survival. Although intrathecal methotrexate results in systemic exposure, there is a previous report of an acute systemic anaphylactic reaction after intrathecal MTX administration [2]. So we decided to pursue methotrexate administration as part of the triple IT chemotherapy, with adequate premedication, which included corticosteroid and antihistamine H1 antagonist with each of the IT treatments.

This case illustrates a typical hypersensitivity urticarial reaction to high-dose MTX, most probably due to an IgE-mediated mechanism, successfully overcome with a 3-step desensitization protocol. We believe that patients with anaphylactic reactions to MTX can be safely managed by using this desensitization protocol [6], allowing them to proceed with their needed chemotherapy.

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