

BRIEF REPORT

Anaphylactoid Reaction to High-Dose Methotrexate and Successful Desensitization

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Anaphylactic/anaphylactoid reaction to methotrexate (MTX) is uncommon. It may occur with the first dose (non-allergic reactions) or after a previous exposure to the drug (allergic or specific reactions). Desensitization has been shown effective in children with allergic-type reactions permitting the continuation of high-dose methotrexate (HDMTX) therapy. We report the case of a child with localized

osteosarcoma who developed an anaphylactoid reaction after a first HDMTX course. A desensitization protocol was successfully applied allowing the administration of four additional courses. In our experience, desensitization can be a safe and effective procedure in children with anaphylactoid reactions to HDMTX. *Pediatr Blood Cancer*. © 2010 Wiley-Liss, Inc.

Key words: anaphylactoid reaction; desensitization; high-dose methotrexate

INTRODUCTION

High-dose methotrexate (HDMTX) plays a key role in the therapy of pediatric osteosarcoma. Common side effects of HDMTX include mucositis and liver or kidney dysfunction. Hypersensitivity or allergic reactions have been also reported in adult and, less frequently, pediatric patients at various doses [1–12]. Although rare, allergic/immunological reactions to HDMTX are clinically relevant, moreover, if we consider that HDMTX discontinuation in such circumstances may negatively impact the final outcome. Thereafter, strategies aimed to permit the readministration of HDMTX for these patients, such as premedication and/or desensitization, have been proposed. We report the case of a child with localized osteosarcoma and recurrent anaphylactoid reactions to HDMTX who was successfully managed by desensitization.

CASE REPORT

Our patient was a 12-year-old female diagnosed with localized osteosarcoma in the proximal tibia. She had no previous history of hypersensitivity or allergic reactions. She was treated according to the protocol of the Spanish Society of Pediatric Oncology which includes six preoperative courses of HDMTX. In each HDMTX course, MTX is given at a dose of 12 g/m² over 4 hr together with intravenous hydration, alkalization, and folinic acid rescue, the last starting 24 hr after completion of the MTX infusion. Antiemetic prophylaxis includes ondansetron and dexamethasone.

Our patient developed generalized urticaria within the first 30 min of the first HDMTX infusion. She developed pruritus and mild facial edema without respiratory or gastro-intestinal involvement. The infusion was stopped and dexchlorfeniramine and hydrocortisone were administered. MTX infusion was resumed, but urticaria reappeared and an extra dexchlorfeniramine dose was required.

One week later another course of HDMTX was administered after premedication with dexchlorfeniramine and hydrocortisone. Again a similar urticarial rash appeared. MTX was discontinued temporarily and a second dose of dexchlorfeniramine was administered. The infusion was resumed at a slower rate and completed successfully.

MTX was the only suspected cause of the reaction. Other medications administered prior to the urticarial reaction included

ondansetron and dexamethasone. Both of them had been repeatedly administered to the patient before and after the urticarial reaction without any adverse effect.

In order to continue HDMTX therapy, essential for the treatment of osteosarcoma, a desensitization protocol was considered (Table I). Total MTX dose was lowered to 8 g/m² to prevent increased toxicity associated with prolonged infusions [1]. Desensitization protocol was performed in the pediatric intensive care unit under continuous monitoring (pulse-oximetry, non-invasive blood pressure, heart rate, and EKG) and appropriate resuscitation equipment and medications at bedside. Folinic acid rescue began 24 hr after the end of MTX infusion and was maintained until serum MTX levels were under 0.2 µmol/L. No allergic or allergic-like reaction occurred during the MTX infusion. Four additional HDMTX courses were uneventfully administered following this protocol.

DISCUSSION

Anaphylactic/anaphylactoid reactions to MTX may be caused by allergic (specific) hypersensitivity [1–7] or by non-allergic (non-specific) hypersensitivity [8–12]. The former requires sensitization, at least one previous exposure, while the latter may be associated with the first administration. Both types of reactions can be life-threatening [6,10]. There are only two previous reports on anaphylactoid non-allergic reactions after first exposure to HDMTX in children [9,12]. In the first case, a patient with metastatic osteosarcoma developing an urticarial rash 30 min after administration of HDMTX (12 g/m²) is described. Rechallenge with premedication (diphenhydramine) was successful. In the second case, a patient with acute lymphoblastic leukemia (ALL) developed pruritus and

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Conflict of interest: Nothing to report.

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TABLE I. Desensitization Protocol

Premedication (30 minutes before MTX)
Dexchlorfeniramine (0.04 mg/kg)
Ranitidina (100 mg)
Hydrocortisone (500 mg)
Antihistamine therapy
Dexchlorfeniramine (0.04 mg/kg) over 24 hours
Incremental MTX doses ^a
1/1,000 total dose over 90 minutes
1/100 total dose over 90 minutes
1/10 total dose over 6 hours
Rest of full dose over 18 hours
Total infusion time: 27 hours

MTX, methotrexate. ^aDrug was immediately discontinued in case of respiratory distress, urticaria, fever, or hypotension with administration of proper drugs (e.g., salbutamol for respiratory distress) if indicated.

rash within the first 20 min of a HDMTX (4 g/m²) infusion. The patient was successfully rechallenged by means of a 3-week stepwise graded protocol to a total MTX dose of 54 mg (weekly low-dose MTX for ALL continuation therapy).

Both premedication and desensitization have been successfully used in case of anaphylactoid reaction to HDMTX. In our case, premedication alone failed to prevent urticaria in the second HDMTX administration so desensitization in addition to premedication was used. Several desensitization protocols have been described [7,9,13]. The present protocol has been successfully used in three patients with allergic-type reaction to HDMTX (2.5–12 g/m²) [1,2,7]. We decided to reduce the total MTX dose to 8 g/m² to diminish the risk of increased toxicity due to prolonged infusion [1,14,15]. Increased toxicity of 12 g/m² following a 27-hr desensitization protocol has been documented in one patient with osteosarcoma. Also, delayed renal excretion after anaphylactic reaction to MTX has been described in another patient [13]. Following this protocol permitted the administration of four HDMXT courses without incidence.

Potential risks associated with desensitization include increased toxicity of prolonged MTX infusion as well as a potentially lower antineoplastic effect [14–18]. Prolonged time of infusion, used in desensitization, may be associated with lower peak levels of MTX than shorter infusions. This could raise concerns about the reduction of its antineoplastic effect [14–18]. MTX serum levels >700 or 1,000 µmol/L at the end of MTX infusion are associated with better histological response and survival in osteosarcoma [17,18]. These levels are achievable in most patients at a dose of 12 g/m² infused over 4–6 hr [19]. In our case, MTX was infused over 27 hr, according to the desensitization protocol, and the total dose lowered to 8 g/m². Median and range serum levels of MTX at the end of 27-hr infusion were 193.2 and 123.1–242.2 µmol/L, respectively. Therefore, our decision to lower MTX dose to 8 g/m² may be controversial. However, the dose needed to reach a peak level of 700 µmol/L when MTX is infused over 27 hr is unknown. In addition, there is no study demonstrating antitumoral advantages/disadvantages, for the treatment of osteosarcoma, of MTX peak serum levels below 700 µmol/L with longer systemic exposure versus peak levels >700 µmol/L for a shorter time. On the other hand, experimental and clinical research studies in other malignancies have shown that efficacy is not reduced in prolonged infusions as compared with short infusions [14–16]. Length of exposure to high systemic levels of MTX seems to be

the major determinant of its toxicity, as demonstrated in children with lymphoma and leukemia [14]. All of these factors guided our decision to lower the total dose to 8 g/m².

Regarding safety, no severe anaphylactic reaction during HDMTX desensitization has been reported, although a publication bias cannot be discarded.

According to the literature and our reported experience, desensitization seems a safe and effective procedure in case of anaphylactoid reaction to HDMTX in children. Importantly, HDMTX desensitization has not been tested after severe anaphylactic reactions, with airway involvement, or cardiocirculatory collapse, so its application in these conditions should be individualized and limited only to high-risk patients.

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