

BRIEF REPORT

Cutaneous Side Effects of Medium Dose Methotrexate in Children With Acute Lymphoblastic Leukaemia

Cor van den Bos, MD, PhD,¹ Marc B. Bierings, MD, PhD,¹ Marrie C.A. Bruin, MD,¹
Carin M.A. Rademaker, PhD,² Christian W. van Haselen, MD,³ and
Tom Révész, MD, PhD^{1*}

Key words: acute lymphoblastic leukaemia; methotrexate; side effects; skin

Methotrexate (MTX) is a folic acid antagonist that is widely used in the treatment of leukaemias and solid tumors. Skin reactions to MTX are rare [1]. Severe bullous dermatosis and onycholysis have been reported [2] as well as generalized erythema in two children [3]. These reports concern high-dose MTX administration for osteogenic sarcoma (6–12 g/m² over 4–6 hr). Moderate (MD) MTX of 1.5 g/m² doses were implicated in the erythema and desquamation of the hands reported in three adults during treatment for non-Hodgkin lymphoma [4]. A 64-year-old man developed severe skin rash in combination with bone marrow aplasia after only 40 mg/m² in the treatment of recurrent metastatic squamous cell carcinoma [5]. A review of the literature did not reveal any reports of moderately severe to severe cutaneous side effects in children treated with MD-MTX. We therefore wish to describe our experience with what we believe to be the first two such cases.

Patient 1 started treatment at our hospital for common-ALL at the age of 16 years. After remission induction, full blood count and blood chemistry before the first of four MTX cycles did not reveal any abnormalities. With hyperhydration and alkalization, MTX was given at a dose of 2 g/m² over 24 hr (1/10 of the total dose as a loading dose over 10 min). Approximately 24 hr after the start of the MD-MTX infusion he developed a patchy, erythematous, and slightly elevated rash on both legs (Fig. 1). MTX clearance during this cycle was delayed (Fig. 2) and necessitated a prolonged period of hyperhydration/alkalination and additional doses of folic acid rescue. The rash was treated topically with a neutral cream and later with hydrocortisone cream. The remaining three MTX cycles were completed with double doses of folic acid rescue. MTX clearances were normal during these cycles, and the skin abnormalities disappeared slowly over time with a period of postinflammatory pigmentation. During maintenance treatment with oral mercaptopurine and methotrexate, no skin problems occurred.

Patient 2, an 8-year-old girl was treated for a common

ALL. A remission was obtained after the induction treatment. The course of the first of three MTX cycles was uncomplicated. The MTX level at 48 hr was 0.19 μmol/liter. A few days later, she developed a pruritic skin rash in her neck, which was still faintly visible when she was admitted 1 week later for her second MTX cycle. It disappeared completely before the second cycle was started the following day. Full blood count and blood chemistry on admission were normal, with a creatinine of 25 μmol/liter. Although she maintained a urine production of well over 5 ml/kg/hr in the first 48 hr, her creatinine increased to 70 μmol/liter, and the MTX clearance was delayed, necessitating prolonged hyperhydration, alkalization and additional folic acid doses (Fig. 2). At the end of the 24 hr MTX infusion, the rash started to reappear. In the following days it spread to include vast areas of the skin (Fig. 3). Peripheral blood analyses showed an eosinophilia of up to 4 × 10⁸/liter, and a skin biopsy was compatible with a medication-induced skin reaction. Treatment was given locally with hydrocortisone cream. Because of this severe skin reaction, administration of the final MTX-cycle had to be postponed. The last cycle was given after exclusion of an immediate-type hypersensitivity reaction to MTX. Because other hypersensitivity type reactions could not be excluded, this final MD-MTX dose was given under the protection of prednisone and clemastine. In view of the delayed MTX clearance during the second course, double doses of fo-

¹Department of Paediatric Hematology, Wilhelmina Children's Hospital, UMC, Utrecht, The Netherlands

²Department of Pharmacy, Wilhelmina Children's Hospital, UMC, Utrecht, The Netherlands

³Department of Dermatology, UMC, Utrecht, The Netherlands

*Correspondence to: Dr. T. Révész, Department of Paediatric Haematology, Wilhelmina Children's Hospital, University Medical Centre, Utrecht, P.O. Box 85090, 3508 AB Utrecht, The Netherlands.
E-mail: t.revesz@wzk.azu.nl

Received 25 August 1999; Accepted 20 October 1999



Fig. 1. Skin reactions observed in patient 1 after the first MTX cycle.

linic acid were given. The skin rash almost completely vanished before the start of the last cycle and continued to fade. Maintenance treatment, including oral mercaptopurine and methotrexate, has thus far not been complicated by further skin reactions.

DISCUSSION

Cutaneous side effects of the severity observed in our two patients have not been reported after medium-dose MTX for childhood ALL. The eosinophilia in our second patient is clearly suggestive of an allergic drug reaction [6]. Because a skin reaction occurred after the first MTX dose, one would have to assume some cross-reactivity between MTX and an antigen encountered earlier. It is known that prolonged antigen exposure in tissues can lead to hypersensitivity reactions with eosinophilia [6], which fits with the observation in our patients that the most severe skin reactions were observed after delayed MTX clearance. However, a toxic origin seems more likely, insofar as no adverse reactions were observed during maintenance therapy that includes oral

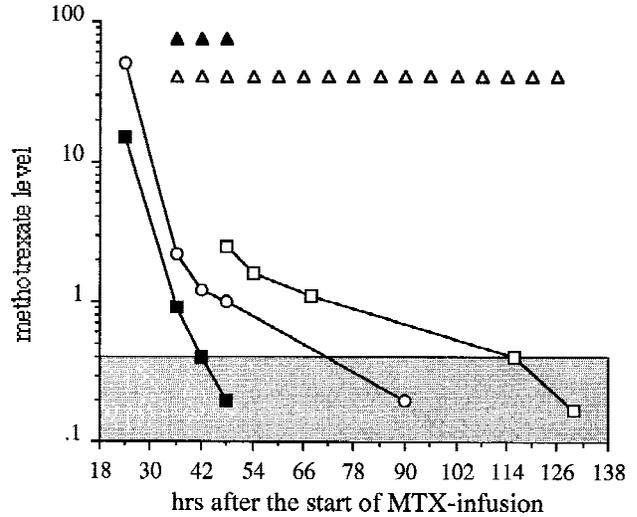


Fig. 2. MTX clearances after MD-MTX therapy. Open circles, clearance in the first MTX cycle in patient 1. Open and solid squares, clearances in, respectively, second and third MTX cycles in patient 2. Solid triangles, normal folinic acid rescue times. Open triangles, folinic acid rescue doses administered to patient 2 during the second MTX cycle. Shaded area represents a level of >0.4 μmol/liter, which allows for discontinuation of hyperhydration, alkalization, and folinic acid rescue.

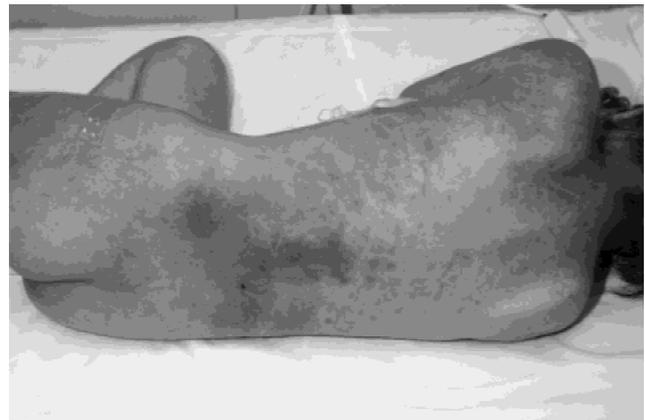


Fig. 3. Severe and extensive skin abnormalities in patient 2.

MTX. Furthermore, the previously mentioned cutaneous side effects observed in adults treated with comparable MTX doses were also presumed to be of toxic origin [4].

Eosinophilia was observed in adult patients with rheumatoid arthritis with MTX-induced pancytopenia, after restoring the intracellular folate levels by folinic acid [7]. The mechanism of that phenomenon remains speculative [7], but it resembles quite closely our observations in patient 2. This might be an alternative explanation for the observed eosinophilia.

The exact pathophysiology of the skin reactions in our patients remains elusive. The cases nevertheless serve to illustrate that adverse cutaneous reactions to MTX can

pose serious clinical problems in the treatment of children with ALL. With adequate supportive measures, it is possible to overcome these problems and continue treatment with methotrexate.

ACKNOWLEDGMENTS

Cor van den Bos is a Fellow of the Dutch Cancer Society "Koningin Wilhelmina Fonds."

REFERENCES

1. Folb PI. Cytostatics and immunosuppressive drugs. In: Dukes MNG, editor. *Meyler's side effects of drugs. An encyclopedia of adverse reactions and interactions*. Amsterdam: Elsevier; 1992. p 1107-1163
2. Chang CJ. Acute bullous dermatosis and onycholysis due to high-dose methotrexate and leucovorin calcium. *Arch Dermatol* 1987; 123:990-992.
3. Takami M, Kuniyoshi Y, Oomukai T, et al. Severe complications after high-dose methotrexate. *Acta Oncol* 1995;34:611-612.
4. Doyle LA, Berg C, Bottino G, Chabner B. Erythema and desquamation after high-dose methotrexate. *Ann Intern Med* 1983;98: 611-612.
5. Copur S, Dahut W, Chu E, Allegra CJ. Bone marrow aplasia and severe skin rash after a single low dose of methotrexate. *Anticancer Drugs* 1995;6:154-157.
6. Dinauer MC. The phagocyte system and disorders of granulopoiesis and granulocyte function. In: Nathan DG, Orkin SH, editors. *Nathan and Oski's hematology of infancy and childhood*. Philadelphia: W.B. Saunders Company; 1998. p 889-967.
7. Bruyn GAW, Velthuysen E, Joosten P, Houtman PM. Pancytopenia related eosinophilia in rheumatoid arthritis: a specific methotrexate phenomenon? *J Rheumatol* 1995;22:1373-1376.