High-dose methotrexate-induced acral erythema in two pediatric patients with acute lymphoblastic leukemia: a 17 pediatric case series of methotrexate induced acral erythema

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TEXT:

Chemotherapy-induced acral skin reaction with sensory disorder has become widely known as acral erythema or hand-foot skin reaction. The incidence of acral skin reactions has increased with usage of kinase inhibitors in addition to conventional chemotherapeutic agents, especially in adult patients. In contrast, only a few dozen pediatric cases of acral skin reaction have been reported, although pediatric patients have increased the chance to receive kinase inhibitor treatment. Here, we report high-dose methotrexate-induced acral erythema in two pediatric patients with acute lymphoblastic leukemia (ALL).

Case 1 was a 6-year-old boy treated with oral 6-mercaptopurine once a day for 8 weeks and 24-h infusion of high-dose methotrexate (2 g/m^2) once every 2 weeks for four infusions. Three days after the first methotrexate infusion, painful erythema and bullae appeared in his left heel (Supplemental Figure 1) and he had disabled walking with spontaneous recovery. Although we prevented acral erythema with topical corticosteroid during and after the second methotrexate infusion, more serious lesions emerged after the third and fourth infusions. Therefore, systemic corticosteroid was needed to completely recover these lesions.

Case 2 was a 12-year-old boy treated with the same chemotherapy regimen as case 1 except for the methotrexate dose being 5 g/m^2. Erythema only with slight pain appeared in his bilateral heels (Supplemental Figure 1) after every methotrexate infusion. However, the lesions did not disturb his activity and systemic corticosteroid therapy was not required. Methotrexate clearance was not delayed in both cases.

The etiology of acral erythema remains unclear. Histopathologic features are nonspecific with findings of vacuolar degeneration of the basal layer, necrosis of keratinocytes, loss of epithelial polarity, and perivascular infiltration. Though acral erythema in much less common in children than in adults, methotrexate has been reported as the prominent causative agent of acral erythema in children. We summarized all 17 reported cases of methotrexate-induced acral erythema thus far,[2-13] including our two cases (Table).

Overall, pediatric methotrexate-induced acral erythema developed 1–3 days after administration and resolved within 1–3 weeks. Almost all cases received high-dose methotrexate. Some physicians speculate that methotrexate clearance delay and renal impairment caused by high-dose methotrexate might be risk factors for acral erythema; however, in reports with data description,[2-6,9,10,13] 9 of 12 pediatric patients did not show delayed methotrexate clearance and 8 of 9 pediatric patients did not show renal impairment. Interestingly, ALL cases with methotrexate-induced acral erythema were older than the susceptible age for ALL, most often in children aged 2–3 years. We speculate that older children may have a higher risk of methotrexate-induced acral erythema.

Although some cases spontaneously recovered, several therapies including moisturizer,[1,7,9] topical corticosteroid therapy,[10] systemic corticosteroid therapy,[4,13] and intravenous immunoglobulin[7] have been reported. Among them, systemic corticosteroid therapy seems to be the most useful treatment, similar to adult cases when the erythema developed.[14]Almost all cases were able to continue to receive high-dose methotrexate therapy repeatedly, even though the dose of methotrexate was reduced in some cases due to acral erythema-related severe pain, probably contributing to maintain excellent cancer prognosis.

(500/500 words)

Conflict of Interest Statement

We have no conflicts of interest to declare.

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