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Methotrexate and Mucositis: A Merry-Go-Round for Oncologists

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Abstract

High-dose methotrexate is the backbone of various regimens for treating lymphoid malignancies. Mucositis is a well-known, dose-related side effect of methotrexate. Prophylactic measures such as folinic acid rescue are useful but do not prevent mucositis in all the cases. Once severe mucositis (WHO Grade IV) sets in, mortality is very high. The index case highlights the natural course of methotrexate-induced mucositis and the need for swift and preemptive intervention.

Keywords: *Lymphoid malignancy, methotrexate, mucositis*

Introduction

Methotrexate is a commonly used drug for lymphoid malignancies as well as connective tissue disorders. It is known to cause an array of complications including myelosuppression, mucosal ulcers, skin rash, and liver toxicity. Because Sidney Farber reported its usefulness in acute lymphoblastic leukemia, it has been used rampantly and successfully in various lymphoid malignancies.[1] Although the incidence of life-threatening complications has decreased with precautionary measures such as folinic acid rescue (after high-dose methotrexate [HDMTX]), yet it is a reality. In this case report, we present a case of HDMTX-induced severe mucositis despite having received folinic acid rescue. We highlight the course of potentially life-threatening mucositis effectively managed with timely intervention with supportive care.

Case Report

A 22-year-old female, a known case of acute lymphoblastic lymphoma, on modified BFM 2000 protocol was admitted with complaints of painful, oral ulcers and difficulty in swallowing for 2 days. One week earlier, she had received HDMTX (5 g/m^2) followed by folinic acid rescue. On examination, she had restricted mouth opening and multiple oral mucosal ulcers [Figure 1a] (mucositis WHO Grade IV). Her investigations revealed hemoglobin 110 g/L, total leukocyte count (TLC) 0.9 × 10^9/L, absolute neutrophil count 0.04 × 10^9/L, platelet 70 × 10^9/L, and normal peripheral blood smear. Her serum urea was 22 mg/dL, creatinine 0.9 mg/dL, and alanine transaminase 42 U/L. She was managed with intravenous (IV) granulocyte-colony stimulating factor, IV morphine, and local application of lignocaine viscous. On day 2, she developed fever (101°F), and her oral lesions worsened [Figure 1b]. She was managed with empirical broad-spectrum IV antibiotics (cefoperazone-sulbactam and teicoplanin) and total parenteral nutrition. Blood cultures and oral swab cultures were sterile. She became afebrile and her white blood cell count normalized by day 7. Oral mucosal lesions markedly improved by day 10 [Figure 2a] and completely resolved by day 14 [Figure 2b]. Methotrexate dose was decreased by 25% in the three subsequent cycles which she tolerated well without any complications.

Discussion

Methotrexate is used as low dose (<50 mg/m^2), intermediate dose (50–500 mg/m^2), and high dose (>500 mg/m^2).[2] HDMTX is used for central nervous system (CNS) prophylaxis in acute lymphoblastic leukemia/lymphoma. It is also used therapeutically in primary CNS lymphoma, leptomeningeal metastasis, and osteosarcoma. The intermediate- and low-dose methotrexate is used for gestational trophoblastic disease and inflammatory disorders such as rheumatoid

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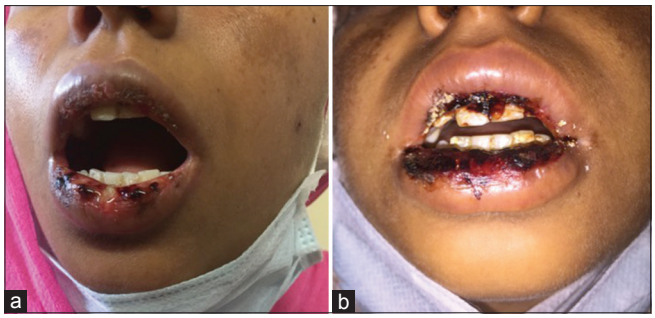

Figure 1: (a) Diffuse oral mucosal ulcers and restricted mouth opening (day 1). (b) Worsening of mucosal lesions (day 2)

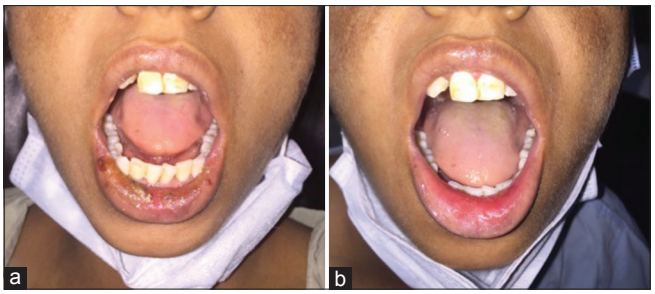

Figure 2: (a) Near-complete clearance of oral lesions with minimal, restricted mouth opening (day 10). (b) Complete clearance of oral lesions with normal mouth opening (day 14)

arthritis, systemic lupus erythematosus, psoriasis, hidradenitis suppurativa, and graft versus host disease. Although HDMTX can be safely administered in most of the patients, it may manifest with toxicity attributable to HDMTX such as mucositis, myelosuppression, and pulmonary, renal, and hepatic toxicity. Prior to folinic acid rescue, the incidence of mucositis has been reported in as high as 52% in children receiving HDMTX.[3] Mucositis of severe grade (WHO Grade III and IV) is a potentially life-threatening oncological emergency.[4] Prophylactic measures such as hydration, urine alkalinization, and folinic acid rescue are universally a part of HDMTX therapy protocol. Folinic acid reduces the incidence of methotrexate toxicity but does not eliminate the risk.[5] Palifermin is another drug shown to prevent mucositis, and it has been used for mucositis prevention in patients receiving HDMTX.[6] Glucarpidase can be used to eliminate toxic level of methotrexate from the blood.[7] It is Food and Drug Administration approved since 2012 for use in HDMTX-induced nephrotoxicity and delayed clearance of methotrexate when the level is >1 μM/L.[8] However, the cost and availability are limiting factors in developing countries. Another limiting factor includes nonavailability of laboratory facility to monitor methotrexate level in developing countries. Close observation after HDMTX is indispensable, as prompt intervention has been shown to improve outcomes in such patients. Moreover, once mucositis sets in, symptomatic and supportive care is the mainstay of management.[9] Opioid analgesics are often required, so is the total parental nutrition. Super-added bacterial infections and delayed presentation frequently complicate the management of methotrexate-related mucositis. It often results in delay in further chemotherapy. In resource-constrained settings, it adds to the cost of therapy and burdens the health-care system. Therefore, increasing awareness regarding this precarious condition among patients and health-care providers shall be beneficial.

Conclusion

Methotrexate-induced mucositis may be fatal if not treated proactively. However, a swift and preemptive intervention results in a rewarding outcome. A resplendent clinical photograph of the index patient demonstrates the natural history of a successfully managed Grade-IV mucositis and the HDMTX cycles continued albeit at a lower dose!

Consent

Informed signed written consent was taken from the patient involved.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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