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Clinical Investigation

Low-Dose Total Skin Electron Beam Therapy Combined With Mogamulizumab for Refractory Mycosis Fungoides and Sézary Syndrome

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Abstract

Purpose: Management of patients with refractory mycosis fungoides and Sézary syndrome (SS) is often challenging, as available therapies lack durable response and consistent activity across disease compartments. Combining low-dose total skin electron beam therapy (LD-TSEBT) upfront with mogamulizumab could optimize the clinical outcome of these patients. LD-TSEBT is effective in clearing skin disease, and mogamulizumab is an antitumor immunotherapy with long-term tolerability, suggesting its potential as a maintenance therapy after maximal response. We examine the combination regimen in patients with SS who were previously treated.

Methods and Materials: Two patients with SS were treated with combination LD-TSEBT and mogamulizumab. Both patients received mogamulizumab 1 mg/kg weekly × 4 and then bi-weekly; LD-TSEBT (12 Gy) was initiated within 2 days of starting mogamulizumab and given over 2-3 weeks. Safety and clinical response were evaluated.

Results: Total skin electron beam therapy plus mogamulizumab (TSE-Moga) was well-tolerated without any unanticipated adverse events. Patient 1 (T4N2bM0B2) was a 63-year-old woman with 4 prior systemic therapies; time to global response with TSE-Moga was 9 weeks. Patient 2 (T4NxM0B2) was a 75-year-old man with 5 prior systemic therapies; time to global response was 4 weeks. Both patients lacked global response to their prior therapies but achieved global complete response (blood and skin) with TSE-Moga. After a follow-up of 72 weeks and 43 weeks, respectively, global complete response continued.

Conclusions: TSE-Moga demonstrated excellent tolerability and promising clinical activity with ongoing global complete responses in 2 patients with refractory SS. This encouraging experience supports our ongoing clinical trial evaluating the efficacy and safety of TSE-Moga in mycosis fungoides and SS.

Introduction

Available therapies for mycosis fungoides (MF) and Sézary syndrome (SS) often lack durable response and consistent clinical activity across disease compartments. Skin-directed treatment combined with systemic treatment is often used to manage refractory MF and SS and is particularly useful in optimizing response across multiple compartments.[1] Combination strategies that leverage or

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enhance radiation effects and augment antitumor immune responses with immunotherapies can be utilized to optimize clinical outcomes in challenging patients.

Total skin electron beam therapy (TSEBT) is a highly effective and reliable skin-directed therapy in MF.[2] Prospective studies using low-dose TSEBT (LD-TSEBT) have demonstrated an 87% to 88% overall response rate (ORR) and 18%-27% complete response (CR) rate in the skin compartment.[2,3]

Mogamulizumab, a monoclonal antibody against CC chemokine receptor 4, is a valuable new immunotherapy option in MF and SS.[4] CC chemokine receptor 4 is consistently expressed on malignant T-cells and regulatory T-cells in MF/SS. Mogamulizumab eliminates malignant T-cells primarily by antibody-dependent cell cytotoxicity, possibly augmented by an immune-mediated mechanism associated with depletion of regulatory T-cells. Mogamulizumab has impressive activity in the blood (68% ORR, 44% CR), but lower skin response (42% ORR, 4% CR) with only 28% global (composite of all compartments) ORR.[4,5] The duration of global responses is quite encouraging (median 14.1 months).

Combination therapy of LD-TSEBT with mogamulizumab (TSE-Moga) may not only improve skin responses, but also clear leukemic disease and provide sustained and improved overall clinical outcome. Furthermore, the long-term tolerability of mogamulizumab suggests its potential as a maintenance therapy after maximal response. Herein, we present our experience in highly refractory SS successfully treated with TSE-Moga.

Report of Cases

Two patients with refractory SS achieved global CR (skin/blood) after treatment with TSE-Moga. Mogamulizumab and LD-TSEBT (initiated within 2 days of starting mogamulizumab) were administered.[1-4]

Case 1 (stage IVA1, T4N2bM0B2) (Fig 1) was a 63-year-old woman with confluent, thick exfoliative erythroderma. She had 4 systemic therapies (methotrexate, romidepsin, anti-KIR3DL2 monoclonal antibody, combination pembrolizumab and interferon-gamma) prior to TSE-Moga. She received LD-TSEBT (12 Gy) in 15 fractions over 3 weeks and 4 cycles of mogamulizumab. During TSEBT, she received boosts to the soles and perineum, to 12 Gy in 15 fractions to each site. External eye shields were used, and no other blocking was performed. Disease assessment showed blood CR after 1 cycle, skin partial response after 2 cycles, and global CR after 4 cycles. Mogamulizumab associated rash (MAR) developed after 4 cycles, which resolved with discontinuation of mogamulizumab and administration of systemic steroids. Low-dose oral methotrexate was started as a steroid-sparing treat-

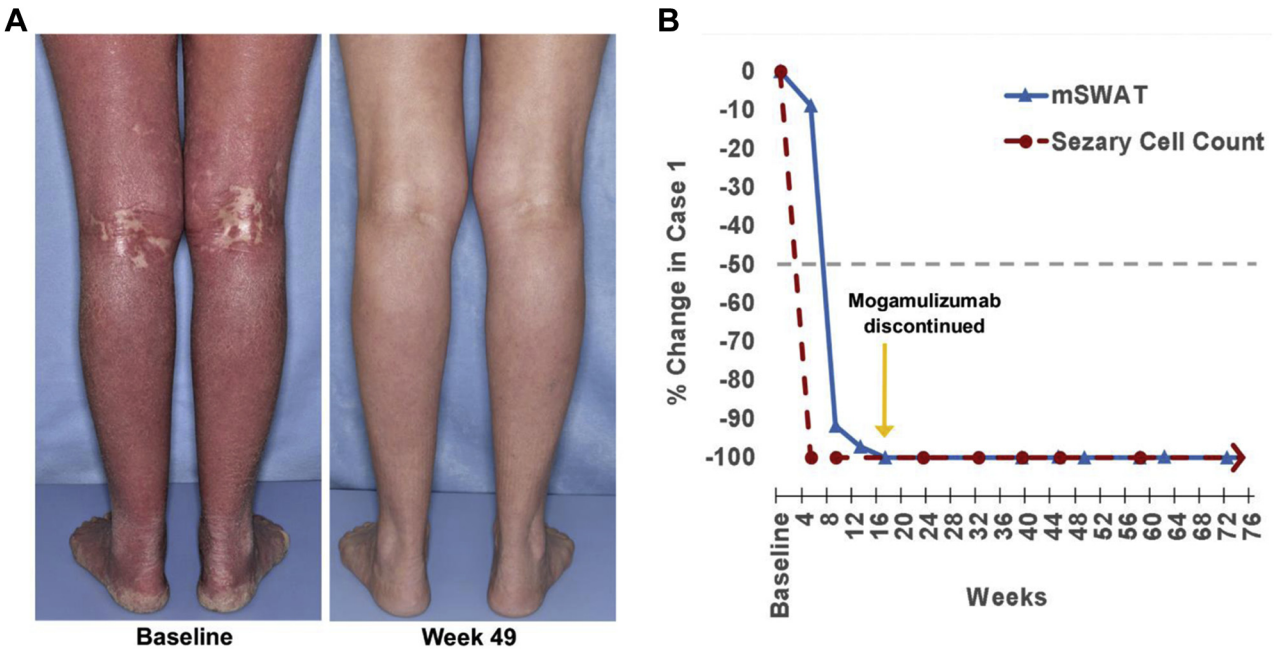

Figure 1 Case 1: Ongoing complete response (CR) in skin and blood. (A) Clinical photographs at baseline with modified severity weighted assessment tool (mSWAT) score = 182 and at week 49 with mSWAT score = 0 (CR in skin). (B) Reduction in skin and blood disease with global CR achieved after 4 cycles (week 17). Horizontal line at −50% represents the threshold for defining partial response in the skin and blood. Yellow arrow indicates the time at which mogamulizumab was discontinued. (A color version of this figure is available at https://doi.org/10.1016/j.adro.2020.11.014.)

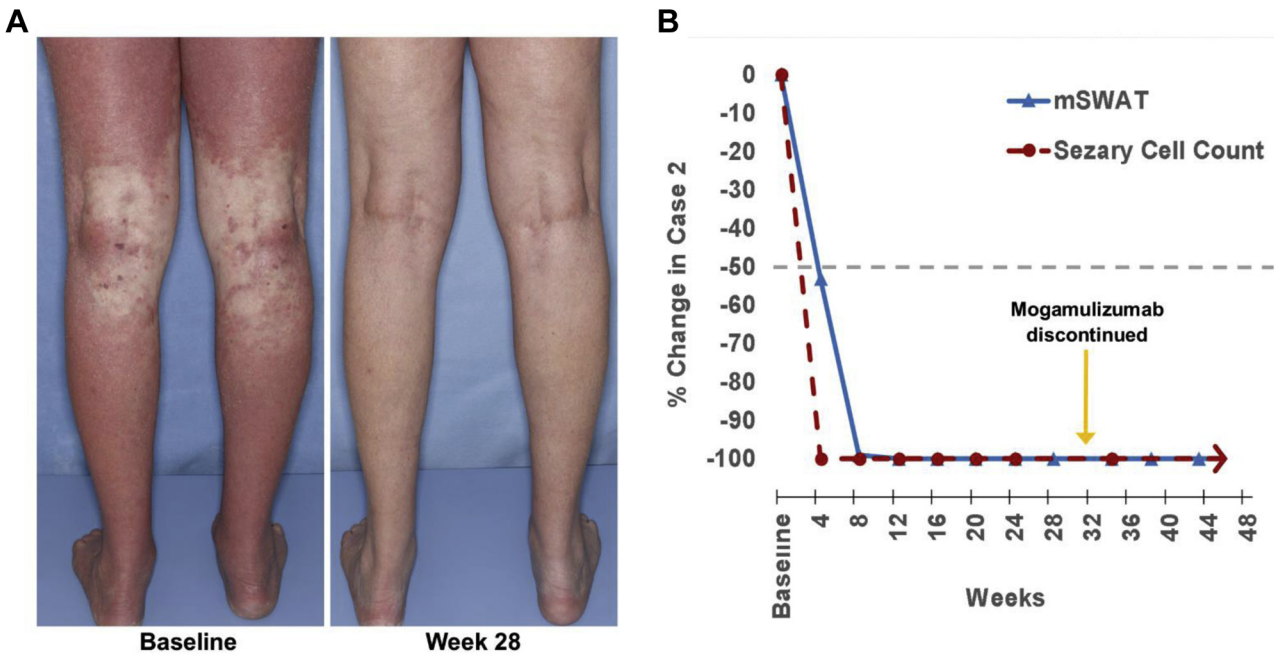

Figure 2 Case 2: Ongoing complete response (CR) in skin and blood. (A) Clinical photographs at baseline with modified severity weighted assessment tool (mSWAT) score = 172 and at week 28 with mSWAT score = 0 (CR in skin). (B) Reduction in skin and blood disease with global CR achieved after 3 cycles (week 12). Horizontal line at −50% represents the threshold for defining partial response in the skin and blood. Yellow arrow indicates the time at which mogamulizumab was discontinued. (A color version of this figure is available at https://doi.org/10.1016/j.adro.2020.11.014.)

ment for MAR and continued to support CR. She remained in global CR after 72 weeks of follow-up.

Case 2 (stage IVA1, T4NxM0B2) (Fig 2) was a 75-year-old man with generalized scaly erythroderma. He had 5 systemic therapies (methotrexate, bexarotene, romidepsin, combination pembrolizumab and interferon-gamma, E7777 [IL-2R-diphtheria toxin fusion protein]) before TSE-Moga. He received LD-TSEBT (12 Gy) in 10 fractions over 2 weeks and 8 cycles of mogamulizumab. During TSEBT, he received boosts to 12 Gy in 10 fractions to the soles and the perineum. Internal eye shields were used due to involvement of the periorbital skin. No other blocking was performed. Skin partial response and blood CR were noted after 1 cycle and global CR achieved after 3 cycles. He experienced mild, transient radiation dermatitis. Localized (scalp) MAR was noted after 4 cycles and resolved with topical steroids. Given sustained global CR, mogamulizumab was discontinued, and low-dose oral methotrexate was initiated to sustain CR. He remained in global CR after 43 weeks of follow-up.

Discussion

TSE-Moga demonstrated excellent tolerability and promising clinical activity in 2 patients with refractory SS. Overall toxicity profile, including radiation-related events, did not worsen with the combination therapy. Of note, the patient in case 1 was treated with a slightly longer course of TSEBT (15 vs 10 fractions) due to fragile erythrodermic skin, in which setting the daily dose given is started at a lower level due to skin sensitivity, and dose per fraction is gradually increased. Neither patient required any treatment modifications to TSEBT when given in combination with mogamulizumab. Both patients experienced manageable delayed rash typical of MAR. This encouraging experience, albeit limited to 2 patients who were treated with this combination therapy, suggests that TSE-Moga has the potential to improve global response rate and outcome in MF and SS as compared to either therapy alone, particularly in cases of severe refractory disease[2-5] To evaluate the role of TSE-Moga in MF and SS, our phase 2 trial is underway with safety and efficacy endpoints.

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