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Case Report

Impressive Continuous Complete Response after Mogamulizumab in a Heavily Pretreated Sézary Syndrome Patient

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Abstract. ***Background*: Sézary syndrome (SS) is a rare lymphoproliferative neoplasm, almost incurable outside the setting of allogeneic transplantable patients. The prognosis for relapsed/refractory patients remains poor, as the available drugs confer short-lasting remission. In this setting, the anti-chemokine receptor type 4 (CCR4) monoclonal antibody mogamulizumab demonstrated efficacy in an international, open-label, randomized controlled phase 3 trial (MAVORIC) versus vorinostat.**

***Case description*: A heavily pretreated 57-year-old SS woman (stage IVA) was randomized in the mogamulizumab arm of MAVORIC at our Institution. She quickly achieved a response, but after 30 cycles, she was discontinued from therapy due to cutaneous toxicity. Nevertheless, she is still in complete response (CR).**

***Conclusions*: mogamulizumab is an anti-CCR4 monoclonal antibody that can induce long-lasting response also in very heavily pretreated patients not responding to any previous treatment. The extraordinary characteristic of our patient is that she is still in CR after 2.5 years since treatment discontinuation.**

Keywords: Complete Continuous Response, Mogamulizumab, Sézary Syndrome, Refractory, Cutaneous T-cell Lymphoma.

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Introduction. Sezàry syndrome (SS) is a rare, aggressive leukemic variant of cutaneous T-cell lymphomas with a 5-year overall survival (OS) of 26%.[1,2] Outside the setting of allogeneic transplantation, SS is considered incurable and requires chronic therapy because a relapse occurs shortly after treatment discontinuation.[3] The prognosis for relapsed/refractory patients is poor, with a low response rate and short remission duration. There are some therapeutic options (alemtuzumab, vorinostat, brentuximab vedotin) but no standard of care.[4] In this setting, patients can benefit from a new therapeutic approach: mogamulizumab, a humanized, glycoengineered IgG1κ monoclonal antibody directed against the chemokine receptor type 4 (CCR4). This drug demonstrated an overall response rate (ORR) of 28% in cutaneous T-cell lymphomas in an international, open-label, randomized, controlled phase 3 trial (MAVORIC, NCT01728805) versus vorinostat, with a peak of 37% in SS.

Case Report. A 57-year-old woman was diagnosed with SS in stage IVA (T4NXM0B2) in 2011.[5] This patient was treated in first-line with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone every two weeks) for three cycles, but this therapy was interrupted for intolerance and absence of response. She subsequently underwent several treatments from May 2011 to April 2014: extracorporeal phototherapy plus bexarotene in 2011, total skin external body irradiation in 2013,

extracorporeal phototherapy plus bexarotene again in 2014 and finally gemcitabine (1000mg/m^2) plus oxaliplatin (100 mg/m^2) for 11 cycles in 2015, with progressive disease after each of them. Because of this reason, in July 2015, this patient was referred to our Institution, where she was enrolled in the MAVORIC trial, and she was randomized in the mogamulizumab arm. She was erythrodermic and symptomatic for intense pruritus and skin exfoliation (**Figures 1A** and **1B**). The patient received mogamulizumab 1mg/kg once a week for the first cycle, in a 28-days cycle, and then a dosage of 1mg/kg every two weeks. The treatment per protocol was intended until progression.

Our patient obtained an impressively rapid improvement of symptoms already from the third cycle, while a partial response (PR) was achieved after the fifth cycle. A complete response (CR) was documented after the 10th cycle (**Figures 2A** and **2B**).[5] Therapy was well tolerated and went on without complications until the 27th cycle when the patient developed a plaque skin lesion in the zygomatic area (without pruritus). In the suspect of disease relapse, a punch-cutaneous biopsy was performed in September 2017 and then again in October 2017 for the persistence of this lesion. Results of both biopsies were consistent with a drug-related lesion, with no signs of active disease. Our patient received 30 cycles of mogamulizumab overall, then we decided to discontinue her from the treatment protocol in October 2017, due to the persistence of this lesion compatible with persistent grade 2 drug toxicity, histologically documented.

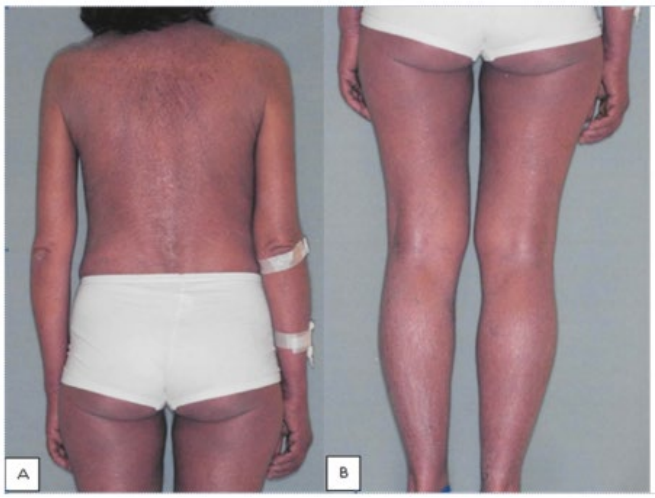

Figure 1. Patient before starting treatment (A, back; B, legs).

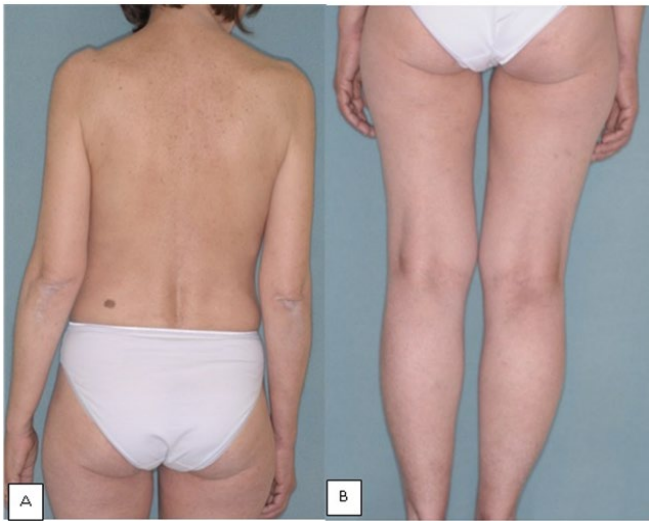

Figure 2. Patient after achieving a complete response (A, back; B, legs).

After mogamulizumab discontinuation, this patient was admitted to the follow-up phase. The cutaneous zygomatic lesion quickly disappeared, and no further lesions appeared after that. At the latest available follow-up, 2.5 years after therapy discontinuation, she is still in CR without having undergone further therapy after mogamulizumab.

The patient gave written, informed consent to publish her data and images.

Discussion. SS is a challenging disease to face, but some new therapeutic options are now available. Among them, we underline the role of the anti-CCR4 monoclonal antibody mogamulizumab. CCR4 is a receptor detectable in a large group of patients with SS, and it plays a central role in the T-lymphocytes homing and migration to the skin.[4,6,7] CCR4 is also expressed on T regulatory cells (T-Regs), a subset of lymphocytes involved in immunotolerance. The activity of mogamulizumab against T-Regs is long-lasting, and it can lead to a loss of immunotolerance. This aspect represents another important way of action of the drug, and, in particular, the restoration of immunosurveillance could explain why it is able to induce a long-lasting response, not limited by the persistence of the drug.[8] In this difficult-to-treat disease, the first-in-class anti-CCR4 antibody mogamulizumab demonstrated an ORR of 37% in the MAVORIC trial, with a median progression-free survival of 7.7 months, and a median duration of remission of 17.3 months.[6] The brilliant results of this trial led to mogamulizumab approval by FDA for mycosis fungoides and SS relapsing after one or more lines of therapy in 2018.

Our patient demonstrates that, in line with the data coming from MAVORIC, mogamulizumab can induce good responses. These responses include few CRs, also if very rare (only 5 out of 186 patients in MAVORIC), and the time to achieve a response is quite short also in heavily pretreated patients. In our case, a clinical response was achieved after the third cycle, and a PR was documented after the fifth one, in line with the median time to mogamulizumab response of 3.3 months.[6] Another observation that our case suggests is that that this drug can induce skin lesions to distinguish from those of the relapsing disease. Unfortunately, we have no more tissue slides to perform the research of T-regs depletion in our patient, nor the CCR4 mutational status. Analysis of T-regs depletion and

mutational status could be a very stimulating starting point to perform new studies and to deepen knowledge about the properties of mogamulizumab in patients who are going to receive it in the future. Skin toxicity was durable and led to treatment discontinuation in our patient, but this case report also showed that this adverse event was reversible and did not invalidate the response. To our knowledge, there is not an update about MAVORIC after its publication in 2018; thus, we do not know if our patient is the only one who achieved this extraordinary long-lasting response, or if also other patients did. All the other patients enrolled in the MAVORIC study at our Institution progressed and required subsequent therapy.

Conclusions. Mogamulizumab is an anti-CCR4 monoclonal antibody that can induce long lasting response also in very heavily pretreated patients not responding to any previous treatment.

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