

Mogamulizumab and bexarotene are a promising association for the treatment of advanced cutaneous T-cell lymphomas: a case series

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Abstract. – BACKGROUND: Treatment choices for patients with advanced-stage mycosis fungoides (MF) or Sézary syndrome (SS) who have failed first-line systemic therapies can be challenging, as several options are available. However, most evidence is based on observational and early phase studies due to the rarity of the disease. Mogamulizumab has recently been approved for the treatment of adult patients with MF or SS who have received at least one prior systemic therapy; it has a good tolerability profile prompting its use in combination with other agents. This article aims at describing the role of the concomitant use of bexarotene with mogamulizumab in this setting.

CASES PRESENTATION: To add information in the field, we describe our experience with four patients with MF/SS who failed first- and second-line treatments and started the combination mogamulizumab in addition to bexarotene. The combination of bexarotene with mogamulizumab in patients with advanced MF/SS after the failure of bexarotene alone obtained a response in all the four patients observed. The response was maintained longer than expected.

CONCLUSIONS: The combination is promising and deserves further study.

Key Words:

Cutaneous T-cell lymphoma, Mogamulizumab, Bexarotene, CCR4, Sezary syndrome, Mycosis fungoides, Systemic therapy, Chemotherapy.

overall, they represent approximately 2% of all lymphomas³. Mycosis fungoides (MF) is the most common CTCL entity; it presents clinically with patches, plaques and/or tumors, with pruritus and heavy quality of life impairment¹. Sézary syndrome (SS) is classified as a rare distinct entity with respect to MF, arising from a different T-helper cell subset⁴; clinically, SS is characterized by diffuse erythroderma, lymphadenopathy, and the presence of tumor cells (Sézary cells) in the peripheral blood. Although MF and SS are treatable, they are not curable with conventional systemic therapy, and symptoms significantly impact the quality of life⁵. Early-stage MF is associated with a good prognosis and can be managed with skin-directed therapies, such as topical therapies, phototherapies and radiotherapies, aiming at symptom control and maintenance. Nevertheless, there is progression to visceral involvement in up to 30% of patients, which is consistent with a poor prognosis⁴. Indeed, advanced-stage MF/SS has a median survival of fewer than 5 years⁶. Systemic regimens capable of being tolerated for long periods with low cumulative toxicity can be effective in patients with limited tumor lesions. In contrast, regimens likely to have more significant cumulative toxicity and immunosuppression can be used for refractory generalized tumor disease, erythrodermic disease, or stage IV disease^{5,6}. Treatment choices for patients who failed first-line systemic therapies can be challenging, as several options are available. However, most evidence is based on observational and early phase studies due to the rarity of the disease^{1,3}.

Among the recently approved systemic agents, mogamulizumab, a humanized anti-CCR4 monoclonal antibody, has shown a higher overall re-

Introduction

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of T-cell lymphomas with primary skin involvement, which can progress to extracutaneous disease of varying extent^{1,2};

sponse rate (ORR; 28% vs. 5%) and median progression-free survival (PFS; 7.7 months [95% CI: 5.7-10.3] vs. 3.1 months [95% CI: 2.9-4.1], $p < 0.0001$), with good tolerability, compared with vorinostat in the MAVORIC trial⁷. Mogamulizumab seems a good candidate for combination therapy with older agents because of its safety profile.

This article presents the authors' experience with patients affected by advanced-stage MF/SS and successfully treated with the combination of mogamulizumab and bexarotene, discussing the potential role of this association.

Study Population

Cases were retrospectively selected at San Gallicano Dermatology Institute – IRCCS, Rome, Italy. Inclusion criteria were age ≥ 18 years, advanced-stage MF or SS, failure of at least one previous systemic therapy, and use of mogamulizumab in addition to bexarotene started between October 2020 and November 2021. The study was conducted in accordance with the ethical principles of the revised version of the declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000). All patients had provided written informed consent to treatment and publication of clinical data. The association therapy was administered according to doses and modalities approved in Europe. Patients participating in a clinical trial and those with hypersensitivity to the active substance were excluded. The Ethics Committee of S. Gallicano Institute – IRCCS was notified.

Cases Presentation

Between October 2020 and November 2021, 34 patients with advanced-stage MF/SS visited our institution. We describe four of them who had disease progression after the failure of the first- and second-line treatments and started the combination bexarotene/mogamulizumab (Tables I and II).

Case 1

In October 2015, a 65-year-old woman presented with polymorphic patches and plaques involving the limbs, scalp, and buttocks; the mSwat score was 87. The clinical examination of the lymph nodes was negative. Similar skin lesions had been present for 10 years, and her past medical history was irrelevant. Based on

the histopathological examination of a skin biopsy and clinical investigations (ultrasound scan and CT scan), she was diagnosed with stage IIB MF.

Treatment was started with an interferon 3 million UI/week at the end of November, obtaining a partial response. After 27 months (in February 2018), nodules on the scalp were observed, and bexarotene 300 mg/day and mechlorethamine gel were added to the interferon. Rosuvastatin 40 mg/day and levothyroxine 150 μg /day were also prescribed to limit the side effects related to bexarotene. On 18 September 2018, the response was limited; mSwat was still 72, and extracorporeal photopheresis (ECP) every 2 weeks was added. Then, a good response was obtained, with mSwat decreasing to 43, until August 2020, when the patient developed ulcerative nodules on the trunk, buttocks, forearms, scalp, and feet (mSwat 228, stage IVB) (Figure 1 A-D). Interferon, ECP, and mechlorethamine gel were discontinued, and compassionate use of mogamulizumab was started in combination with bexarotene. After only four therapy cycles (about 1 month), complete resolution of nodules and an excellent improvement of skin lesions with reduction of patches and plaques (mSwat 52) were obtained (Figure 1 E-H). Disease control was maintained for 12 months until August 2021. The patient died in September 2021 due to sepsis.

Case 2

A 65-year-old man was referred to our unit in 2019 with generalized erythema and edema, ectropion, marked scaling, and intense pruritus (mSwat was 230). He had had blood hypertension for many years (current treatment was 10 mg/day olmesartan medoxomil) without coronary complications. Peripheral inguinal and axillary nodes were palpable, and CT confirmed this enlargement. The largest axillary node measured 2.5 cm and was biopsied, revealing dermatopathic change. The histopathological examination of a skin biopsy showed an upper dermal lymphohistiocytic T-cell infiltrate with no antigen loss and minimal cytologic atypia. A complete blood count (CBC) showed $5 \times 10^9/\text{L}$ peripheral blood lymphocytes (PBL). At the same time, flow cytometry detected a CD4⁺ lymphocytosis ($4.5 \times 10^9/\text{L}$ cells) with a relatively low CD8 count ($1.50 \times 10^9/\text{L}$ cells), an expanded CD4⁺CD26⁻ (67%), and CD4⁺CD7⁻ (69%) population, and abnormal mononuclear cells on a peripheral blood smear consistent with Sézary cells. All

Table I. Clinical onco-hematological characteristics of patients. ECP = extracorporeal photoapheresis. M/B= mogamulizumab/bexarotene.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	65	65	50	65
Male or female	Female	Male	Male	Female
Diagnosis	Stage IIB MF	Stage IVA SS	Stage IVA SS	Stage IIB MF
Previous therapy	Interferon + bexarotene, mechlorethamine	Bexarotene	Interferon + methotrexate Methotrexate, ECP Bexarotene, ECP	Bexarotene + ECP
Stage at M/B start	IVB	IVA	IVA	Stage III
Severity at M/B start	mSwat = 228	Erythroderma, mSwat = 212	mSwat = 115	mSwat = 182
Outcome of M/B treatment	At 4 months: resolution of nodules, reduction of patches and plaques mSwat = 52	At 2 weeks: improvement of erythema and ectropion At 14 months: lesions controlled mSwat = 39	At 4 weeks: mSwat = 78 M/B stopped for intolerance	At 4 weeks: mSwat = 97; reduced erythema

these findings were consistent with the diagnosis of SS (stage IVA).

In June 2019, treatment with bexarotene 300 mg/day was started, with rosuvastatin 40 mg/day, levothyroxine 150 µg/day, and ECP every 2 weeks. After 3 months, a relevant improvement of erythema and pruritus was recorded, and the PBL count was reduced to $3.5 \times 10^9/L$ cells. This partial response was sustained for 4 months, after which erythroderma occurred, mSwat was 212, and the PBL count increased to $7 \times 10^9/L$ cells (Figure 2A-D). In October 2020, the combination of mogamulizumab and bexarotene 300 mg/day was started. After only 2 weeks, improvement of erythema and ectropion was observed, but the patient reported sternal pain, and unstable angina was diagnosed (Figure 2E-H). Treatment with mogamulizumab/bexarotene was discontinued, and the patient underwent angioplasty with stent placement. After 1 month, the cardiologist allowed the resumption of the systemic combination therapy. The disease was controlled after 14 months of follow-up (mSwat was 39), and no coronary symptoms were reported.

Case 3

In June 2015, a 50-year-old man presented with generalized erythema and marked scaling

involving >90% of body surface associated with intense pruritus and presence of edema, fissuring, and lichenification in about 50% of the skin (mSwat = 257). The patient had reported similar symptoms for the previous 4 years. The clinical examination of the lymph nodes was negative, and the general medical history was not relevant. The pathologic examination of a skin biopsy showed a lymphohistiocytic T-cell infiltrate of the upper dermis, with no antigen loss and minimal cytologic atypia. A CBC count showed the presence of $5.9 \times 10^9/L$ PBL. At the same time, the flow cytometry detected a CD4⁺ lymphocytosis ($4.7 \times 10^9/L$ cells) with a relatively low CD8 count ($1.40 \times 10^9/L$ cells), an expanded CD4⁺CD26⁻ (59%), and CD4⁺CD7⁻ (56%) population, and abnormal mononuclear cells on a peripheral blood smear consistent with Sézary cells. A diagnosis of stage IVA SS was made based on these findings.

In July 2015, interferon 3 million UI 3 times/week was prescribed, which resulted in a poor response. Therefore, subcutaneous methotrexate was associated in September 2015, achieving a good response (mSwat score = 97) after only a few months. However, the administration of interferon was interrupted due to the onset of tiredness and flu-like symptoms. ECP every 2 weeks was started in March 2016, but recurrence

Table II. Adverse events in the 4 patients during treatment with mogamulizumab/bexarotene.

	Patient 1	Patient 2	Patient 3	Patient 4
AE	Sepsis	Sternal pain, unstable angina	Unstable angina	
Related/unrelated to M/B	Unrelated	Related	Related	
Outcome of AE	Death	Resolved, M/B restarted	Resolved at treatment interruption and relapse at treatment re-start	

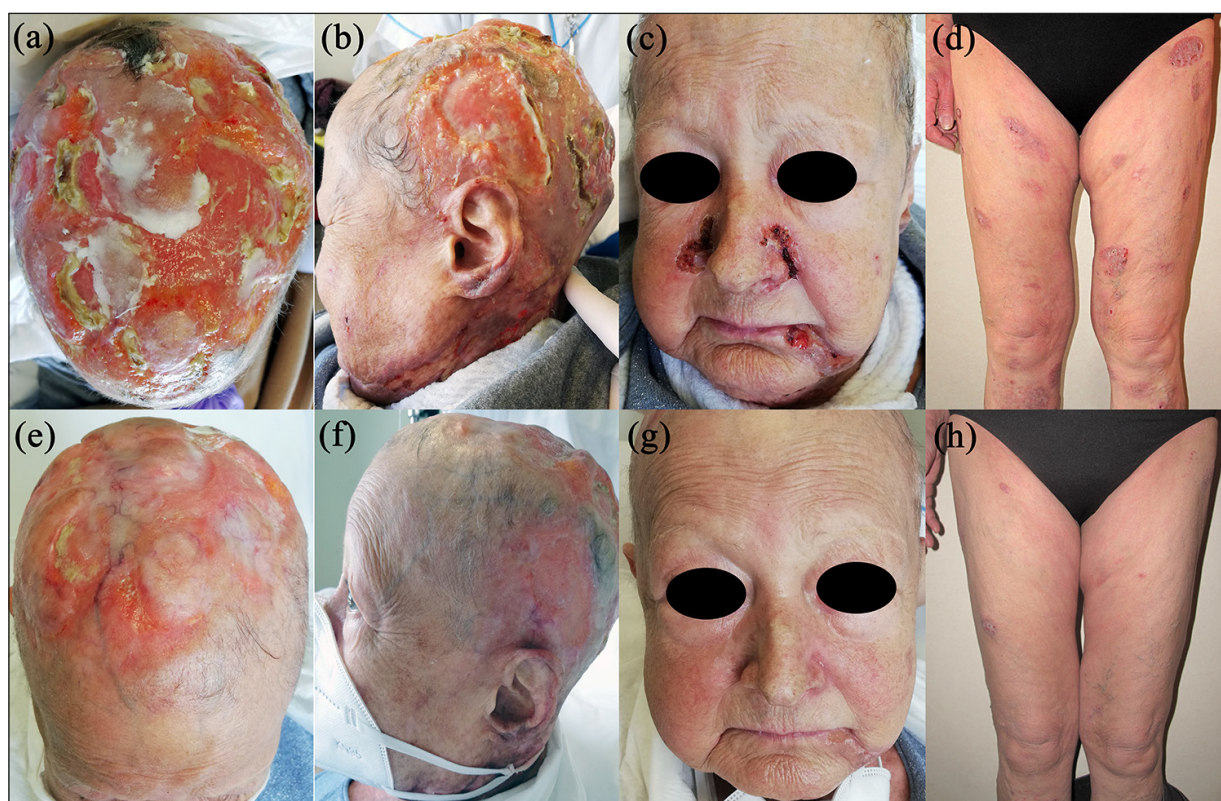


Figure 1. Diffuse involvement of the scalp (a-b), face (c), and legs (d) in a patient with stage IVB mycosis fungoides before starting the association of mogamulizumab and bexarotene and after four therapy cycles (about 1 month) (e-h).

of generalized erythema and marked scaling occurred (mSwat = 232). Methotrexate was substituted with bexarotene 300 mg/day, obtaining a partial response (mSwat = 115) maintained for 5 years. In order to achieve better control of the disease, ECP was discontinued, and mogamulizumab was introduced in April 2021 (Figure 3 A-D). Rosuvastatin 40 mg/day and levothyroxine 150 µg/day were also prescribed to limit the side effect related to bexarotene. A remarkable cutaneous improvement (mSwat = 78) was obtained after only a few weeks, but the patient reported sternal pain, and unstable angina was diagnosed in July 2021 (Figure 3 E-H). Therefore, mogamulizumab and bexarotene were stopped and restarted after 2 months when the cardiologist allowed it. The sternal pain and unstable angina recurred 1 month after the reintroduction of the combination therapy. The cardiologic symptoms disappeared quickly after the interruption of the association therapy. The patient chose to discontinue any treatment for the SS, and he is now only under follow-up.

Case 4

In October 2020, a 65-year-old woman presented with a 4-year history of plaques and marked scaling (the mSwat score was 83.5). She had a major depressive disorder under treatment with 5 mg/day of sertraline. The clinical examination of the lymph nodes was negative. A diagnosis of MF (stage IIB) was made based on the histopathological examination of a skin biopsy.

At the end of November 2020, therapy with bexarotene 300 mg/day, rosuvastatin 40 mg/day, and levothyroxine 150 µg/day was started, obtaining a partial response. However, ECP every 2 weeks was associated after 6 months due to the onset of generalized erythema with intense pruritus (mSwat = 182; stage III). A good improvement was achieved, but an episode of atrial fibrillation occurred after 5 months, and ECP was discontinued because contraindicated. Consequently, MF manifestations worsened (Figure 4 A-B), and the association with mogamulizumab/bexarotene was started in November 2021. A good improvement was obtained in a few months (mSwat = 97), and

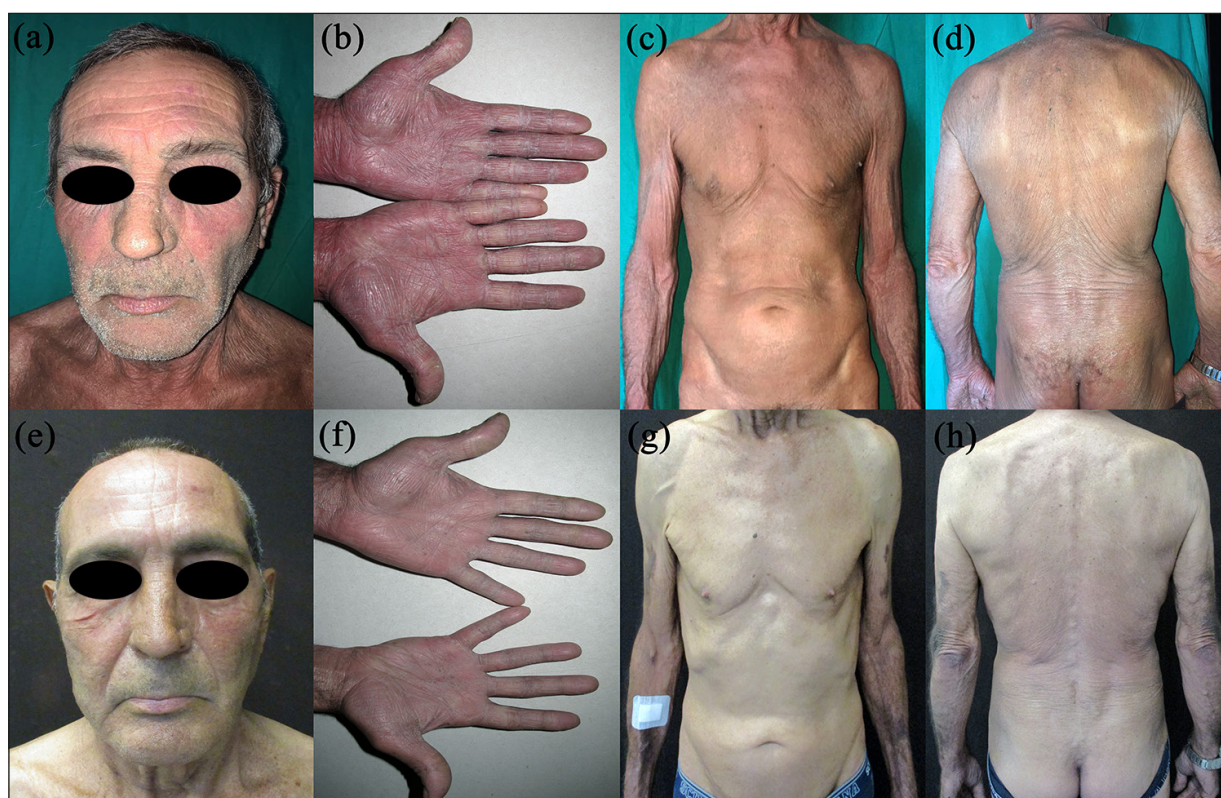


Figure 2. Diffuse erythroderma and ectropion in a patient affected by Sézary syndrome (a-d). Improvement of erythema and ectropion achieved after only 2 weeks of treatment with mogamulizumab and bexarotene (e-h).

the treatment was tolerated (Figure 4 C-D). This treatment was continuing when this report was written.

Discussion

This article describes the Authors' experience with four patients affected by stage III-IV MF/SS who had disease progression due to failure of previous therapy for intolerance or poor efficacy. All these patients were treated with bexarotene, a well-established tool for CTCL, and received concomitant treatment with the novel anti-CCR4 mogamulizumab.

Patient 1 survived the combination therapy for 12 months, which was longer than expected with bexarotene alone, with an acceptable quality of life, and died of sepsis unrelated to the therapy or the CTCL. Patient 2 benefited from the treatment and could continue it after a short interruption for the occurrence of angina and the positioning of a stent. Patient 3 also had angina pectoris, which relapsed at the reintroduction of bexarotene/mogamulizumab and chose to stop any treatment de-

spite the benefit he had experienced. The last patient was under treatment with good efficacy and tolerability.

Although early stages of MF and SS can be easily managed and guidelines are available for treatment choice, evidence for identifying a safe and efficient treatment for advanced stages of MF or SS is lacking. In clinical practice, both FDA- or EMA-approved and non-approved agents are used in these patients, including immune modulators, antibodies, single agent or combination chemotherapy, or other investigational agents. The National Comprehensive Cancer Network (NCCN) current guidelines recommend a variety of medications or a clinical trial as first-line therapy⁵. Among the recommended drugs, bexarotene, vorinostat, romidepsin, brentuximab vedotin, and more recently mogamulizumab, are approved by the FDA and EMA (vorinostat is not approved in Europe) and indicated for patients who have failed at least one other systemic therapy.

Evidence of the efficacy of mogamulizumab and brentuximab vedotin was produced by phase III randomized trials (MAVORIC and ALCA-



Figure 3. Diffuse erythroderma in a patient with Sézary syndrome (a-d) and the remarkable cutaneous improvement obtained after only 1 month (e-h).

NZA, respectively)^{7,8}. In contrast, evidence on bexarotene^{9,10}, vorinostat¹¹⁻¹³ and romidepsin¹⁴⁻¹⁶ was obtained in phase II studies. Only older studies are available for other treatments, such as IFN- α , IFN- γ and methotrexate, which may still offer clinical benefits¹⁷⁻¹⁹.

Gemcitabine was initially reported to be associated with a good response rate in advanced MF without blood involvement and with good tolerability²⁰. However, a later randomized study found a high incidence of severe complications, including visceral and cutaneous involvement²¹. Multiagent chemotherapy regimens are associated with great toxicity and are generally used for refractory disease, with a high tumor burden in lymph nodes or solid organs⁵.

Bexarotene is considered one of the most active single agents for treating recurrent or refractory CTCL, but there is no standard for step-up therapy after bexarotene failure. A phase II study found that the addition of IFN- α -2b did not increase the response rate that would have been expected with bexarotene alone²². The combination of bexarotene with gemcitabine for the treatment of CTCL proved to produce a lower overall response rate than gemcitabine alone²³.

Based on the available evidence, we decided to add mogamulizumab to patients with an unsatisfactory response or intolerant to bexarotene alone. This decision was prompted by the tolerability of mogamulizumab and the evidence for efficacy in CTCL⁷. Mogamulizumab offers some unique benefits over alternative therapies in CTCL, such as the relatively long duration of remission confirmed in a large trial, high response rates within the blood compartment and in SS.⁷ It was supposed to be usefully combined with other systemic agents, both as a direct antineoplastic agent and as an immune modulator. A clinical trial in advanced/metastatic solid tumors combined mogamulizumab with a checkpoint inhibitor as a means to deplete undesirable Treg cells and enhance their immune effects, with an acceptable safety profile, mogamulizumab had antitumor activity²⁴. One trial of combined chemotherapy and mogamulizumab in ATLL found an increased complete response rate in patients receiving chemotherapy with mogamulizumab compared with chemotherapy alone. However, the safety profile was poor²⁵.

Little after we had begun this combination therapy in one patient, in October 2020, a case



Figure 4. Sub-erythroderma observed in a patient with stage III mycosis fungoides before starting the association with mogamulizumab/bexarotene (a), and detail of the trunk showing the lamellar scaling and sparing areas (b). A good and progressive cutaneous improvement was achieved after 4 (c) and 8 (d) weeks of treatment.

report was published confirming the possibility of successful and tolerated treatment of MF in the advanced stages²⁶. The clinical results we obtained were very encouraging as all our patients responded, and the response has been maintained for a long period in two cases.

Two out of four patients had acute coronary syndrome (ACS) 3-4 months after initiation of mogamulizumab in concomitance with bexarotene. Patient 2 had unstable angina; he underwent coronary angioplasty and positioning of a medicated stent. This patient had had arterial hypertension for some years. Patient 3 had non-ST-segment elevation myocardial infarction during treatment with bexarotene/mogamulizumab. Coronary angiography could not be performed due to hypersensitivity to contrast agents, while myocardial scintigraphy, both at rest and on exertion, showed no myocardial perfusion deficit before discharge. Based on this result, the cardiologic team recommended the reintroduction of bexarotene/mogamulizumab. One month later, angina relapsed, and mogamulizumab therapy was discontinued. The summary of product characteristics reports that

one patient affected with MF/SS and treated with mogamulizumab in the MAVORIC study had a myocardial infarction^{7,27}. An analysis of the International World Health Organization database, Vigibase, showed that adverse cardiovascular events affected 28 out of 650 patients with T-cell leukemia/lymphoma treated with mogamulizumab between 2013 and 2019. Among these patients, two had an acute myocardial infarction²⁸. The mechanism of cardiotoxic adverse events correlated with mogamulizumab is not clear. However, we can speculate that it is related to the specific link of mogamulizumab to tumor cell CCR4, which increases the activity of antibody-dependent cytotoxic activity and facilitates the release of inflammatory cytokines, including TNF- α ²⁹. Increased expression of cytokines and TNF- α is a well-known mediator of myocardial infarction damage. It is possible that indirect activation of inflammatory factors by mogamulizumab may induce increased thrombosis and vasoconstriction in subjects with coronary risk^{30,31}. Currently available data suggest that cardiac function should be monitored, particularly in the first few months

in patients receiving mogamulizumab therapy²⁸. Based on their experience, the Authors suggest that patients with familiar history and/or risk factors for coronary disease should be screened with coronary CT angiography before mogamulizumab therapy and/or receiving aggressive preventive treatment and be monitored during therapy.

Review of the Literature

Mogamulizumab

Mogamulizumab is a humanized monoclonal antibody directed against CCR4, a transmembrane receptor for CCL17 and CCL22, involved in homing and migration of T cells to the skin. CCR4 expression in CTCL is highly variable, from 14% to 97%, with higher proportions in the presence of blood involvement. The relation of CCR4 expression with response to mogamulizumab is still controversial. The MAJORIC study found that while higher baseline CCR4 expression on circulant Sézary cells was associated with early complete blood response, the proportions of patients achieving an overall response were not related to the skin CCR4 expression^{7,32}.

Based on the results of phase III, open-label, MAJORIC trial (NCT01728805), the European Medicines Agency (EMA) approved mogamulizumab in 2018 for the treatment of adult patients with previously treated CTCL, MF or SS, after the failure of at least one prior systemic therapy. Monotherapy with mogamulizumab resulted in longer investigator-assessed PFS compared with vorinostat monotherapy (median = 7.7 months [95% CI: 5.7-10.3] vs 3.1 months [95% CI: 2.9-4.1] respectively, $p < 0.0001$). In addition, the ORR was 28% (36% in stage IV MF and 37% in stage IV SS) for mogamulizumab and 5% for vorinostat. The median duration of response to mogamulizumab was 14.1 months, and the median time to response was 3.3 months⁷. Mogamulizumab was well tolerated, and the most common adverse events were infusion-related reactions (32%), rash (20%), diarrhea (23%), and fatigue (22%)³³. Noteworthy, an increased risk of graft-vs-host disease was reported in patients undergoing allogeneic bone marrow transplantation after mogamulizumab treatment³⁴. In agreement with such findings, a washout period is recommended from mogamulizumab before hematopoietic stem cell transplantation²⁷.

Bexarotene

Bexarotene is a third-generation synthetic retinoid that binds the nuclear retinoid X receptors,

affecting the transcription of specific genes and inducing terminal differentiation of malignant cells³⁵. The Food and Drug Administration (FDA) approved bexarotene specifically for the treatment of CTCL in 1999 and is now widely employed. It was investigated in two phase II-III trials in 94 patients with advanced-stage (IIB-IVB) MF/SS, obtaining a clinical improvement in about 50% of subjects^{9,10}. However, these early studies used comparatively simple response criteria, such as physician global assessments, compared to those in current use (i.e., modified Severity-Weighted Assessment Tool [mSWAT])³. In phase III AL-CANZA study on patients with previously treated CD30-expressing MF or cutaneous anaplastic large cell lymphoma, bexarotene was one option for the control researcher's choice, which obtained ORR lasting ≥ 4 months in only 12% of patients and median PFS of 3.5 months. However, among the responders in the physician's choice group, the median duration of response was 18.3, suggesting that a minority of patients could achieve meaningful and durable responses to bexarotene³⁶.

Bexarotene has been reported to have more potent activity in MF than previous retinoids. However, not all patients respond to monotherapy, and some remissions have a limited duration. Combination therapy with extracorporeal photopheresis, interferon-alfa, methotrexate, denileukin diftitox, gemcitabine, pralatrexate, and psoralen with ultraviolet-A (PUVA) has been proposed to improve the incidence and duration of responses³. The most common adverse events associated with bexarotene are hypertriglyceridemia (82%), fatigue (32%), hypercholesterolemia (30%), hypothyroidism (29%), and headache (20%)^{3,35}.

Association of Mogamulizumab and Bexarotene

Mogamulizumab is indicated to treat adult patients with MF or SS who have received at least one prior systemic therapy. It has a good tolerability profile as shown by Affi et al³⁷, that prompts its use in combination with other agents. Soon after this clinical experience started, one single case of successful treatment with the combination of mogamulizumab and bexarotene in one patient with MF was published²⁶. We decided to use this combination in patients with advanced MF/SS who failed systemic therapy and had limited therapeutic options because of the low risk of serious adverse events.

Mogamulizumab 1 mg/kg was administered as an intravenous infusion over at least 60 minutes

on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of each subsequent cycle according to the European regulation, while bexarotene dosage was continued.

Conclusions

In conclusion, the combination of bexarotene with mogamulizumab in patients with advanced MF/SS after the failure of bexarotene alone obtained a response in the four patients observed. The response was maintained longer than expected. Further study is needed to confirm these encouraging observations, assess the safety of the combination, and identify a strategy to prevent cardiovascular adverse events.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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Availability of Data and Material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contributions

Study conception and design: MT, MA; Collection and interpretation of data: MT, CF, PLS, MPC; Manuscript drafting: VDM; Manuscript editing: VDM, MA; Approval to submit: MA.

Informed Consent

All subjects provided informed written consent to the treatment.

Ethics Approval

All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments. The present study was notified to the Ethics Committee of S Gallicano Institute – IRCCS, Rome, Italy.

Consent for Publication

All subjects provided consent to the publication of clinical data.

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