Hindawi
Dermatologic Therapy
Volume 2023, Article ID 7625926, 6 pages
https://doi.org/10.1155/2023/7625926

Research Article

Mogamulizumab Multimodality Therapy with Systemic Retinoids, Interferon, or Extracorporeal Photopheresis for Advanced Cutaneous T-Cell Lymphoma

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Received 22 February 2023; Revised 15 October 2023; Accepted 27 November 2023; Published 19 December 2023

Academic Editor: Nicola Pimpinelli

Mogamulizumab is a novel monoclonal antibody designed to target CC chemokine receptor 4 (CCR4), which is expressed by tumor cells in cutaneous T-cell lymphoma (CTCL). In clinical trials, mogamulizumab monotherapy has demonstrated efficacy in reducing tumor burden in advanced CTCL, particularly in the peripheral blood. In clinical practice at our center, mogamulizumab has been combined with other agents such as systemic interferon, systemic retinoids, and extracorporeal photopheresis for an enhanced synergistic effect. There is limited published research on mogamulizumab combination therapy. This study evaluates the clinical efficacy of mogamulizumab in combination with systemic interferon, retinoids, and/or extracorporeal photopheresis for therapy of CTCL. Nineteen patients on this regimen at our academic center were identified. Treatment response rates, progression-free survival, duration of response, and adverse effects were characterized by retrospective chart review. All patients on this regimen at our center had an initial partial or complete response. Moreover, responses were durable, and the regimen was well-tolerated with few grade 3 adverse effects. These results demonstrate the utility of a multimodality approach to the therapy of CTCL with mogamulizumab and warrant further confirmation.

1. Introduction

Cutaneous T-cell lymphoma (CTCL) is a rare non-Hodgkin lymphoma involving infiltration of the skin by malignant skin-trafficking T-lymphocytes. Mycosis fungoides (MF) is the most common subtype of CTCL, and it typically presents with skin patches and plaques [1]. Sezary syndrome (SS) is a more aggressive form of CTCL characterized by blood involvement with malignant T cells called Sezary cells, as well as erythroderma and often lymphadenopathy [1].

There is an unmet need for improved therapies for advanced MF and SS, which have a poor prognosis in patients refractory to previous systemic treatments. Mogamulizumab is a new therapy that targets C-C chemokine receptor 4 (CCR4) and eliminates malignant T cells via antibody-dependent cellular cytotoxicity (ADCC) [2]. In the MAVORIC study that led to its approval in 2018 by the Food and Drug Administration, mogamulizumab demonstrated superior progression-free survival (7.7 months) and overall response rate (37%) compared to vorinostat [3]. Nevertheless, few patients achieved a complete response to

therapy, and the majority relapsed within one year of treatment initiation [4].

Multimodality therapy is an important method of maximizing the treatment efficacy of CTCL by combining immunomodulatory agents with complementary mechanisms of action. Mogamulizumab may have a synergistic effect with bexarotene, extracorporeal photopheresis (ECP), and interferon, as bexarotene and ECP both cause tumor cell apoptosis, and interferon enhances dendritic cell processing of apoptotic cells [5]. Interferons also mediate ADCC by stimulating natural killer cells [5].

At the University of Pennsylvania, we have successfully used mogamulizumab in tandem with interferon, retinoids, and ECP for patients who were recalcitrant to prior systemic treatment regimens. We describe the outcomes of these patients in this short report.

This retrospective study was approved by the Institutional Review Board at the University of Pennsylvania. We reviewed records of CTCL patients treated at the University of Pennsylvania to identify those who received combination therapy with mogamulizumab. We evaluated global disease response and individual response in the skin, blood, lymph nodes, and viscera using the consensus global response score (GRS) criteria for complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) in CTCL [6]. We also evaluated for adverse events and graded them according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [7].

There were a total of 19 patients (11 male and 8 female; 17 SS, 2 MF) treated between August 2018 and June 2023 with a mogamulizumab-based combination therapy (Table 1; Figure 1). Seventeen patients had advanced-stage CTCL (IIIA-IVA2) at the start of mogamulizumab, and two patients had stage IB disease. The mogamulizumab multimodality regimen included extracorporeal photopheresis in 14 patients, interferon-alpha in 11 patients, bexarotene in 9 patients, and interferon-gamma in 7 patients.

Prior to mogamulizumab, 14 patients were already on a regimen of ECP, bexarotene, and/or interferon; 10 of these patients had eventually progressed on their prior regimen, while 4 patients had partially improved or stable disease that required further treatment. Mogamulizumab was added to these 14 patients' regimens without stopping their other therapies. Five patients had previously received mogamulizumab monotherapy. In four patients, other systemic therapies (ECP, bexarotene, and/or interferon) were added to mogamulizumab monotherapy due to inadequate response or worsening disease after an initial response. One patient had previously progressed on mogamulizumab monotherapy, subsequently progressed on pembrolizumab monotherapy, and then was initiated on mogamulizumab combination therapy.

Patients started mogamulizumab a median of 15.8 months (range: 0.2–116 months) after CTCL diagnosis, and the median duration of mogamulizumab therapy was 21.6 months (range: 3.6–40 months). Sixteen patients were evaluated for response; three patients did not have sufficient chart records to evaluate response in lymph nodes and/or blood due to limited imaging and/or peripheral flow cytometry results. All sixteen evaluable patients had a global response, of which 9 (56%) had a complete response. Rates of complete response were similar between MF ($N = 1/2$; 50%) and SS ($N = 8/14$; 57%). There was no association between the best response to prior treatment and the best response to mogamulizumab. After a median follow-up of 28.3 months (range: 3.6–47 months), eighteen of nineteen patients are alive, and 11 patients remain on combination treatment without progression. Mogamulizumab was eventually discontinued in eight patients due to disease progression ($n = 6$), severe MAR ($n = 1$), or financial concerns ($n = 1$). Median progression-free survival and median duration of response were not yet reached by Kaplan–Meier analysis.

The most common toxicities were mogamulizumab-associated rash (MAR; $n = 9$), neutropenia ($n = 5$; grade 4: $n = 1$), lymphopenia ($n = 14$; grade 3: $n = 3$), and anemia ($n = 6$; none grade 3). All cases of MAR were biopsy-confirmed. MAR was grade 1 in three patients, grade 2 in four patients, and grade 3 in two patients. Six grade 1 and 2 patients had asymptomatic or mildly pruritic thin pink plaques and/or scaly papules on the trunk, extremities, and/or the forehead and periauricular areas that either improved with topical steroids or did not require treatment. One grade 2 patient had a diffuse morbilliform eruption that was mildly pruritic; this patient's rash resolved with topical steroids and holding of mogamulizumab for two months. Both cases of grade 3 MAR patients developed a severely pruritic diffuse eruption on the trunk and extremities; one patient's eruption was morbilliform, while the other presented as MF-like diffuse erythematous patches. Both cases of grade 3 MAR were ultimately resolved; one patient required methotrexate and discontinuation of mogamulizumab, while the other patient required prednisone and tapering of mogamulizumab every four weeks.

In total, seventeen patients developed a cytopenia ($N = 17/19$; 89%). Sixteen patients received combination therapy with interferon, either interferon-alpha ($N = 11$) or interferon-gamma ($N = 7$). Fourteen of sixteen patients (88%) who received interferon developed cytopenia during treatment with mogamulizumab, in comparison to three of three patients who did not receive interferon. One patient developed grade 4 neutropenia while on mogamulizumab, extracorporeal photopheresis, and bexarotene; they later received interferon-alpha once the neutropenia had resolved. Three patients developed grade 3 lymphopenia while on interferon; however, this correlated with CR in the blood in two patients; in one patient, blood was uninvolved. No patients experienced neutropenic fever. Only one patient had a >G1 infection (grade 2 cellulitis); this patient did not receive interferon and did not have neutropenia or lymphopenia during mogamulizumab therapy. Treatment-related neutropenia responded briskly to dose reductions or intermittent use of growth factor. There were no treatment-related deaths.

Advanced CTCL is challenging to manage, with median survival ranging from 1–4 years and median progression-free survival ranging from 4–9 months on typical

Table 1: Patient characteristics and responses to mogamulizumab multimodality therapy.

Age at start of mogamulizumab	Median (range)	72 (45–86)					
Sex, *N* (%)	Male	11 (58)					
	Female	8 (42)					
Race, *N* (%)	White	17 (89)					
	Black	2 (11)					
CTCL subtype, *N* (%)	Mycosis fungoides	2 (11)					
	Sezary syndrome	17 (89)					
Stage at start of mogamulizumab, *N* (%)	IB	2 (11)					
	IIIA	1 (5)					
	IIIB	3 (16)					
	IVA1	10 (53)					
	IVA2	3 (16)					
Number of systemic therapies prior to mogamulizumab	Median (range)	4 (0–7)					
Systemic treatment prior to mogamulizumab	No prior systemic treatment	3 (16)					
	Pembrolizumab	2 (11)					
	Multimodality regimen of ECP, interferon, and/or bexarotene (without mogamulizumab)	14 (74)					
Response to prior systemic treatment regimen, *N* (%)		CR	PR	SD	PD	Unknown	No prior treatment
	Best response	3 (23)	7 (54)	2 (15)	1 (8)	3	3
	Response immediately prior to mogamulizumab	—	2 (14)	2 (14)	10 (72)	2	3
Mogamulizumab timing, *N* (%)	Mogamulizumab added to prior multimodality regimen	14 (74)					
	Mogamulizumab monotherapy followed by multimodality therapy	5 (26)					
Therapies included in mogamulizumab combination regimens, *N* (%)	Bexarotene	9 (47)					
	Isotretinoin	1 (5)					
	Extracorporeal photopheresis	14 (74)					
	Interferon-alpha	11 (58)					
	Interferon-gamma	7 (37)					
Best response to mogamulizumab combination therapy, *N* (%)		CR	PR	SD	PD	Unknown	Uninvolved
	(i) Global ($N = 16$)	9 (56)	7 (44)	—	—	3	—
	(ii) Skin ($N = 18$)	9 (50)	7 (39)	2 (11)	—	—	1
	(iii) Blood ($N = 15$)	13 (87)	1 (7)	1 (7)	—	1	3
	(iv) Lymph nodes ($N = 7$)	5 (71)	—	2 (29)		3	9
	(v) Viscera ($N = 0$)	—	—	—	—	—	19
Best global response by disease subtype, *N* (%)	(i) MF ($N = 2$)	1 (50)	1 (50)	—	—	—	—
	(ii) SS ($N = 17$)	8 (57)	6 (43)	—	—	3	—
Duration of response, months	Median (range)	Not yet reached					
Progression-free survival, months	Median (range)	Not yet reached					

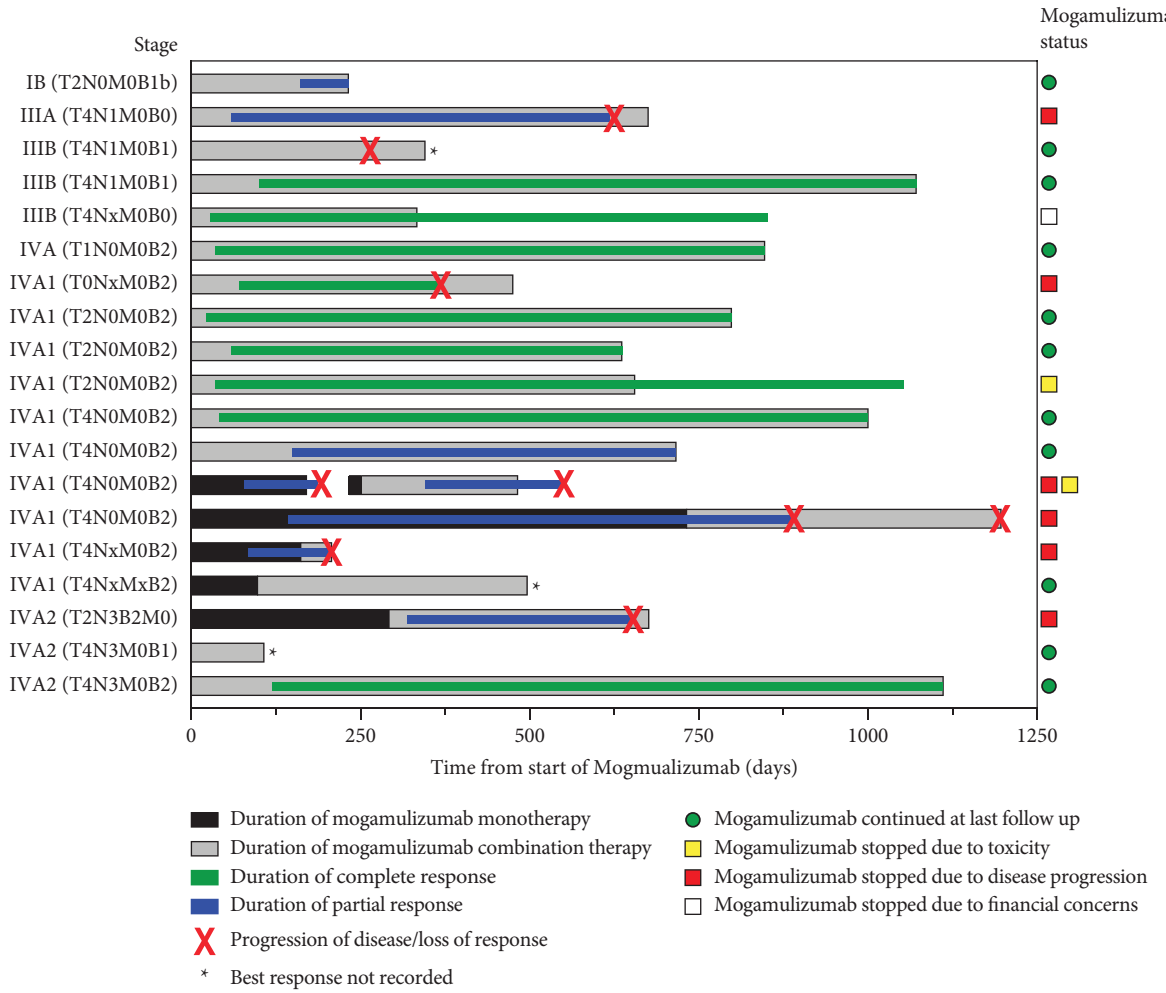

Figure 1: Swimmer plot of patients receiving mogamulizumab combination therapy. This swimmer plot shows the duration of mogamulizumab combination therapy and outcomes for patients ($n = 19$) ranked by disease stage at initiation of mogamulizumab. Overlying bars depict the duration of mogamulizumab therapy and the duration of response for evaluable patients ($n = 16$). Time on mogamulizumab combination therapy is shown in gray. Time on mogamulizumab monotherapy, if occurred, is shown in black. The duration of a complete response to therapy, if occurred, is shown in green. The duration of a partial response to therapy, if occurred, is shown in blue. A red X represents the time point at which progressive disease (PD) and/or loss of response (LOR) occurred. Response to mogamulizumab, progression of disease, and loss of response is defined by the ISCL/USCLC/EORTC criteria [6]. Of note, patient 13 received pembrolizumab in between courses of mogamulizumab. Patient 14 progressed twice while receiving mogamulizumab; initial progression in the skin was treated by low-dose total skin electron beam therapy, resulting in temporary improvement followed by subsequent progression.

monotherapies [8]. There is no curative treatment for CTCL other than allogeneic hematopoietic cell transplantation, after which patients often relapse or develop graft-versus-host disease [9]. We observed a high rate of durable responses to mogamulizumab combination therapy in heavily pretreated patients, and the regimen was effective in all compartments, especially the blood. Importantly, mogamulizumab combination therapy resulted in durable responses even in patients refractory to a prior component of the regimen; ten patients had progressed on prior ECP, bexarotene, and/or interferon, while one patient (Figure 1, Patient 13) had progressed on prior mogamulizumab monotherapy.

Adverse events were manageable and mainly grade 1-2 hematologic or cutaneous adverse events. The incidence of MAR (47%) in this study was higher than the 23.9% frequency of rash documented in the MAVORIC clinical trial [3]. This may be due to increased awareness of MAR as a side effect of mogamulizumab, increased detection of MAR in patients seen frequently for ECP, and possibly further immune activation by interferon. Interestingly, a recent study observed superior outcomes in CTCL patients who developed MAR [10].

These encouraging findings likely stem from a synergistic effect of mogamulizumab, interferon, retinoids, and ECP on the tumor microenvironment. MF/SS is characterized by the migration of CCR4+ malignant T cells to the

skin, facilitated by increased expression of CCR4 ligands (CCL17 and CCL22) by macrophages and dendritic cells [11]. This process is thought to occur via a positive feedback loop, in which Th2 cytokines produced by CCR4+ malignant cells lead to an upsurge in CCR4 ligand expression and thus recruitment of additional CCR4+ malignant cells [11]. Furthermore, CCR4 is frequently expressed in skin-homing Tregs. In contrast to CCR4-negative Tregs, CCR4+ Tregs are primed to inhibit effector cytotoxic CD8+ T cells, which, among other immunosuppressive functions, promote a Th2-polarized skin environment [12].

In addition to the direct elimination of CCR4+ tumor cells, anti-CCR4 treatment induces several salutary effects including reduced production of serum CCL22 ligand [13], improved Th1 polarization of CD4+ cells [12], and depletion of immunosuppressive Tregs [12]. Combination therapy can further enhance these effects. For example, interferons promote the activity and cytotoxicity of NK cells, which mediate ADCC, the mechanism by which mogamulizumab induces tumor cell death [14]. Activation of NK cells has been observed in two patients who responded to treatment with mogamulizumab and pegylated interferon-alpha [14]. Reduced serum CCL22 levels have been described in patients who responded to oral bexarotene monotherapy, which likely signifies reduced activity of tumor-associated M2 macrophages [15].

Notably, a substantial proportion of patients with MF/SS eventually develop gain-of-function mutations and deletions in CCR4, which can lead to resistance [16]. Combination regimens may offer a way to preclude or delay resistance by clearing the circulating malignant T cells prior to mutation or deletion of CCR4. From a broader perspective, combination therapy is likely effective because mogamulizumab is most potent in the blood compartment, while other therapies effectively target the skin and lymph node compartments. Combination therapy may be effective in patients who have lost response to mogamulizumab alone. As depicted in the swimmer plot, one of our patients responded to the combination of mogamulizumab and interferon even after losing response to mogamulizumab monotherapy.

2. Conclusion

In conclusion, the combination of mogamulizumab, interferon, and retinoids was a well-tolerated and effective regimen in patients with advanced CTCL. This regimen avoids cytotoxic agents and has a strong immunologic basis. These results warrant confirmation in future prospective studies with a larger number of patients.

Data Availability

Data are available from the corresponding author upon reasonable request.

Ethical Approval

This study is approved by the IRB at the University of Pennsylvania (IRB #833679).

Disclosure

Some data from this study were presented at the 2022 Annual Meeting of the Society of Investigative Dermatology.

Conflicts of Interest

AR is a consultant for TLR Biosciences and speaker for Mallinckrodt. SB is a consultant for Acrotech, Affimed, Daiichi Sankyo, Kyowa Kirin, and Seagen, and is on the independent data monitoring committee for Janssen. EK is a consultant for Soligenix, received research funding (clinical trial grants) from Innate, FDA, and received honoraria from UptoDate. RB is a consultant for Alva10. SN received research funding from Ono, Pharmacyclics, Loxy/Lilly, Genentech/Roche, Rafael, ASTEX, ATARA, and honoraria from Accrotech, Ono, ADC therapeutics; DSMB member for Merck. JS is a consultant for Seagen, Pharmacyclics, Incyte, Genmab, BMS, Atara, Astra Zeneca, Adaptive, ADCT, and received research funding from TG, Seagen, Pharmacyclics, Merck, Incyte, BMS, Astra Zeneca, Adaptive. All other authors declare that they have no conflicts of interest.

Authors' Contributions

All authors contributed to patient care and revision of the manuscript. DW, SR, DL, LC, and SC collected data and drafted the initial manuscript.

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