Systemic treatments with monoclonal antibodies in mycosis fungoides and Sézary syndrome

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Abstract

Mycosis fungoides (MF) and Sézary syndrome (SS) are the most prevalent non-Hodgkin lymphomas that comprise cutaneous T-cell lymphomas (CTCL), accounting for more than 70% of cases. Following the Tumor Lymph nodes Metastasis Blood system, disease staging is carried out, and within ten years, about thirty percent of patients in the early stages will have advanced disease. Plaques, folliculotropism, and age over 60 are risk factors for progression. A 5-year survival rate of less than 20% is associated with LCT in MF. Treatment requires an interdisciplinary approach; skin-directed therapies are available for early stages of the disease, but there are no curative options for advanced stages of the disease other than allogeneic stem cell transplantation. Because of their severe symptoms and poor treatment efficacy, patients in advanced stages have a lower quality of life and a lower chance of survival. In patients with CD30-expressing CTCL, Brentuximab Vedotin has demonstrated better response rates and progression-free survival (PFS); in advanced SS, mogamulizumab has significantly increased PFS. These findings emphasize the need to standardize prognostic factors and improve CTCL treatment.

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Introduction

Cutaneous T-cell lymphomas (CTCL) constitute a heterogeneous group of extranodal non-Hodgkin lymphomas with diverse clinical presentation and prognoses. Mycosis fungoides (MF), along with its variants, stands as the most prevalent entity among CTCL, and, given its numerous similarities with the much rarer Sézary syndrome (SS), encompassing both pathological and clinical aspects, a common staging system and overlapping treatment options are often applied to address both disorders together.[1]

MF, SS, and CD30+ CTCL collectively account for more than 70% of cases. The disease staging follows the current Tumor (skin) Lymph nodes Metastasis (viscera) Blood (TNMB) system.[2]

Approximately 30% of patients diagnosed with early-stage CTCL (IA-IIA) will progress to advanced-stage disease within 10 years. The PROCLIPI study identified risk factors in MF/SS patients with a higher likelihood of progression when presenting with early-stage disease, including age over 60 years, the presence of plaques, and folliculotropism. However, the development of novel standardized prognostic factors is desirable to aid the decision-making process in diagnosis and therapy.[2]

MF with large-cell transformation (LCT) represents a particularly aggressive subtype, where large cells constitute over 25% of the lesion infiltrate or manifest as microscopic nodules. This transformation is prevalent in 20-55% of advanced cases of MF, serving as a histological marker that indicates a poor prognosis. Notably, it is associated with a mean 5-year survival rate of less than 20%.[2] The treatment of MF and SS needs a multimodal approach involving hematologists, dermatologists, and radiotherapists. While skin-directed therapies can effectively control initial stages of MF for years or even decades, advanced MF and SS prove to be aggressive diseases with no curative treatment currently available, with the exception of allogeneic stem cell transplant.[4]

Patients with these advanced stages often endure severe pruritus, diminished quality of life, and reduced survival due to disease progression, immunosuppression, and side effects associated with multiple lines of therapy. Treatment options at second and third lines are diverse, encompassing systemic therapies in the majority of patients, alongside radiotherapy and topical therapies. The time to relapse and refractory disease is significantly shortened, emphasizing that time to next treatment (TTNT) or progression-free survival (PFS) serves as more meaningful endpoints to measure the efficacy and safety of systemic therapy approaches.

Recent findings reveal that following first-line systemic treatment, 48% of patients experienced a relapse, and 52% developed refractory disease. Even with chemotherapy administered as second-line treatment, 80% of patients progressed to a second relapsed or refractory MF, with approximately 60% experiencing

a third relapse or becoming refractory within 1 year.[5] Recently, Brentuximab vedotin (BV) has been approved for the treatment of CD30-expressing CTCL patients.[1-3] In the ALCANZA study, a phase III randomized, controlled, multicentric clinical trial, BV showed a superior objective response rate when compared with physician's choice (bexarotene or methotrexate) in patients with CD30-expressing MF or pcALCL. A significant improvement in PFS with BV (median of 16.7 months) with respect to the group with conventional therapy (3.5 months) was observed.[6] If BV was primarily studied in MF, the most progress for patients with CTCL has been made in advanced-stage SS due to the advent of Mogamulizumab treatment. Results from the phase 3 MAVORIC study showed that mogamulizumab had a significant PFS increase (median of 7.7 months) over the control arm vorinostat (3.1 months) in both the MF and SS settings.[7]

Brentuximab vedotin

Brentuximab vedotin (BV), a humanized anti-CD30 antibody conjugated with the antimitotic agent monomethyl-auristatin, acts by binding the antibody component to CD30-positive cells, followed by endocytosis and release of monomethyl auristatin E (MMAE) upon exposure to intracellular lysozymes, and inhibition of tubulin formation resulting in cell apoptosis.[8] It is assumed that the antitumor effect is not only based on the cytotoxicity of the antimicrotubule agent within tumor cells but also due to the diffusion of MMAE into the tumor microenvironment. The effectiveness of CD30 targeted therapy in CTCL was initially demonstrated through a phase 2 study involving a naked anti-CD30 antibody, SGN-30, with a 70% overall response rate (ORR). Subsequent trials tested BV in relapsed/refractory CD30+ CTCL. In one trial with 48 patients, after ≥1 prior systemic therapy, BV showed a 73% ORR and a 35% complete response (CR) rate. Another multicenter trial focused on CD30+ MF/SS patients progressing after ≥1 prior systemic therapy, revealing a 70% ORR but only one global CR. Patients with low (<10%) CD30 expression showed a statistically significant inferior response in both trials.[8,9]

The ALCANZA trial, a randomized phase 3 study, investigated patients with CD30+ MF or primary cutaneous anaplastic large cell lymphoma who had undergone at least one prior systemic therapy. The trial compared BV to physicians' choice of standard care (oral methotrexate or bexarotene). BV, administered intravenously at 1.8 mg/kg for up to 16 cycles every 3-week interval, demonstrated superior outcomes with a 56% ORR lasting at least 4 months (ORR4), compared to 12% in the control arm. Complete response rates were 16% and 2%, respectively, with median PFS of 16.7 and 3.5 months, and median duration of response (DOR) of 15.1 and 18.3 months, respectively. BV's toxicity profile mirrored previous experiences, with peripheral neuropathy being the most common adverse event (67% incidence). Notably, 82% reported symptom improvement or resolution. Nausea (36%), diarrhea (29%), and fatigue (29%) were also common but predominantly low-grade. Serious adverse reaction (SAR) occurred in 29% of BV-treated patients, leading to discontinuation in 24%.[7]

Due to the low frequency of these lymphomas, there is limited real clinical practice on the use of BV in this setting. To evaluate the real-world impact of BV as a second or later line of therapy for CTCL, a retrospective chart review of 139 patients treated with BV and 164 with other standard therapy (OST) was conducted. Most BV recipients (96.4%) received BV as second-line therapy, while common OSTs included methotrexate, mogamulizumab, and bendamustine. In the BV cohort, real-world outcomes revealed an 82.1% ORR and a 42.5% ORR4, with a median duration of therapy of 8.4 months. Comparatively, OST showed a 66.5% real-world ORR and a 25.0% ORR4 with a median duration of therapy of 5.2 months. Real-world 1- and 2-year PFS, TTNT, and OS were significantly longer (all P<.01) for BV compared to OST, and healthcare resource utilization was lower. These real-world outcomes align with ALCANZA trial results, underscoring the favorable impact of BV over OST in CTCL patients previously treated with systemic therapies. Observational data from the Spanish Primary Cutaneous Lymphoma Registry and a retrospective analysis from European Organization for Research and Treatment of Cancer (EORTC) centers confirmed BV's efficacy in MF, SS, and other CD30+ lymphoproliferative disorders. Response rates varied, with ORRs of 63% in MF, 71% in SS, and 84% in other CD30+ lymphoproliferative disorders among Spanish registry patients.[11] EORTC centers reported similar ORRs of 69% and 62%, with a median DOR of 9 months, demonstrating higher ORR in the skin (72%) than in lymph nodes (47%) or blood (40%).[12] Despite these excellent results, there are still important issues to be addressed, such as its effectiveness in re-treatment and the management of the peripheral neuropathy frequently associated with its use.

Mogamulizumab

Mogamulizumab is a defucosylated humanized IgG1K monoclonal antibody directed against C-C chemokine receptor 4 (CCR4) with enhanced antibody-dependent cellular cytotoxicity activity. CCR4, which is involved in cell trafficking of lymphocytes to the skin, is consistently expressed on the surface of tumor cells of CTCL (including MF and SS), adult T-cell leukaemia-lymphoma, and peripheral T-cell lymphoma.[13] The drug is approved in Europe for the treatment of adult patients with MF or SS who have received at least one prior systemic therapy. Safety and efficacy of mogamulizumab were shown in a large open-label, randomized, controlled phase 3 trial (MAVORIC trial) where 372 patients (204 with MF and 168 with SS) were randomly assigned to receive mogamulizumab (n=186) or vorinostat (n=186). Mogamulizumab significantly prolonged median PFS (the primary end-point in MAVORIC) compared to vorinostat (7.7 *vs.* 3.1 months) with a superior ORR. Analysis of predefined subgroups revealed that efficacy is superior in SS compared to MF and stage III/IV disease compared to stages IB/II.[7]

A *post hoc* analysis evaluated the effect of baseline blood tumor burden on patients' response and identified blood involvement (B1 and B2) as predictor of response to mogamulizumab for all the end-points, including PFS, ORR, TTNT, and skin involvement (modified Severity-Weighted Assessment Tool). Mogamulizumab induced rapid and sustained reductions in CD4+ CD26-cell counts and CD4/CD8 ratio.[13] A further *post hoc* analysis showed that prior systemic therapies did not affect ORR, PFS, and DOR to mogamulizumab.[15] Subsequent studies revealed that in cases of CTCL, the progression of mogamulizumab often occurs when the tumor cells experience a loss of CCR4 expression.[16] The real-world French OMEGA study, conducted retrospectively on 122 adult patients with CTCL, aimed to evaluate mogamulizumab's effectiveness and tolerability, focusing on MF and SS. Patients initiated mogamulizumab after a median disease duration of 2.5 years and multiple prior systemic CTCL therapies. The majority (77.8%) had advanced disease, often with blood involvement. During a median treatment period of 4.6 months, 96.7% of patients received all planned mogamulizumab infusions.

The ORR was 58.7%, with distinct rates for SS (69.5%) and MF (46.0%). Notably, compartmental responses in the blood were observed in 81.8% of SS patients. Skin responses were noted in 57.0% of patients overall, with higher rates in SS (66.7%) compared to MF (46.0%). Common SAR included rash (8.1%) and infusion-related reactions (2.4%), leading to treatment discontinuation in 7.3% and 0.8% of patients, respectively.

A patient with SS succumbed to tumor lysis syndrome associated with mogamulizumab. This extensive French study affirmed mogamulizumab's effectiveness and tolerability in routine medical practice for both SS and MF patients, providing valuable insights into real-world outcomes.[17] The most common adverse effects of mogamulizumab were largely grade 1 and included infusion-related reactions (32%), drug rash (20%), diarrhea (23%), and fatigue (22%). Of note, the rate of treatment-emergent adverse events was independent of B-class (7,14). Mogamulizumab-associated rash (and probably also other immune-mediated toxicity) is presumed to be related to the depletion by mogamulizumab of regulatory T-cells in the skin allowing cytotoxic T-cells to cause inflammation and skin disease.[18] The resulting rash is highly variable, can clinically resemble MF/SS and was the most common TEAE leading to treatment discontinuation. The differentiation of mogamulizumab-associated rash from persistent/progressive MF/SS is essential to prevent premature drug discontinuation. Skin rashes have been reported to be associated with higher OS. Recommendations as to their characterization and management have been published recently.[19]

Conclusions

Managing MF and SS, particularly in advanced-stage disease, presents challenges due to the lack of consistently curative treatments, the potential for a substantial symptom burden that significantly affects quality of life, and the frequent requirement for continuous systemic therapy. The DOR is frequently constrained, and treatment is typically sustained until either intolerance develops or progression occurs. Since neither BV nor Mogamulizumab offer a cure for advanced MF/SS, our priority is to encourage combination therapies in clinical trial, targeting specific compartments, and employing an algorithmic approach to optimize treatment outcomes.

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