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Review Article

The Treatment of Advanced-Stage Mycosis Fungoides and Sezary Syndrome: a Hematologist's Point of View

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Abstract. Cutaneous T-cell lymphomas are a heterogeneous group of T-cell neoplasms involving the skin, the majority of which may be classified as Mycosis Fungoides (MF) or Sézary Syndrome (SS).
Mycosis fungoides (MF) is usually associated with an indolent clinical course and intermittent, stable, or slow progression of the lesions. Extracutaneous involvement (lymph nodes, blood, or less commonly other organs) or large cell transformation (LCT) may be seen in advanced-stage disease. Sezary syndrome (SS) is a rare leukemic subtype of CTCL characterized by significant blood involvement, erythroderma, and often lymphadenopathy.
Although the early-stage disease can be effectively treated predominantly with skin-directed therapies, systemic therapy is often necessary to treat advanced-stage disease. Systemic therapy options have evolved in recent years with the approval of novel agents such as vorinostat, brentuximab vedotin, and mogamulizumab. This review aims to discuss the diagnosis and management of advanced-stages MF and SS.

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Introduction. Mycosis fungoides (MF) and Sezary syndrome (SS) are the most common variants of cutaneous T-cell lymphoma (CTCL), which represent, in the Western world, ~75% to 80% of all primary cutaneous lymphomas, being the B cutaneous lymphoma 20% to 25% The prognosis of MF and SS depends on the type and extent of skin lesions and extracutaneous disease, which were first captured in the TNM classification published for CTCL in 1979. Suggested modifications published in 2007 for MF/SS revised the nodal clinicopathologic classification adding blood involvement to the staging of MF/SS.[1]

Mycosis fungoides (MF) is the most common subtype and is usually associated with an indolent clinical course with intermittent, stable, or slow progression of the lesions. Extracutaneous involvement (lymph nodes, blood, or less commonly other organs) or large cell transformation (LCT)[5] may be seen in advanced-stage disease. Sézary syndrome (SS) is a rare erythrodermic, leukemic variant characterized by significant blood involvement, erythroderma, and often lymphadenopathy.[1]

The incidence of CTCL has increased in recent decades; currently, it is 6.4 per 1,000,000 people with a median age of presentation 55-60 years old, predominantly Caucasian males. Retrospective epidemiological studies have shown that African-American, Hispanic, and Middle Eastern individuals

may have a higher incidence of CTCL (especially MF) than white individuals and younger age and more aggressive course.[2]

MF is caused by the malignant transformation of skin-resident effector memory T cells, while SS is thought to arise from thymic memory T cells, supporting the contention that SS is a process distinct from MF. However, cases presenting as an overlap of these two conditions also exist.[3]

Folliculotropic MF (FMF), granulomatous slack skin, and pagetoid reticulosis are recognized as distinct clinicopathologic variants of MF in the WHO-EORTC classification.[1]

SS is defined by a triad of erythroderma, generalized lymphadenopathy, and the presence of clonally related neoplastic T cells with cerebriform nuclei (Sezary cells) in the skin, lymph nodes, and peripheral blood.[4] This review describes systemic approaches for advanced-stage disease (stage IIB-IV).

Staging, Molecular Biology, and Prognosis. Adequate staging should be carried out to exclude the presence of extracutaneous disease.

Initial work-up for patients with MF/SS also includes a complete physical examination, representative skin biopsy, complete and differential blood cell count, routine serum biochemistry with lactate dehydrogenase (LDH), and appropriate imaging studies (CT and/or FDG-PET scans).[6] Bone marrow biopsy and aspirate should be carried out in cutaneous lymphomas with an intermediate or aggressive clinical behavior but is not required in cutaneous lymphomas with an indolent clinical behavior unless indicated by other staging assessments.[7]

Flow cytometry of the peripheral blood is usually recommended for all stages of MF.

The following immunophenotypes characterize MF and SS cells: CD2+, CD3+, CD5+, CD4+, CD8-, CCR4+, TCR-beta+, and CD45RO+ and absence of certain T-cell markers, CD7 and CD26. However, there are subtypes of MF that are CD8+ (especially the hypopigmented variant) or CD4/CD8 double-negative (in those with LCT), although rare.[7,8]

For clinical staging of MF and SS, the revised tumor, node, metastasis, and blood (TNMB) staging system should be used. Apart from the clinical stage, older age, large cell transformation, and increased LDH values have been identified as independent unfavorable prognostic factors in MF.[8,9]

Despite some uncontrolled clinical trial results that have been reported to suggest "cures" in this disease, the general perception remains that this disease is not curable with standard therapies available today. The disease behaves similarly to other low-grade lymphomas, with periods of remission gradually becoming shorter with subsequent therapeutic interventions. Patients with significant nodal involvement (N3 or N4) or extensive skin involvement (T4) have median life expectancies of 30–55 months.[10] Therefore, a driving force in the development of treatments for this disease is altering the natural history of this group of poor prognosis patients. Recently, through the next generation sequencing (NGS), we have understood the mutational profile that underlies the pathogenesis of cutaneous T-cell lymphomas, and specifically, we have identified the fundamental genetic and epigenetic alterations. Within pathogenetic mechanisms, the role of T-cell clones with the presence of inflammatory cytokines related to the TH2 profile is very important to favor both the dysregulation of the immune system with a consequent deficit of immunosurveillance and the creation of a favorable microenvironment. Furthermore, there are numerous cytokines involved in addition to Th2-secretion related, particularly IL-10, IL-15, IL-16, IL-17A, IL-17F, IL-22, and IL-32 which have the primary purpose of suppressing the immunological response regarding the tumor immunosurveillance function. From the molecular point of view, the cellular stimulation mediated by cytokines and chemokines generates TH2 based inflammatory context with constitutive activation of the STAT pathway and loss of complexity of the TCR. Therefore, forming a clonal population of T cells with specific genetic-molecular alterations results in precarious equilibrium with the cellular and humoral part of the microenvironment.[11]

In 2007 staging system was revised by the International Society for Cutaneous Lymphomas (ISCL) and the EORTC to incorporate advances related to tumor cell biology and diagnostic techniques, including the status of blood involvement. Investigators at the National Cancer Institute retrospectively analyzed 152 patients who underwent uniform pathologic staging. They were able to identify three distinct prognostic groups. Good-risk patients had plaque-only skin disease without lymph node, blood, or visceral involvement and a median survival of more than 12 years. Less than 10% of patients with stage 1A (localized patches) and less than 30% with stage 1B (extensive patch or plaque) progress to more advanced disease. Intermediate-risk patients had skin tumors, erythroderma, or plaque disease with lymph node or blood involvement (but no visceral disease) and a median survival of 5 years. Poor-risk patients had a visceral disease or complete effacement of lymph nodes by lymphoma, and a median survival of 2.5 years.[12]

Cytogenetic analysis precisely identifies the individual chromosomal structure and number. Bunn et al. demonstrated that in MF/SS, the presence of aneuploidy karyotype during the clinical course was associated with more aggressive disease. Hyperdiploid cell clones were demonstrated in patients with large-cell histology, aggressive disease, and shortened survival time.

Specific chromosomal deletions also influenced prognosis.[13]

Currently, there are no valid markers to measure the prognosis of patients with cutaneous T-cell lymphoma. However, in a recent paper, Shen et al. showed that miR-155 and miR-200b expression in association with elevated Ki-67 was significantly associated with worsening overall survival in CTCL patients. Through this association, it was possible to create a risk score classification projected on 5-year survival.[14] Furthermore, the identification of this mechanism and the understanding of epigenetic phenomena in the pathogenesis of LCT-MF have determined a potential therapeutic role. Notably, a phase 1 study of MRG-106 (Cobomarsen), an inhibitor of miR-155, demonstrated efficacy in patients with MF.[14]

From the prognostic point of view, Di Raimondo et al. demonstrated the specific expression of twelve miRNAs in MF patients undergoing clinical transformation to LCT-MF, thus identifying the possibility of early progression markers.[15]

The nuclear contour index has been used by several groups to separate "benign" cutaneous lymphocytic disorders, such as Lymphomatoid Papulosis and Pityriasis Lichenoides, from MF/SS.[16]

Treatment. Most patients with early-stage MF (stage I or IIA) follow an indolent course, and in particular, patients with stage IA MF have a similar life expectancy as age, sex, and race-matched control populations. For early-stage MF, the treatment concept is to control skin lesions mainly by skin-directed therapies, such as topical therapies, phototherapies, and radiotherapies, with the lowest possible side effects. Unfortunately, early aggressive therapy does not appear to improve survival when compared with skin-directed therapies.[17]

Systemic Therapy. Currently, systemic chemotherapy is reserved for those patients with relapsed or refractory disease after topical interventions or for those patients with advanced nodal or visceral disease at presentation.

Bexarotene is available and is EMA-approved for the treatment of the skin manifestations of advanced stage (IIB–IVB) CTCL in adult patients refractory to at least one systemic treatment.[18] In the US, Bexarotene is FDA-approved as a second-line treatment for the early and late-stage refractory disease (IB–IVB).[19] The recommended initial dose is 300 mg/m^2/day, and this is taken as a single oral daily dose with a meal. The dose is adjusted up or down according to clinical response and toxicity to a maximum of 650 mg/m^2/day. In the poor responders, Bexarotene may also be safely combined with other anti-CTCL therapies, including PUVA, ECP, methotrexate, and alpha-interferon to augment responses.[20] It is 99% protein-bound and metabolized by cytochrome P450 3A4 (CYP3A4) to hydroxybexarotene and oxybexarotene and excreted in the bile. Therefore, it is recommended that Bexarotene should be avoided in patients with hepatic impairment. Other contraindications include a history of pancreatitis, hypervitaminosis A and pregnancy.

Older agents studied previously include alkylating agents such as chlorambucil or cisplatin, the microtubule inhibitors such as etoposide, vincristine, and vinblastine, or the antitumor antibiotics, such as bleomycin and doxorubicin. In general, the responses are modest, and the duration of response is typically less than six months. McDonald and Bertino reported particularly good results with the antimetabolite methotrexate administered intravenously followed by oral citrovorum factor. Patients received 1–5 mg/kg of intravenous methotrexate every five days. If a patient tolerated the lowest dose, each subsequent dose was escalated. After five intravenous doses, patients were switched to oral methotrexate (25–50 mg) with oral citrovorum as weekly maintenance. All 11 patients achieved "good" or better clearing (>60%) for a median duration of 24 months. Mucositis and skin ulcerations were the most significant toxicity witnessed. Myelosuppression was mild in general.[21]

Gemcitabine monotherapy is an effective treatment option resulting in an ORR of 48% to 71% in patients with heavily pretreated advanced-stage MF and SS. In a retrospective observational study of 25 patients with advanced MF and SS, after a long-term follow-up of 15 years, the estimated OS, PFS, and DFS rates were 47%, 9%, and 40%, respectively.[22] Gemcitabine monotherapy has also demonstrated front-line therapy activity in untreated MF and SS patients.

Pegylated liposomal doxorubicin has shown single-agent activity in patients with pretreated, advanced, or refractory MF and SS. In an EORTC multicenter trial (phase II) of 49 patients with advanced MF (stage IIB, IVA, IVB), relapsed/refractory after at least two prior systemic therapies, liposomal doxorubicin resulted in an ORR of 41% (6% CR). The median time to progression was seven months, and the median duration of response was 6 months. Pegylated liposomal doxorubicin was well tolerated with no grade 3 or 4 hematologic toxicities; the most common grade 3 or 4 toxicities included dermatologic toxicity other than hand and foot reaction (6%), constitutional symptoms (4%), gastrointestinal toxicities (4%), and infection (4%).[23]

In phase III randomized study (ALCANZA),[24,25] brentuximab vedotin (anti-CD30 antibody-drug conjugate) attained clinical outcomes superior to physicians' choice of methotrexate or Bexarotene in patients with previously treated CD30-expressing MF. In this study, 131 patients with previously treated CD30-expressing MF and primary cutaneous anaplastic large cell lymphoma (PC-ALCL) (97 patients with MF) were randomized to receive either brentuximab vedotin or

Table 1. Literature review.* In these trials all enrolled patients were relapsed/refractory t-cell lymphomas underwent at least one prior therapy.

Ref.	*N°*	*Drug*	*Median of previous therapies**	*Phase trial*	*ORR (Cr)*	*AEs*
Duvic et al., 2001 [18]	56	Bexarotene (300mg/mq)	2	II-III	45% (2%)	Pancreatitis, hypertrigliceridemia, thyroid disease
Zackheim et al., 2003 [21]	69	Low-dose Methotrexate	1	retrospective	34% (12%)	Mucositis, mielosuppression, eleveted transaminase level
Zinzani et al., 2000 [22]	44	Gemcitabine	3	II	70.5% (11.5%)	Mielosuppression, eleveted liver enzymes
Dummer et al., 2012 [23]	49	Peg-L-Doxorubicin	2	II	40.8% (6.1%)	Mielossuppression, gastrointestinal toxicity
Prince et al., 2017 [24]	131	Brentuximab Vedotin	1	III (Alcanza)	67% (16%)	Peripheral neuropathy
Duvic et al., 2006 [27]	33	Vorinostat	5	II	24.2% (no Cr)	Fatigue, diarrhea, nausea, thrombocytopenia
Kim et al. 2018 [31]	186	Mogamulizumab	3	III (Mavoric)	28% (n.r.)	Infusion related reaction, thrombocytopenia

physician's choice (methotrexate or Bexarotene). At a median follow-up of 23 months, the primary endpoint, ORR lasting for ≥4 months, was significantly higher for brentuximab vedotin compared to methotrexate or bexarotene in the intent-to-treat population (56% [16% CR] vs. 13% [2% CR]; $P < .0001$). In addition, peripheral neuropathy was the most common adverse event reported in 67% of patients treated with brentuximab vedotin.[26]

Vorinostat 400 mg daily orally was tested in an open-label trial of 74 patients who had progressed on at least two prior systemic therapies. The ORR (skin only) was 29.5%, with 1 CR and 18 PRs. Common adverse events included diarrhea (49%) and fatigue (46%). Grade 3 events were less common but included fatigue (5%), deep venous thromboses/pulmonary emboli (5%), and thrombocytopenia (4%). Reports from the National Cancer Institute with romidepsin have provided confirmatory results by using this class of agents to treat patients with T-cell lymphomas, including some with MF/SS. In several phase I and II trials, 50% of patients with MF/ SS appeared to have had a PR. Two additional clinical trials demonstrated activity in Cutaneous T Cell Lymphoma(CTCL).[27] Vorinostat is currently only approved in the United States.

In general, toxicity to romidepsin and vorinostat has included alterations in the cardiac conduction that could potentially predispose to arrhythmias, and treatment of patients has required ongoing telemetry monitoring in some trials. However, no evidence for acute or chronic impairment in cardiac function has been noted. Vorinostat therapy led to drug-related grade 1 electrocardiographic changes in five patients and grade 2 in one patient. Therefore, using these agents in the outpatient setting appears safe with a periodic assessment of cardiac rhythm and QTc interval with an electrocardiogram base.[28] Unfortunately, romidepsin is a substrate for the MDR protein (a P-glycoprotein) and upregulates the expression of MDR1. Preliminary molecular analyses confirmed the upregulation of MDR1. These data suggest that when resistance to this agent develops, other chemotherapeutic drugs handled by MDR1 may be rendered ineffective.[29]

IFN-α is an active agent for the treatment of MF. Dosages and routes of administration have differed among studies. Initially, high-dose IFN was used, with maximum doses of 36–50 million International Units (IU). Bunn et al. and Olsen et al. independently demonstrated complete response rates of 10%–27% in heavily pretreated patients. However, the duration of response was only 5.5 months. Later trials of untreated patients with doses of 3–18 million IU given subcutaneously daily have demonstrated an overall response rate of 80%–92%.[30] From all these studies, it appears that a reasonable and tolerable single-agent dose is 12 million IU/m^2 administered subcutaneously daily. We recommend starting at 3 million IU and gradually increasing as the patient tolerates the treatment.

Side effects of all IFNs are dose-dependent. The most common adverse effects are constitutional symptoms: fever, chills, myalgias, malaise, and anorexia. Rarely, cytopenias, elevations of liver function test results, renal dysfunction, cardiac dysfunction, or changes in mental status (psychiatric syndromes).

Recently Mogamulizumab, a humanized anti-CCR4 monoclonal antibody, was approved for the treatment of relapsed or refractory MF and SS after at least one prior systemic therapy. The approval was based on a phase III randomized, open-label, multicenter trial (MAVORIC).[31] In this trial, 372 eligible patients with relapsed or refractory MF and SS were randomized to either mogamulizumab (n = 186) or vorinostat (n = 186). Mogamulizumab resulted in significantly higher investigator-assessed ORR (28% vs. 5%; $P < .0001$) and superior investigator-assessed median PFS (8 months vs. 3 months; $P < .0001$) compared with vorinostat, after a median follow-up of 17 months. The ORR was higher in patients with SS than in those with MF (37% vs. 21%). Among the 186 patients randomly assigned to vorinostat, 136 patients (109 patients with disease progression and

27 patients after intolerable toxicity) crossed over to mogamulizumab. The ORR was 31% for the 133 patients who crossed over from vorinostat to mogamulizumab and subsequently received mogamulizumab.

In the post-hoc subgroup analysis by clinical stage, the ORRs for mogamulizumab were higher for patients with stage III (23%) or stage IV disease (36%) than those with stage IIB (16%) or stage IB/IIA disease (19%). For skin, blood involvement, and lymph nodes, the compartment-specific ORRs for mogamulizumab were 42%, 68%, and 17%, respectively. The corresponding ORRs for vorinostat were 16%, 19%, and 4%, respectively. This trial, however, was not powered to detect OS differences between the two groups within the defined follow-up period.[32] The most common adverse events associated with mogamulizumab were mostly graded 1–2 and manageable (infusion-related reactions [37%], skin eruptions [25%], and diarrhea [14%]). Pyrexia (4%) and cellulitis (3%) were the most common grade 3 adverse events in the mogamulizumab group. Patients with the greatest symptom burden and functional impairment took advantage, in terms of quality of life, mostly from mogamulizumab.

In a phase II study of 24 patients with MF and SS (stage IIB–IV) treated with at least one prior systemic therapy, at a median follow-up of 40 weeks, pembrolizumab, an immune checkpoint inhibitor, resulted in an ORR of 38% (the ORR was slightly higher in patients with MF [56% vs. 27% for SS]) and a one-year PFS rate of 65%. In addition, Pembrolizumab was associated with a skin flare reaction, occurring exclusively in patients with SS. The flare reaction correlated with high PD-1 expression on Sézary cells and should be distinguished from disease progression.[33]

Role of Stem Cell Transplantation. Allogeneic HCT has a role in a subset of patients with advanced-stage MF and SS who have received multiple lines of therapy, as shown in retrospective studies and small prospective series of patients with advanced MF and SS.

In a multicenter retrospective analysis of 37 patients with advanced-stage primary CTCL treated with allogeneic HCT (24 patients [65%] had stage IV MFSS or disseminated nodal or visceral involvement), after a median follow-up of 29 months, the incidence of relapse was 56%, and the estimated 2-year OS and PFS rates were 57% and 31%, respectively.[34]

In a retrospective analysis of patients with advanced-stage MF and SS in the European Group for Blood and Marrow Transplantation (EBMT) database (n = 60) treated with allogeneic HSCT, the 5-year PFS and OS rates were 32% and 46%, respectively. The corresponding 7-year survival rates were 44% and 30%, respectively. The non-relapse mortality (NRM) rate at 7 years was 22%. Outcomes were not significantly different between histology types. However, patients with advanced-stage disease had an increased risk of relapse or progression and lower PFS, and myeloablative conditioning was associated with poorer NRM and OS.

Besides, transplants from unrelated donors had a statistically borderline impact on NRM and a significantly lower PFS and OS. In a case series of 47 patients with advanced-stage MF and SS who underwent allogeneic HCT after the failure of standard therapy, the estimated 4-year OS and PFS rates were 51% and 26%, respectively. While there was no statistical difference in the OS in patients who had MF without LCT, SS, MF with LCT, or SS with LCT, the 4-year PFS rate was superior in patients who had SS versus those who did not (52% vs.10%; P = .02). Recent systematic reviews and meta-analyses have reported pooled PFS and OS rates of 36% and 59%, respectively. Autologous HCT is not recommended for patients with CTCL due to the short duration of response despite its toxicity, thus limiting its utility.[35]

Emerging Therapies and Conclusion. The advanced stages of mycosis fungoides still have a poor prognosis. Current treatment options have improved the management of skin manifestations without significantly increasing survival. In our experience, conventional chemotherapy still plays a valid role, especially in a high burden disease. The new therapies represented by monoclonal antibodies, sometimes conjugated with cytotoxic agents, aim to maximize the therapeutic effect through a biological target and reduce adverse events. Notably, targeted therapy has shown some interesting recent developments in many cancers and could have major implications for CTCL.

Anti-drug conjugates, which target surface markers such as CD30, have shown better results, although with a toxicity profile that makes them unsuitable for all patient categories. AFM13 is a chimeric antibody with an anti-CD30 murine domain. An open-label Phase II multicenter study is underway to evaluate the efficacy and safety of AFM13 in patients with transformed mycosis fungoides (REDIRECT).

In addition, immune checkpoint inhibitors such as anti-PD-1 should be considered in the treatment of CTCL. Activation of innate immune mechanisms that support Th1 responses must be investigated alone or in combination with depletion of malignant T cells.

Finally, Zanolimumab is a humanized anti-CD4 + mAb expressed on most T lymphocytes and is therefore useful in most CD4+ lymphoproliferative diseases. Kim et al. described 47 relapsed/refractory MF/SS patients in two phase II trials that showed a high response rate in the maximum dose group (56%) with a median duration of response of 81 weeks.[36]

Therefore, we needed further studies to understand the targeted therapy's timing and possibly combination treatments. Nevertheless, the use of the molecular target

is certainly a valid strategy to reduce the minimum measurable disease and confer an advantage on consolidation treatments, especially concerning allogeneic stem cell transplantation.

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