

CLINICAL UPDATE

Current Developments in the Management of Cutaneous T-Cell Lymphoma

A New Target in CTCL: Treating the Skin, Blood, and Lymph Nodes



Steven M. Horwitz, MD
Associate Attending
Lymphoma Service
Memorial Sloan Kettering Cancer Center
New York, New York

H&O What are the main subtypes of cutaneous T-cell lymphoma?

SH Cutaneous T-cell lymphoma (CTCL) refers to a group of non-Hodgkin lymphomas that present primarily or exclusively in the skin. The most common subtypes are mycosis fungoides, which is often used synonymously with CTCL, and Sézary syndrome.

Mycosis fungoides is an epidermotropic T-cell lymphoma; the malignant T cells are near the epidermis in the dermal epidermal junction. Patients may have skin lesions consisting of patches, plaques, or tumors, or diffuse red skin identified as erythroderma.

Sézary syndrome was formerly considered a leukemic variant of mycosis fungoides, but it is now recognized as a distinct subtype of CTCL. The malignant cells associated with mycosis fungoides and Sézary syndrome are similar but not identical. Sézary syndrome is often associated with erythroderma.

In the United States, the incidence of mycosis fungoides and Sézary syndrome is approximately 2000 new cases a year. The prevalence is probably much higher because many patients with earlier-stage disease or those who benefit from newer treatments often have long-term or even normal rates of survival.

H&O Does the prognosis vary?

SH The prognosis varies according to the disease stage. Staging is based on the type of skin lesions (patches and plaques vs tumors vs erythroderma), the extent of body

surface area (less than or greater than 10%), the absence or presence of extracutaneous involvement, and, when present, the type of extracutaneous involvement. For example, patients with patches and/or plaques covering less than 10% of their body surface area are classified

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as 1A, and those with patches and/or plaques covering more than 10% are classified as 1B. Patients with tumor disease (2B) or extracutaneous manifestations involving the blood, lymph nodes, or organs are considered to have more-advanced disease.

The majority of patients with mycosis fungoides present with early-stage disease, and these patients typically have a good or normal prognosis. Patients with stage 1A disease, and many patients with 1B disease, will have the same life expectancy as people of similar age and health without mycosis fungoides. In part, this is due to the low rates of progression to higher-stage disease, which can be partially attributed to the success of skin-directed therapy.

Patients with advanced-stage disease (2B or higher) will often have a shorter life expectancy. Our understanding of their prognosis, however, is based largely on historical data. In the past decade, several new systemic therapies were developed, and it is possible that the prognosis for patients with advanced-stage disease is improving.

H&O What is the goal of treatment?

SH The goal of treatment is most often to effectively treat the lymphoma to ameliorate symptoms (improve quality of life) and minimize the risk of progression (hopefully, increase the length of life). Although there are no conclusive data showing that any specific therapy can improve overall survival, the hope is that with long-term, safe disease control (often with continuous or maintenance therapy), it is possible to maximize survival while minimizing day-to-day symptoms of the disease and side effects of therapies.

H&O How do dermatologists and oncologists work together to manage patients with CTCL?

SH CTCL, in my opinion, is best managed in an interdisciplinary setting. For most patients, the first hurdle is an accurate diagnosis. The diagnosis of mycosis fungoides is usually made by a dermatologist who performed biopsies of clinically suspicious lesions (often multiple), in conjunction with a pathologist (dermatopathologist or hematopathologist) with experience in cutaneous lymphomas. In Sézary syndrome, the diagnosis involves examination of skin biopsies as well as the peripheral blood, if the disease is suspected clinically. In many cases, the diagnosis cannot be made based on skin biopsy alone, but requires clinicopathologic correlation to exclude other processes, such as drug reactions and other types of rash, lymphomas, or mimics.

Many patients with early-stage disease will receive treatment only with skin-directed therapy, such as topical corticosteroids, phototherapy, or other medications. These patients are adequately managed by a dermatologist alone. However, with the incorporation of more systemic agents that are safe and effective into earlier lines of therapy, oncologists now often play an integral role earlier in the treatment course, as opposed to just prescribing chemotherapy to patients with very advanced disease. Oncologists may prescribe oral retinoids, interferons, histone deacetylase (HDAC) inhibitors, antibody drug conjugates, novel antibodies, other immunotherapies, and eventually chemotherapy. Of course, in any clinical setting, the interest, comfort, and expertise of the individual physician outside of his or her specific training (oncology vs dermatology) may dictate who primar-

ily guides and manages which treatments. Even if the oncologist is primarily providing the systemic therapy, dermatologists bring critical expertise to address skin symptoms, which often correlate strongly to the patient's quality of life. In addition, as immunotherapy is becoming more incorporated into standard therapy, identifying treatment-related rash—and distinguishing it from progression of lymphoma—is becoming an essential part of CTCL management.

H&O How is therapy selected?

SH Initially, the selection of therapy is largely based on the disease stage. Most patients will have their disease managed for the long-term, usually with sequential therapies.

Skin-only disease can be well-managed with skin-directed therapy, with or without a milder systemic agent. Many therapies are available, and there are little data to guide a preferred sequence. However, patients most often begin treatment with the safest or least toxic therapy that has a chance of controlling the disease. In patients with earlier-stage or less-symptomatic disease, the selected therapy may not always be the most potent option. Frequently in these patients, the goal is to provide long-term disease management while minimizing severe side effects and avoiding cumulative toxicities. Examples of this strategy include patients with early-stage skin disease who receive phototherapy, such as narrowband ultraviolet B; or patients with low-burden Sézary syndrome who receive extracorporeal photopheresis. With both of these treatments, more time may be needed to see a response, but they can be given safely, often over years, without cumulative toxicity. Of course, for patients with very symptomatic or more quickly progressive disease, a “slow go” approach may not be adequate. Treatment plans must be individualized and frequently reassessed.

Patients with significant disease beyond the skin require systemic treatment, often in conjunction with skin-directed therapy. In our center, the early-line systemic therapy, when appropriate, often consists of milder agents, such as oral retinoids or low-dose oral methotrexate. Many centers use interferon for patients with early disease. For patients with a higher burden of disease, HDAC inhibitors, such as romidepsin (Istodax, Celgene), may have a quicker time to response.

New data for therapies with high efficacy, such as mogamulizumab-kpkc (Poteligeo, Kyowa Kirin) and brentuximab vedotin (Adcetris, Seattle Genetics) support the importance of adding these agents into routine care. These therapies were initially studied in the multiply-relapsed setting, but some are now being used earlier in the treatment course based on the demonstration of high

response rates in randomized studies comparing them with other standard medications. We tend to reserve more traditional cytotoxic chemotherapies for later lines of treatment because these agents are not necessarily more efficacious than other therapies and can lead to more significant immunosuppression.

H&O What type of drug is mogamulizumab?

SH Mogamulizumab is a monoclonal antibody that targets the chemokine receptor type 4 (CCR4), with enhanced antibody-dependent cellular cytotoxicity as its primary mechanism of action. Mogamulizumab is administered as an intravenous infusion on a weekly basis initially, and then every other week. It was first studied in Japan in patients with human T-cell leukemia/lymphoma virus type 1 (HTLV-1)-associated lymphoma. CCR4 is highly expressed on many T cells, and most patients with mycosis fungoides or Sézary syndrome are CCR4-positive. In early studies, mogamulizumab appeared active in patients with these diseases, with particularly high response rates in patients with Sézary syndrome.

H&O What do phase 3 data show?

SH Results from these early studies led to the large, randomized phase 3 MAVORIC trial (Mogamulizumab Anti-CCR4 Antibody Versus Comparator in CTCL). In this study, patients were randomly assigned to mogamulizumab (n=186) or the oral HDAC inhibitor vorinostat (Zolinza, Merck; n=186). Eligible patients had previously treated mycosis fungoides or Sézary syndrome. Patients were excluded if they had large-cell transformation of mycosis fungoides. The primary endpoint was progression-free survival. Secondary endpoints included overall response rate, duration of response, safety, improvement in quality of life, and response by compartment (the skin, blood, lymph nodes, and viscera).

Progression-free survival was more than double with mogamulizumab vs vorinostat, at 7.7 months vs 3.1 months (hazard ratio, 0.53; 95% CI, 0.41-0.69; stratified log-rank $P<.0001$). The overall response rate was 28% for mogamulizumab vs 5% for vorinostat, a significant difference. Mogamulizumab was particularly effective in patients with Sézary syndrome, with a response rate of 37% (vs 2% with vorinostat). In patients with mycosis fungoides, the response rates were 21% for mogamulizumab vs 7% for vorinostat.

Vorinostat was approved in 2006. A phase 2 study by Duvic and colleagues showed a response rate of 24.2% in the intention-to-treat population. In a subsequent phase 2b trial by Olsen and coworkers, the overall response rate was 29.7%. Somewhat surprisingly, the response rate of

vorinostat in the MAVORIC trial was only 5%. This discrepancy is partly explained by the more stringent use of a global response (assessing all compartments) in the MAVORIC trial as compared with a primary skin assessment in the pivotal phase 2 study of vorinostat. When examining the skin compartment only, the response rate was 42% for mogamulizumab vs 16% for vorinostat. Responses in the blood were seen in 67% of the mogamulizumab arm vs 18% of the vorinostat arm. The lymph node response rate was 15% vs 4%. In both treatment groups, the response rate in viscera was 0%.

The study also assessed quality of life. Symptoms, function, and overall quality of life were improved with mogamulizumab vs vorinostat at all study points. Patients with the highest levels of symptom burden and functional impairment experienced the strongest quality-of-life benefit from mogamulizumab.

H&O What is the importance of having progression-free survival as an endpoint in CTCL?

SH Among the major issues for patients with CTCL are the day-to-day symptom burdens of skin disease. Improvement in quality of life is often based on the lymphoma's response to treatment. The longer the treatment is effective, the longer the symptoms may be controlled. Among patients with advanced-stage disease, however, the goals of therapy may be more focused on minimizing the risk of progression or death. In both cases—assuming the side effects of treatment are manageable—longer progression-free survival is likely to correlate with longer clinical benefit.

To date, no therapies in CTCL have shown a benefit in overall survival, although there are few randomized trials completed to assess this endpoint. In addition, patients are generally treated with sequential therapy, so unless a treatment is curative, it may be difficult to identify how any one therapy independently impacts overall survival. However, the MAVORIC trial showed that mogamulizumab increased progression-free survival with a reasonable response rate, while also improving quality of life. Mogamulizumab therefore both improved how patients felt and provided longer-term control of the disease.

H&O What are the toxicities associated with mogamulizumab?

SH In the MAVORIC trial, grade 3 or 4 adverse events of any cause occurred at a rate of 41% in both treatment groups. Overall, mogamulizumab was relatively well-tolerated. Rash, a known side effect, occurred in 35% of patients. Grade 3 or 4 rash occurred in 5%. Most of the rashes resolved after treatment with corticosteroids.

It can be challenging to distinguish whether the rash is a symptom of the disease or a treatment-related adverse event. It is sometimes possible to make that judgment clinically, but a biopsy may be required.

The rates of all-grade upper respiratory tract infection were 22% with mogamulizumab vs 16% with vorinostat. Skin infections occurred in 19% vs 13%, respectively. All-grade infusion-related reactions, which are seen with other antibodies, were reported in 33% of patients treated with mogamulizumab.

A study in Japan identified a potential safety concern among patients treated with mogamulizumab for adult T-cell leukemia lymphoma (ATL) who then proceeded to allogeneic stem cell transplant. A retrospective analysis suggested that patients who went to transplant within 2 months of their last injection of mogamulizumab had higher rates of high-grade graft-vs-host disease. In the MAVORIC study, few patients with CTCL went to transplant, so there were no data to support or refute the observation seen among ATL patients in Japan. However, clinicians should be aware of this risk when the management course involves treatment with mogamulizumab followed directly or immediately by allogeneic transplant.

H&O What are your conclusions from the MAVORIC trial?

SH Based on the MAVORIC trial, mogamulizumab is an important and much-needed new therapy for CTCL. The most potent efficacy of mogamulizumab may be in the blood compartment, and the highest rates of response are seen in patients with Sézary syndrome. The strong activity in the blood raises the potential that in addition to use as a single agent, mogamulizumab might be used in

combination with skin-directed therapies or other treatments that might synergize with a monoclonal antibody.

Disclosure

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Suggested Readings

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