ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Update in T-cell Lymphoma

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H&O How are T-cell lymphomas characterized?

OO The T-cell lymphomas represent a very heterogeneous group of diseases. Typically, we characterize these diseases with respect to their development relevant to the thymus gland. T-cell lymphomas that emerge from cells before undergoing differentiation in the thymus are referred to as the precursor T-NK cell lymphomas. Those that develop after thymic differentiation are referred to as the more mature peripheral T-cell lymphomas (PTCL), not to be confused with the specific diagnosis of PTCL not otherwise specified (PTCL-NOS). Similar to the B-cell lymphomas, these diseases come in 2 forms: indolent and aggressive. The indolent T-cell lymphomas commonly include many forms of cutaneous T-cell lymphoma, including mycosis fungoides (MF) and the cutaneous CD30-positive T-cell malignancies. The more aggressive forms of these diseases include the more common PTCL-NOS, angioimmunoblastic lymphoma, and anaplastic large cell lymphoma, both ALK-positive and ALK-negative. Recent efforts by the World Health Organization have led to the reclassification of these different lymphomas based on a better understanding of both the cell of origin and the natural history of these diseases.

H&O What is the current standard of care for the treatment of T-cell lymphomas?

OO Despite the fact that there are more than 30–35 forms of T-cell lymphoma, there still remains very little consensus on upfront treatment or management of relapsed or refractory disease. Presently, there are no currently accepted standards of care for many forms of peripheral T-cell lymphoma. There are some forms of this disease, like ALK-positive anaplastic large cell lymphomas—namely, that set of anaplastic large cell lymphomas that carry the 2;5 translocation—that have a very favorable prognosis. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy is known to be curative in approximately 70–80% of patients with ALK-positive anaplastic large cell lymphoma and would be the recommended standard of care for this specific entity. For many forms of cutaneous T-cell lymphoma, topical strategies upfront are recommended for most patients, with an emphasis on utilizing the least toxic regimen and avoiding systemic therapy for low-stage disease.

For the overwhelming majority of T-cell lymphoma subtypes however, there is essentially little to no consensus on the upfront management, let alone consensus on management in the relapsed/refractory setting. Most physicians treating these diseases will use a CHOP-like chemotherapy regimen, which is typically associated with response rates of approximately 50%, though with dismal long-term survivals of only 10–15% across the larger spectrum of mature, peripheral T-cell lymphomas. Other regimens known to be active in these diseases include infusional chemotherapy, such as etoposide, vincristine, and doxorubicin (EPOCH), and leukemia regimens such as cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine (hyper-CVAD) alternating with methotrexate (Ara-C). There are no randomized data comparing CHOP to any of these therapies, making it difficult to judge the superiority of one regimen over another.

Other regimens are now being developed for the relapsed or refractory setting. Some of these agents and regimens include gemcitabine (Gemzar, Lilly), which

seems to have significant activity in patients with T-cell lymphoma, especially those patients who have relapsed or refractory disease. Gemcitabine has been combined with a number of other different agents, including vinorelbine and doxorubicin HCl in the GND regimen, which first emerged in a cooperative group study in patients with Hodgkin's disease. Gemcitabine has also been studied in combination with oxaliplatin in a regimen known as GEMOX for patients with relapsed or refractory disease.

The US Food and Drug Administration (FDA) has recently approved pralatrexate (Folotyn, Allos Therapeutics), a novel antifol targeting the reduced folate carrier, for patients with relapsed or refractory peripheral T-cell lymphoma. Pralatrexate has been shown to produce a response rate of nearly 30%, with a duration of response benefit of over 10 months in a patient population that had received a median of 3 prior chemotherapy regimens. Last November, pralatrexate became the first drug ever approved for the treatment of relapsed or refractory PTCL, based on data from the largest prospective trial ever conducted in PTCL, namely the PROPEL (Pralatrexate in Patients With Relapsed Or Refractory Peripheral T-cell Lymphoma) study.

H&O Is stem cell transplant an option for patients with T-cell lymphoma?

OO There are still many questions about how best to manage patients with peripheral T-cell lymphoma in the upfront setting. There is significant debate regarding the role of autologous stem cell transplant in first remission. A large clinical trial from Italy has established the merits of taking patients with peripheral T-cell lymphoma in first remission directly to an autologous stem cell transplant, an approach that appears to be associated with a survival advantage. Of course, the biggest drawback to autologous stem cell transplant in T-cell lymphoma revolves around the ability to achieve complete remission with conventional therapy prior to transplant. One of the most important factors portending the benefit of high-dose chemotherapy (HDC) and autologous stem cell transplant in lymphoma is the ability to achieve a complete remission prior to HDC. Given that this disease is so chemotherapy-resistant, far fewer patients with T-cell lymphoma move on to autologous stem cell transplant following induction therapy because of a suboptimal response to the initial chemotherapy.

The other modality of therapy that may have value in this patient population is allogeneic stem cell transplant. Due to the rarity of this disease, the data regarding the role of allogeneic stem cell transplant in patients with relapsed or refractory peripheral T-cell lymphoma have been limited. Presently, there are a number of studies examining the role of allogeneic stem cell transplant in T-cell lymphoma. These data indeed suggest that there may be a robust graft-versus-lymphoma effect for patients with peripheral T-cell lymphoma, at least based on both the bone marrow transplant registry data as well as a study recently reported by Zain and colleagues from City of Hope, in Duarte, California.

It is important to point out that although there are a number of conventional therapies that can be used to manage these patients, both upfront and in the relapsed setting, the lack of consensus for the management of patients with T-cell lymphoma still warrants consideration of clinical trials in either of those settings. When a clinical trial is available, the National Comprehensive Cancer Network (NCCN) has recommended that the trial should be regarded as the primary therapy in both upfront and relapsed/refractory settings for these patients.

H&O What is the role of immunotherapy in T-cell lymphoma?

OO The prominent role of immunotherapy in T-cell lymphoma revolves around 2 discrete considerations. First is the role of monoclonal antibodies, and the second is the role of T-cell mediated effects against the lymphoma as seen in allogeneic stem cell transplant. Similar to the experience in B-cell lymphomas, where monoclonal antibodies targeting CD20 have emerged as an important component of combination chemotherapy, there has not been one single antibody that has emerged as having sufficient activity in patients with T-cell lymphoma either alone or in combination. There are a number of antibodies that have been developed, including one now targeting CD4—an agent that has been resurrected and is again being studied in patients with T-cell lymphoma. In addition, there are other monoclonal antibodies targeting CCR4, namely KW-0761 (Kyowa Hakko Kogyo Co), which appears to be very active in CCR4-positive adult T-cell leukemia/lymphoma and PTCL. Other important targets that seem to be emerging that will have relevance in T-cell lymphoma include CD52, targeted by alemtuzumab (Campath, Genzyme), and CD30 and CD2, targeted by antibodies. Given that there does not seem to be an antigen that is universally expressed in T-cell lymphoma (analogous to CD20 in B-cell lymphoma), it is likely that these antibodies will find restricted use in specific biologic subtypes of the disease.

The second form of immunotherapy that is likely to be active in patients with T-cell lymphoma revolves around exploiting a graft-versus-lymphoma effect. A number of studies now seem to be demonstrating that there is a bona fide graft-versus-lymphoma effect in patients with peripheral T-cell lymphoma similar to what we have seen previ-

ously in patients with both follicular and mantle cell lymphoma. While the role of allogeneic stem cell transplant in peripheral T-cell lymphoma continues to emerge as our experience becomes more significant, for many patients with relapsed or refractory peripheral T-cell lymphoma following autologous stem cell transplant, consideration of allogeneic transplant is worthwhile.

H&O What is the future direction of therapy for T-cell lymphoma?

OO The future development of novel therapies for T-cell lymphomas is going to revolve around the development of innovative platforms that are not CHOP-centric. CHOP chemotherapy has found its way to the upfront management of patients with T-cell lymphoma based on our experience in B-cell lymphomas. The lack of drugs with T-cell specific activity has preempted consideration of the development of other combination therapies. There has been a recent emergence of a variety of new drugs and classes of drugs with demonstrated single-agent activity in T-cell lymphoma, including pralatrexate, histone deacetylase inhibitors, proteasome inhibitors, and purine nucleoside phosphorylase inhibitors. There is real excitement regarding the combination of these drugs to develop new platforms for these patients. A number of these drugs have been studied as single agents in T-cell lymphoma patients, and there are now several preclinical studies that have validated their synergistic activity in combination. There are a number of phase I and phase II clinical trials that will be examining various combinations of these new drugs, including combinations of pralatrexate and bortezomib (Velcade, Millennium), pralatrexate and depsipeptide, and combinations of depsipeptide and bortezomib. In each of these cases, all of the agents being studied in the doublet have demonstrable activity as single agents. The evolution of these trials is likely to gradually involve systematic study of these combinations to achieve 2-, 3-, or 4-drug regimens active in the disease.

Once we have developed novel, T-cell centric combinations of chemotherapy active in the disease, the next logical step would be to look at the integration of various immunotherapies, be it monoclonal antibodies targeting CD4, CD52 (alemtuzumab), or CCR4 antibodies as discussed above. Many clinical studies in T-cell lymphoma are going to be oriented toward identifying, defining, and categorizing a regimen like rituximab (Rituxan, Genentech) plus CHOP for B-cell lymphoma, using agents with their own independent activity in the disease. Interestingly, I see that the T-cell lymphomas today are where the treatment of multiple myeloma and mantle cell lymphoma were 5–10 years ago. The paradigm is the same: new targets, new drugs, change the natural history.

Suggested Readings

Corradini P, Dodero A, Farina L, et al. Allogeneic stem cell transplantation following reduced-intensity conditioning can induce durable clinical and molecular remissions in relapsed lymphomas: pre-transplant disease status and histotype heavily influence outcome. *Leukemia*. 2007;21:2316-2323.

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