ADVANCES IN LLM

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

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Advances in the Classification and Management of Patients With T-Cell Lymphoma

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H&O What are the most common types of T-cell lymphoma?

LP T-cell lymphoma is a heterogeneous group of disorders that encompass many subtypes. T-cell lymphomas that present in the skin tend to be indolent, although there are some aggressive subtypes. T-cell lymphomas with blood involvement, nodal involvement, or extranodal involvement, such as the nasal subtype of extranodal natural killer/T-cell lymphoma, tend to be much more aggressive. The most common types of skin T-cell lymphoma include mycosis fungoides and CD30-positive lymphoproliferative disorders. Nodal T-cell lymphomas include peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), the subtype now known as T-follicular helper lymphoma, and anaplastic large-cell lymphoma, both with and without overexpression of anaplastic lymphoma kinase.

H&O Are there any recent changes to the diagnosis and classification of T-cell lymphomas?

LP An overview of the fifth edition of the *World Health Organization Classification of Haematolymphoid Tumours* focusing on lymphoid neoplasms was published in June 2022. The biggest change is the creation of a group of lymphomas known as peripheral T-cell lymphomas with T-follicular helper phenotype. This umbrella category includes angioimmunoblastic lymphoma, as well as lymphomas that would have previously been grouped under the term "PTCL-NOS." This classification not only helps to reduce the number of lymphomas that are diagnosed as not otherwise specified, but also enables physicians to select treatments more intelligently. Some treatments seem to work much better for T-follicular helper phenotype lymphomas than for other subtypes of T-cell lymphoma.

H&O How are T-cell lymphomas diagnosed?

LP Most T-cell lymphomas are diagnosed by tissue biopsy, be it from the skin, a node, or an extranodal site. Occasionally, T-cell lymphomas may be diagnosed in the blood. Most important in the diagnosis is immunohistochemistry to confirm the T-cell origin, as well as review by an expert hematopathologist.

H&O Is there a standard approach to the treatment of T-cell lymphoma?

LP There is no standard approach, which is a problem. There are many different treatments for cutaneous or indolent T-cell lymphomas. It can be difficult for less-experienced physicians to select the best option. My choice of treatment is based on the areas of the body I am trying to target. Some treatments are better at targeting certain areas.

Selection of treatment for the more aggressive T-cell lymphomas was aided by results from the phase 3

ECHELON-2 trial, which compared cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) vs cyclophosphamide, doxorubicin, and prednisone (without vincristine) plus brentuximab vedotin (Adcetris, Seagen) among patients with treatment-naive systemic anaplastic large-cell lymphoma or another CD30-positive peripheral T-cell lymphoma. The addition of brentuximab vedotin was very advantageous for patients with anaplastic large-cell lymphoma and should probably become the new standard of care in this setting. It is less clear whether this regimen should be the standard of care for other types of CD30-positive peripheral T-cell lymphomas, but it certainly could be an option. It is still necessary to improve on the first-line treatments for patients with more aggressive peripheral T-cell lymphomas.

H&O Do T-cell lymphomas pose any treatment challenges?

LP The biggest challenge is that chemotherapy is less effective in T-cell lymphomas compared with B-cell lymphomas. The rate of overall survival among patients with aggressive peripheral T-cell lymphoma is far lower than 50%, which would be the worst outcome among patients with diffuse large B-cell lymphoma. Chemotherapeutic approaches that work for aggressive B-cell lymphomas are less effective in patients with T-cell lymphoma. The current focus of research in T-cell lymphoma is to ascertain which treatments work better for these patients. New treatments might include agents that are not considered standard chemotherapy.

The other big obstacle is that many patients with aggressive peripheral T-cell lymphoma present at a very advanced stage and are very ill. Treatment can be complicated for patients with more advanced disease, who may be debilitated.

H&O What are the unmet needs in T-cell lymphoma?

LP There are many unmet needs in T-cell lymphoma. One unmet need concerns diagnosis. There is no good way to demonstrate clonality with T-cell lymphomas, although there is in B-cell lymphomas. In some cases, the diagnosis itself presents challenges. It would be helpful to have more diagnostic tools, which I expect will be available in the future.

Another unmet need is to have better therapies upfront. There are many choices of single-agent therapies for relapsed/refractory patients. These therapies could also be improved. However, better frontline therapy might decrease the use of treatments for relapsed/refractory disease, which are currently needed by most patients.

H&O Are there any newer treatments undergoing evaluation in T-cell lymphoma?

LP The treatment evaluated in ECHELON-2—cyclophosphamide, doxorubicin, and prednisone plus brentuximab vedotin—is a newer induction regimen that is particularly effective in anaplastic large-cell lymphoma. Newer treatments for T-cell lymphoma revolve around the exploration of pathway inhibitors, such as phosphoinositide 3-kinase inhibitors and inhibitors of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. These treatments are currently in clinical trials. They have shown efficacy in other disease states, and investigators are trying to repurpose them to treat aggressive T-cell lymphomas.

An experienced hematopathologist can help with both the diagnosis and the subtyping, which will guide selection of therapy.

H&O Are there any promising areas of research in T-cell lymphoma?

LP Everything is promising in T-cell lymphoma. T-cell lymphomas are not very common, and they may be found in disparate areas globally. For a long time, research in T-cell lymphoma has greatly lagged behind other types of lymphomas, specifically B-cell lymphoma. The advent of more global cooperation has been helpful. Exploration of nonchemotherapeutic agents is promising. The field is much more hopeful now than 10 years ago.

H&O Do you have any other recommendations regarding the management of T-cell lymphomas?

LP My biggest recommendation for physicians with less experience in diagnosing or treating T-cell lymphoma is to first consult a hematopathologist with expertise in this area to confirm or solidify the diagnosis. An experienced hematopathologist can help with both the diagnosis and the subtyping, which will guide selection of therapy. Because these patients are so rare in a general oncology practice, it might be appropriate to obtain a second

opinion from a physician who specializes in this area. A specialist could also help devise a treatment pathway for a given patient to optimize outcome. Whether they practice in a community or academic setting, physicians who lack expertise in this area may find it difficult to identify the best treatment for a patient with T-cell lymphoma. Even for those of us who have focused on this area for a long time, these patients remain a challenge in terms of both diagnosis and treatment.

Disclosure

Dr Pinter-Brown has no real or apparent conflicts of interest to report.

Suggested Readings

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