

ADVANCES IN LLM

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

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T-cell Lymphomas

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H&O How are T-cell lymphomas different from other lymphomas?

SH T-cell lymphomas are incredibly heterogeneous; some are indolent or slow growing, and others are aggressive. T-cell lymphomas present in lymph nodes, but they also frequently involve extranodal sites. Most lymphomas are sporadic, and we do not know of the causes.

It is estimated that T-cell lymphomas make up approximately 10% of all lymphomas in the United States. The majority are aggressive and fall into the categories of peripheral T-cell lymphomas not otherwise specified, angioimmunoblastic T-cell lymphoma, or anaplastic large-cell lymphoma, which, combined, make up approximately 60–75% of all T-cell lymphomas. Mycosis fungoides, a low-grade skin T-cell lymphoma, has an estimated incidence of 2,000 cases a year, but a recent paper claimed that the incidence may be higher—3,000 cases per year—partly due to better diagnosis.¹

H&O What are the known causes for T-cell lymphomas?

Viral

There is a subset of T-cell lymphomas that are caused by viruses: the human retrovirus HTLV1 or HTLV2, which are in the same family as the human immunodeficiency virus. In certain places in the world—a few areas in Japan, the Caribbean, Africa, etc.—these virus are endemic in the population, and people carry the virus in their body. Approximately 1–4% of people who carry the virus may develop a lymphoma at some

time in their life, with the lymphoma being caused by the virus entering the T-cell and transforming it into a malignant T-cell.

The Epstein-Barr virus (EBV) can also cause certain forms of lymphomas—both B- and T-cell. Some kinds of NK/T-cell lymphomas commonly occur in the nasopharynx (predominantly in Asia). Some kinds involve the gastrointestinal tract and are more common in Central America; these lymphomas are always EBV-positive NK/T-cell lymphoma nasal type from a direct viral cause. Angioimmunoblastic T-cell lymphoma also has an EBV component; EBV may not be a cause, but rather a product of the local immunosuppression.

Inflammation

In general, people who have celiac disease or enteropathy are more at risk of developing lymphomas. They are prone to developing a particular type of lymphoma called enteropathy-associated T-cell lymphoma, which is usually an aggressive type of T-cell lymphoma that starts in the gastrointestinal tract. Again, we do not know the direct cause, but it seems to be part of an inflammatory process. There are some data that say if the celiac disease is well controlled, then there is less risk of getting lymphoma.

Immunosuppression

In patients—primarily children—with inflammatory bowel disease, Crohn's disease, or ulcerative colitis, there has been a small cluster of cases called hepatosplenic T-cell lymphoma. This rare type of lymphoma comes from a T-cell that is believed to be gut-derived and immature. It seems to happen particularly in people who

have inflammatory bowel disease, and may be more so in people who have received anti-TNF drugs. It is thought to be related to chronic inflammation, immunosuppression, or a combination of both.

H&O There seems to be a range in prevalence rates among different countries. Do we know why?

SH United States and Europe seem to have similar prevalence rates: peripheral T-cell lymphoma unspecified of the aggressive types of T-cell lymphomas would be approximately 1/3 of the cases. In Europe, for reasons unknown, there seems to be more angioimmunoblastic T-cell lymphomas and less anaplastic large-cell lymphomas.

In Asia, we have a much greater incidence rate of NK/T-cell lymphomas or the HTLV1-associated lymphomas because of the high prevalence rate in Japan. NK/T-cell lymphomas in the United States comprise a very small percentage of all lymphomas, whereas in Asia, it may be 20–25% and even higher in some parts of Japan. HTLV1-associated lymphomas in the United States are about 1–2% or less of the T-cell lymphomas, whereas in Japan, it may be 20–25% and even higher in certain parts of Japan.

As far as we know, there is no known genetic component related to these prevalence rate differences. There are associations with a concurrent strongyloides infection—a parasitic infection—and people who have this infection and carry the HTLV-1/2 virus may have a higher rate of developing HTLV-associated lymphomas. However, a direct causative effect is unclear.

I have personally had very few patients with multiple members of their family develop lymphomas with HTLV1; these cases are rare. Most of my HTLV1 patients are the only members in their family who develop lymphoma, although many of their family members probably have the virus, seeing that transmission is usually mother to child.

H&O What treatments are available for T-cell lymphomas today?

Indolent T-cell Lymphomas

Indolent T-cell lymphomas are primarily cutaneous: mycosis fungoides or the cutaneous CD30+ lymphomas. For these lymphomas, we will often use minimal therapy, which includes skin-directed therapy (ie, topical therapy, ultraviolet light, radiation). Many of these patients do not require systemic therapy. However, for those that do require systemic therapy, we often prefer biologic therapies such as retinoids, histone deacetylase (HDAC) inhibitors, or interferons, more so than traditional chemotherapy. Chemotherapy is often reserved for patients with lymphomas in advanced stages. Allo-

genic stem cell transplantation (ASCT) is used on a case-by-case basis in patients with severe disease and has some success, but long term data with this approach are still largely anecdotal.

Aggressive T-cell Lymphomas

Aggressive T-cell lymphomas altogether tend to have a poor prognosis. Median survival is usually a few years, and the cure rates with standard combination chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) are low, most likely in the 15–25% range.

Patients with aggressive T-cell lymphoma who have a low international prognostic index and are at an early stage of the disease may receive standard chemotherapy and radiation and achieve better results; however, this is a limited subset of patients. The majority of aggressive T-cell lymphoma patients have poor risk factors such as advanced stage disease and multiple extranodal sites, and the best treatment remains unclear for these patients. It is known that when given CHOP, the majority of these patients are not going to be cured. Remission rates for CHOP are approximately 60–75%, but relapse rates are high, and survival is often short. One exception is among patients with a particular subtype of anaplastic large cell lymphoma. There are 2 types of aggressive anaplastic large-cell lymphomas: anaplastic lymphoma kinase (ALK)-positive and ALK-negative. The subset of patients who have ALK-positive disease expresses the ALK protein and has a higher cure rate with therapies such as CHOP—perhaps as high as 70–90%, depending on risk factors.

As a result of generally poor outcomes, there has been much that has been looked at in terms of improving upfront treatment. Although there is no randomized data, the most data available are with upfront ASCT, that is, first remission consolidated with high dose therapy. This strategy seems helpful in retrospective series, but its true efficacy is still unclear.

A recent paper by Dr. Peter Reimer, of Universitätsklinikum Würzburg, the first prospective multicenter study on upfront ASCT in peripheral T-cell lymphomas, reported the good feasibility and efficacy of this approach. The treatment regimen consisted of 4–6 cycles of CHOP followed by mobilizing therapy with either 1) dexamethasone, carmustine, melphalan, etoposide, and cytarabine protocol, or 2) etoposide, methylprednisolone, cytarabine, and cisplatin protocol, and stem cell collection. Patients in complete remission or partial remission underwent myeloablative chemoradiotherapy and ASCT. The main subgroups in the 83 patients enrolled were those with peripheral T-cell lymphoma not specified (n=32) and angioimmunoblastic T-cell

lymphoma (n=27); a total of 55 (66%) patients received transplantation. Results showed that the estimated 3-year overall survival rate, 3-year disease-free survival rate for patients in complete remission, and 3-year progression-free survival rate were 48%, 53%, and 36%, respectively, suggesting a substantial impact on outcome for upfront ASCT in peripheral T-cell lymphoma.² However, there is still no randomized data on this subject.

It is believed that ASCT offers very little benefit to those with HTLV1-associated adult T-cell lymphoma. Also, there are reports of success but too few cases to determine whether ASCT is beneficial as a general approach for other rare subtypes of lymphoma such as the enteropathic subtypes or the NK/T-cell lymphomas.

People have looked at other chemotherapy regimens—intensified CHOP, gemcitabine-based regimens, combination with drugs such as alemtuzumab (Campath, Genzyme)—to improve the upfront regimens, but none have yet shown significantly better results. Therefore, they are not the preferred upfront strategy at this time outside of a clinical trial.

H&O Are there any particular drugs that you are interested in?

SH The available drugs that currently seem to have some activity in the relapse setting are few—gemcitabine, bortezomib (Velcade, Millenium Pharmaceuticals)—so there is much investigation being done in this setting. My colleagues and I worked on a drug called pralatrexate, which was initially developed at our institution for lung cancer. When the drug moved on to be studied in lymphomas, we found that there was particular activity in T-cell lymphomas. We recently completed a multicenter phase II registrational study that was presented by Dr. Owen O'Connor, at the annual meeting of the American Society of Hematology (ASH) 2008³; we looked at over 100 patients with relapsed or refractory T-cell lymphoma—a heavily pretreated group—and there was a 27% response rate with some durable responses. It is difficult to know how good these results are because there are no approved drugs for aggressive T-cell lymphomas to serve as comparators; however, if one observes the population treated, it seems to be a substantially active drug. I believe that pralatrexate is one of the more exciting drugs investigated in this field and that it will probably go to the U.S. Food and Drug Administration (FDA) later this

year. If it is approved, it would be the first approved drug for aggressive T-cell lymphoma.

We are currently working on combination studies with pralatrexate, such as combining it with gemcitabine, etc. The goals of these studies are to identify the drugs that have activity in the relapse setting and then to figure out a better combination regimen to move upfront. If there is a disease that is not cured by CHOP, it is unlikely that it will be cured by a single drug.

We are also working on another drug called romidepsin, which is one of many HDAC inhibitors being studied for these patients. There was a study done in both aggressive and cutaneous T-cell lymphoma by the National Cancer Institute that showed a response rate in the 30–35% range.^{4,5} I am the co-primary investigator of a multicenter registrational study that is currently looking at romidepsin, specifically in the relapsed/refractory aggressive T-cell lymphomas.

We are also studying the above 2 drugs and clofarabine (Clolar, Genzyme), which received FDA approval for pediatric leukemia. Currently, we have just finished a phase I study and have begun a phase II study.

Bortezomib, lenalidomide (Revlimid, Celgene), and SGN-35 (a CD30-targeted antibody primarily for anaplastic large cell lymphoma) are other drugs of interest. The SYK and mTOR pathways are also good targets for T-cell lymphomas, and much of these drugs were presented at last year's ASH meeting.^{3,4,5}

I believe that ultimately providing better treatment at diagnosis is where we will truly be able to impact survival; but to get there, we need to identify the best drugs and then figure out the best combinations to move upfront, which will take a series of clinical trials.

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