Nasal NK/T-cell Lymphoma: Where Are We Now?

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Since the creation of the World Health Organization’s nasal natural killer (NK)/T-cell lymphoma category, the attempt to further classify, describe, and improve treatment in this entity has been underway. There has been quite a bit of confusion and frustration regarding diagnosis, staging, and treatment approaches. With his article in this issue of ONCOLOGY, Dr. Au has attempted to improve our knowledge of current approaches to NK/T-cell lymphomas, providing a thorough and contemporary review of the clinical management of these difficult tumors. The following commentary reflects a deep appreciation for the author’s work and expands upon a few points not previously highlighted.

Epidemiology

One of the first challenges to improving overall outcomes in this disease is the rarity and distinct geographic distribution. As described in the paper and documented previously, this disease’s incidence varies profoundly based on geographic location, with a known increased incidence in Asia. By comparison, in the United States, the Surveillance Epidemiology and End Results (SEER) registry database has been explored to determine variations on subtypes of T-cell lymphomas by year, race, sex, and geographic distribution. The incidence rate for extranodal NK/T-cell lymphoma, nasal type, increased from 1992 through 2005, with an annual percentage change of 11.4%. The incidence rate ratios were also found to be higher in men and dominant in people of Asian and Pacific Island descent.[1] The “nature vs nurture” curiosities in this disease state remain open for ongoing investigation. Questions regarding the role of Epstein-Barr virus in lymphomagenesis, possible environmental exposures, or genetic variations in T-cell markers may explain the regional and racial predilection for this disease.

Pathology

The pathology of this disease is distinct from other T-cell lymphomas. Dr. Au describes the challenges of diagnosis with regard to biopsy condition and size. The tumor is characteristically seen with marked necrosis and angioinvasion, which makes this tumor clinically and pathologically unique. Genetic expression of the characteristics that make this lymphoma so distinct is the subject of ongoing investigation, not reviewed in this paper.

In one recent study, investigators described gene-expression profiling in extranodal NK/T-cell lymphoma, nasal type, and compared it to peripheral T-cell lymphoma, not otherwise specified (NOS), and normal NK cells in order to identify unique genomic signaling.[2] Their findings demonstrated overexpression of granzyme H in comparison to peripheral T-cell lymphoma, NOS, and may be an important marker that could be used to distinguish these entities diagnostically. This same work noted increased platelet-derived growth factor receptor expression, compared to normal NK/T cells. This entity is known to be associated with the JAK-STAT and AKT pathways, which may lead to new approaches to therapeutic options in this disease.

Treatment
As Dr. Au notes, the outcomes for patients with NK/T-cell lymphoma are inferior to many other types of non-Hodgkin lymphoma. The combination of radiation and chemotherapy and newer combination chemotherapy regimens are actively being studied. The author reviews the complexity of treatment for localized and disseminated disease, and newer regimens including VIPD (etoposide, ifosfamide, cisplatin, dexamethasone) and SMILE (etoposide, ifosfamide, methotrexate, dexamethasone, asparaginase), which are being studied as alternatives to anthracycline-based regimens. The results of these experimental regimens appear to be promising. Additional prospective studies are currently underway, looking at these and other combination regimens in additional T-cell lymphoma subtypes. The review also mentions preclinical studies looking at newer classes of drugs, including histone deacetylase inhibitors, proteasome inhibitors, and biologics for NK/T-cell lymphoma. Other drugs designed to inhibit dihydrofolate reductase, spleen tyrosine kinase (Syk), and mammalian target of rapamycin (mTOR) are also currently being explored in T-cell lymphomas. Novel pathways and combinations with biologics will hopefully improve failure-free and overall survival for these patients.

**Future Directions**

At the recent 2010 T-cell Forum meeting, members of the Asian and Western T-cell lymphoma physician groups were able to discuss variations in their approach to specific T-cell lymphoma subtypes. Most T-cell lymphoma trials include a mixture of subtypes in order to meet accrual. Recent strides in the diagnosis, staging, and treatment of NK/T-cell lymphoma, as a prime example, demonstrate the importance of collaboration in clinical research and trials. This work also exemplifies novel approaches to future study design in T-cell lymphomas. As we understand each subtype of T-cell lymphoma more extensively, distinct clinical treatments may be derived. This notion will dictate the need for subtype-specific clinical trials in the future. International T-cell subtype trials will be a great step toward improving the quality of life and survival of these patients.

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**Financial Disclosure:** Dr. Lechowicz is a consultant for Allos Therapeutics

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