Natural Killer/T-Cell Lymphomas in Pediatric and Adolescent Patients

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Abstract: Natural killer/T-cell (NK/T-cell) lymphomas are rare in children and adolescents and consist predominantly of nasal-type extranodal NK/T-cell lymphomas. More than half of pediatric/adolescent patients with NK/T-cell lymphomas present with localized nasal/sinus involvement, but the disease may involve many organs. NK/T-cell lymphoma cells are cytotoxic and associated with necrosis and angioinvasion; they express CD56, CD2, cytoplasmic CD3 epsilon, and to a variable degree CD30. The cells contain Epstein-Barr virus (EBV)–encoded RNA. Loss of chromosome 6q is frequent, and multiple other genetic changes may occur. The Janus kinase/signal transducers and activators of transcription (JAK/STAT) and other pathways are activated in NK/T-cell lymphoma. Adults with stage I/II disease receive radiation with or without chemotherapy, whereas adults with advanced disease receive multiagent chemotherapy, including asparaginase and drugs not affected by P-glycoprotein–mediated resistance. Outcomes data for pediatric patients come from retrospective reviews and retrospective case series. The overall survival of pediatric patients is 77% for those with stage I/II disease and 36% to 59% for those with advanced disease. Bone marrow transplant (BMT) is used in children, but with little evidence regarding the indications and rationale for type of transplant. BMT achieves better outcomes for adult patients in remission, but with high levels of morbidity and mortality. Improved understanding of the biology of this disease will allow the development of targeted approaches, including JAK/STAT inhibitors, checkpoint inhibitors, anti-CD30 agents, epigenetic modifiers, and reduced-intensity conditioning for BMT, to improve outcomes in pediatric patients.

Introduction

Mature B-cell lymphomas (Burkitt lymphoma and diffuse large B-cell lymphoma), lymphoblastic lymphomas, and anaplastic large cell lymphomas are the most common non-Hodgkin lymphomas (NHLs) in the pediatric and adolescent population, accounting for 90% of cases.[1] The remaining 10% of pediatric and adolescent cases of NHL are types that either are seen more commonly in adults or are

rare at any age. Rare pediatric NHLs can be divided into (1) B-cell disease, which includes follicular lymphoma, marginal zone lymphoma, mucosa-associated lymphoma, and lymphoproliferative diseases, and (2) T-cell disease, which encompasses peripheral T-cell lymphomas (not otherwise specified), cutaneous T-cell lymphomas, hepatosplenic T-cell lymphoma, subcutaneous panniculitic T-cell lymphoma, and extranodal natural killer/T-cell (NK/T-cell) lymphomas.[2,3] This review focuses on the epidemiology, pathology, biology, clinical presentation, and therapy of rare NK/T-cell lymphomas in pediatric and adolescent patients. The challenges that oncologists who treat young patients must address are the following: (1) recognizing these rare cancers; (2) selecting the most effective frontline therapy; (3) determining biological targets of therapeutic potential; and (4) evaluating the role of autologous or allogeneic bone marrow transplant (BMT) in treatment.

Epidemiology

Adult Patients

NK/T-cell lymphomas are more common in adults than in children (the median age of patients at onset is 45 years) and occur most frequently in Central and South America and the Far East.[4] The Surveillance, Epidemiology, and End Results (SEER) data demonstrate an increasing frequency of NK/T-cell lymphomas in the United States from 1992 to 2005 (annual percentage change, 11.4%).[5] The SEER data also show that the incidence rate ratio (a ratio of 2 age-adjusted incidence rates) is higher in Asian or Pacific Islanders than in whites (2.7; $P<.01$), indicating that the Asian predominance in the United States is consistent.[5] Adams and colleagues, looking at SEER data from 2000 to 2012 in patients older than 15 years, found that the epidemiology in the United States was similar to the global patterns, and that the incidence of NK/T-cell lymphoma was much higher in Asian or Pacific Islanders than in non-Hispanic whites. These investigators also found that the median age of patients at diagnosis was 54 years. Of the patients with NK/T-cell lymphoma in the SEER analysis, 35% were born outside the United States, suggesting that the increasing incidence within the United States may reflect immigration patterns and the diversity of the US population.[6] Al-Hamadani and colleagues queried the National Cancer Database, which contains data from Commission on Cancer–accredited community cancer registries, and described the characteristics of rare NHL types from 1998 to 2011 in adults (N=596,476). NK/T-cell lymphomas made up 3.6% of the cases. The proportion of NK/T-cell lymphomas was higher in both Native Americans and people of Asian ethnicity than in other groups (1.52% and 1.23% vs 0.18%-

0.28%). The proportion of NK/T-cell lymphomas was also higher in Hispanics than in all non-Hispanics and those of unknown ethnicity (0.98% vs 0.14%-0.17%).[7]

Pediatric and Adolescent Patients

Among children and teenagers, it is difficult to estimate a population-based incidence of NK/T-cell lymphomas owing to the lack of national registry data. The only population-based registry of peripheral T-cell lymphomas, published in the United Kingdom, reported no cases of NK/T-cell lymphoma in 1551 children with newly diagnosed NHL.[8] Several retrospective studies of children and adolescents from pediatric cancer centers show that NK/T-cell lymphomas constitute between 0.2% and 1.6% of newly diagnosed cases of NHL in children and adolescents.[9-11] The European Intergroup for Childhood NHL (EICNHL) and the International Berlin-Frankfurt-Münster group (I-BFM), comprising 16 pediatric cancer centers in Europe, reported a survey study identifying 21 cases of NK/T-cell lymphoma.[12] The Pediatric Oncology Group (POG) reported on 4 patients with NK/T-cell lymphoma in a clinical therapeutic trial designed to study localized lymphomas, and the prospective Rare and Cutaneous Non-Hodgkin Lymphoma Registry of the Children's Oncology Group (COG) described 6 cases of NK/T-cell lymphoma.[13,14] A retrospective clinicopathologic review of 286 patients in a single institution in China in whom NK/T-cell lymphoma was diagnosed over a 30-month period from 2012 to 2014 found 17 patients younger than 17 years old, with a median age at diagnosis of 13 years. The youngest patient was 2 years old.[15]

Of the 3 retrospective studies of patients registered at pediatric oncology centers, the one of children at Polish centers showed a median age at diagnosis of 13 years (range, 3-18 years), with a male-to-female ratio of 1.[9] A review from multiple pediatric study groups in Japan showed a median age at diagnosis of 11 years (range, 1-21 years), with a nearly equal male and female distribution.[11] Kontny and colleagues reported a retrospective analysis of patients from the BFM database and found a median age at diagnosis of 10.1 years, with two-thirds of the patients male.[10] The pediatric patients reported by Mellgren and colleagues on behalf of the EICNHL and the I-BFM had a median age at diagnosis of 12.8 years (range, 4.5-17 years), with a slight male predominance (male-to-female ratio of 4:3). One-third of the patients were from Japan or Hong Kong; the remainder were from Europe.[12]

Pathology

In the World Health Organization classification of mature T-cell and NK-cell neoplasms, *extranodal NK/T-cell lymphomas, nasal type* are a distinct entity.[16] Histologic

evaluation of NK/T-cell lymphoma typically shows a lymphoid infiltrate consisting of cells of variable size with prominent necrosis, angioinvasion, and angiocentricity. These pathologic changes occur against a background of mixed inflammatory cells (Figure 1). The tumor cells are positive for CD2 and CD56, with the surface negative for CD3. The cytoplasm is positive for CD3 epsilon.[15,17-19] NK/T-cell lymphoma is an Epstein-Barr virus (EBV)–associated lymphoma, with EBV-encoded RNA (EBER) demonstrated by in situ hybridization in nearly 100% of cases.[16] EBV may contribute to the cytotoxic effects of the tumor by producing interleukin 9 (IL-9) and IL-10.[18,20] The cell of origin for the lymphoma, however, may be an NK cell or a T cell; there is considerable overlap immunophenotypically.[15,20] The malignant cells produce cytotoxic proteins, including granzymes B and H, T-cell restricted intracellular antigen 1 (TIA1), and perforin.[18,19,21,22] Analysis of lineage by T-cell receptor is difficult owing to the necrosis and apoptosis within the tumor cells, and tumor cell lineage, when it has been studied, does not alter outcome.[17,23] Other immunophenotypic markers that may be expressed are CD43, CD45RO, HLA-DR, CD25, Fas, Fas ligand, and occasionally CD7 and CD30. Hong and colleagues found that 47% of 108 cases expressed CD30.[23] Au and colleagues also reported CD30 expression in 39% of nasal-type cases and 63% of non-nasal cases.[21]

Descriptions in the literature of a *non-nasal* type of extranodal NK/T-cell lymphoma refer to the anatomic location of the primary disease. It is recognized that because of advances in imaging and the routine use of nasal biopsies in patients without clinical evidence of disease in the nasal cavity, this distinction from the nasal type may not be valid. There is no evidence of differences in histology, cell marker expression, genetics, and biological characteristics between the 2 types.[17,21] However, patients with skin or gastrointestinal primary disease must be evaluated very carefully owing to overlap with more benign NK cell disorders.[22]

Genetic Changes and Cancer Pathways in NK/T-Cell Lymphomas

NK/T-cell lymphomas demonstrate frequent changes in chromosome 6, specifically a deletion at 6q21-25 or isochromosome 6p, as well as a gain at 2q and loss of 1p36.23-p36.33.[19,24,25] Studies of aberrations in gene copy number show many candidate genes in regions of interest that may be of importance in the biology of NK/T-cell lymphomas. Several exist in the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway. JAK3 is noted to be constitutively activated in 87% of NK/T-cell lymphomas.[26] Koo and colleagues identified 4 patients with *JAK3* mutations, and Bouchekioua and colleagues identified JAK3 overexpression in 21% of their study patients with NK/T-cell lymphoma.[27,28] *JAK3* activation mutations were also identified by next-generation sequencing.[29] Several groups found STAT3 to be constitutively activated.[19,29] STAT3 is important in the regulation of many genes involved in proliferation and immune function, and it can be extrinsically activated by EBV.[29]

Mutations have been identified within the *STAT3* gene itself in NK/T-cell lymphoma and also in the *PTPRK* gene, which encodes a specific phosphatase (receptor-type tyrosine-protein phosphatase kappa). The *PTPRK* gene is located in the 6q region, and loss of function of its phosphatase can lead to STAT3 activation.[26]

Sequence analysis of 602 cancer genes in 25 frozen NK/T-cell lymphomas showed mutations of *BCOR* (co-repressor of BCL6) in 32%. The *BCOR* mutations are interesting because they are frequently found in myeloid cancers.[29,30] NK/T-cell malignancies are the only lymphoid cancers in which *BCOR* is mutated.[30] BCOR interacts with histone deacetylases and may implicate epigenetic phenomena in the development of NK/T-cell lymphomas.[29]

PD-L1 (programmed death ligand 1) is expressed by approximately 80% of tumor cells and tumor-infiltrating immune cells in NK/T-cell lymphomas. The role of the PD-L1/programmed death 1 (PD-1) pathway in NK/T-cell malignancy is not clear at this time.[31]

Many other candidate genes suggested by copy number differences may be implicated in the pathogenesis of NK/T-cell lymphoma, including genes involved in angiogenesis and cell cycle progression, tumor suppressor genes, and others that are currently under investigation.[19]

Clinical Presentation

Children and teenagers, like adult patients, present with NK/T-cell lymphoma in either of 2 ways. First, a nasal or paranasal mass may cause obstructive symptoms, so that the patient seeks medical attention (Figure 2). Second, a patient may present with aggressive systemic disease—often with B symptoms of night sweats, fevers, and weight loss—and involvement of non-nasal sites, including the skin, central nervous system, testes, kidneys, ovaries, adrenal gland, lungs, and others.[9,11,12,14] Evaluation of a child or adolescent with NK/T-cell lymphoma includes staging, which historically has been done with the Ann Arbor staging system.[32] Positron emission tomography is useful in initial staging.[33] There are no data regarding the use of positron emission tomography in assessing response to therapy. In the 3 large retrospective analyses of pediatric patients with NK/T-cell lymphoma, stage I/II disease was present in half of the patients in the study from Japan,
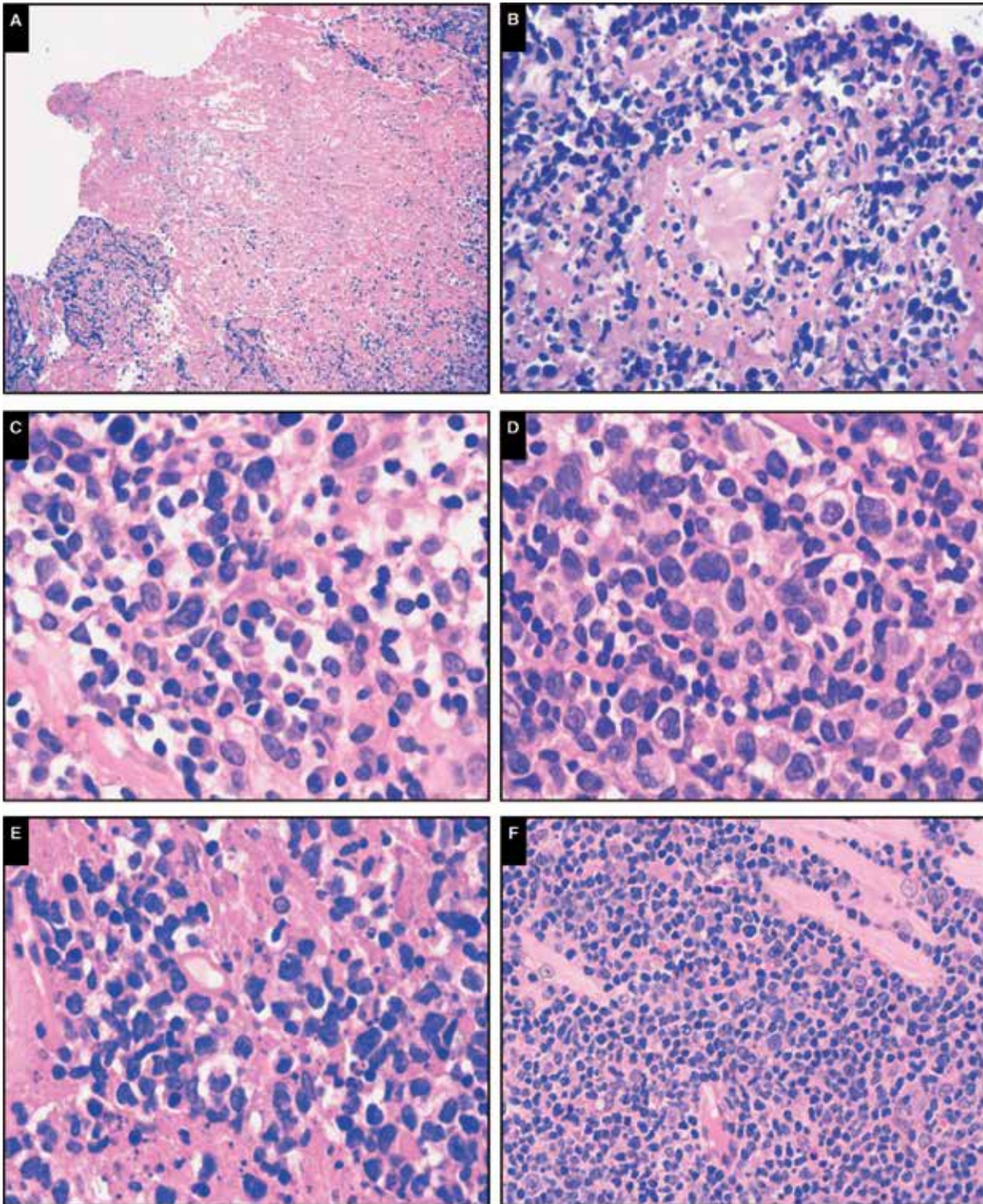
Figure 1. Morphology of nasal-type extranodal natural killer/T-cell lymphoma in children and adolescents. **A,** Extensive mucosal ulceration and coagulative necrosis (hematoxylin and eosin [H&E], ×100). **B,** The growth pattern is angiocentric and angiodestructive (H&E, ×400). **C,** The tumor is accompanied by a heavy admixture of inflammatory cells: small lymphocytes, plasma cells, and histiocytes (H&E, ×400). **D,** Pleomorphic large tumor cells with irregularly folded nuclei (H&E, ×400). **E,** Medium-size tumor cells with pale cytoplasm admixed with inflammatory cells (H&E, ×400). **F,** This orbital tumor is composed predominantly of small cells infiltrating the skeletal muscle tissue (H&E, ×400). Republished with permission from Huang et al. *Am J Clin Pathol.* 2016;145(1):46-54.[15]
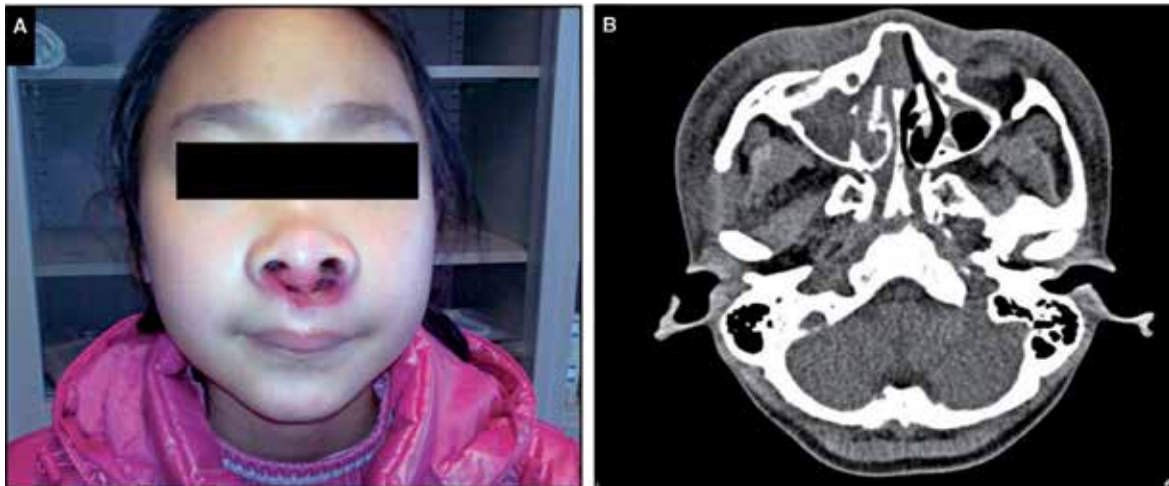
Figure 2. Clinical and imaging features of nasal-type extranodal natural killer/T-cell lymphoma in children and adolescents. **A,** The tumor extends outside the nasal cavity, resulting in reddening and swelling of the skin. **B,** Computed tomogram. The tumor affects the right nasal and paranasal sinuses. Republished with permission from Huang et al. *Am J Clin Pathol.* 2016;145(1):46-54.[15]

62% of those in the study from EICNHL/I-BFM, and 67% of those in the BFM study.[10-12] The primary site was nasal in 71% of the EICNHL/I-BFM cases, 100% of the BFM cases, and 40% of the cases from Japan. In the single-institution series of Huang and colleagues, there was a 3.25:1 male predominance, 70.6% of patients had stage I/II disease, and 59% of patients had nasal/sinus involvement. One 2-year-old patient had widespread disease that involved the liver, spleen, and lungs.[15] In a dual-institution study of patients consecutively treated in China, 89% of patients had stage I/II disease, 65% were male, and 89.2% had nasal/nasopharyngeal primary disease.[4] Of the 4 cases of stage I or II NK/T-cell lymphoma treated with a POG protocol for localized NHL—based on cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)—3 patients had nasal primary disease and 1 patient had stage II skin disease.[13] In the cases registered in the COG study, all 6 patients were male and 2 patients had localized disease.[14]

Prognostic Factors

In the SEER data, race or ethnicity had no prognostic correlation with survival.[6] In one study of adult patients undergoing the same treatment, no difference in outcome was found between Asian and non-Asian patients in whom the disease was diagnosed.[34] Across many treatment studies in adults, a greater disease burden—evidenced by a more advanced stage, non-nasal presentation, high lactate dehydrogenase (LDH) levels, poor performance status, and a high proliferative index in the tumor cells—imparts a poor prognosis.[34,35] Qi and colleagues found stage to be

an important prognostic factor in patients treated with chemotherapy (CHOP or the combination of a corticosteroid, methotrexate, ifosfamide, asparaginase, and etoposide [modified SMILE]), radiation, and transplant in some cases. In 37 patients, the 2-year overall survival (OS) rate was 87% (95% CI, 64%-95%) for patients with early-stage disease vs 21% (95% CI, 5%-43%) for those with advanced disease. The progression-free survival (PFS) rates at 2 years were 56% (95% CI, 33%-73%) and 18% (95% CI, 4%-38%), respectively. Patients with early-stage disease who received the modified SMILE regimen demonstrated improvements in OS and PFS of borderline significance, whereas no difference was found between patients with advanced disease who received CHOP-based therapy and those who received modified SMILE.[34]

Measurement of the viral load by EBV copy number in both whole blood and plasma during a phase 2 study in which standardized chemotherapy (SMILE) was used demonstrated that a copy number greater than 10^5/mL in whole blood and a copy number greater than 10^4/mL in plasma were associated with a poorer outcome than lower copy numbers. Interestingly, a high EBV copy number before treatment was associated with increased toxicity during chemotherapy. In univariate analysis, a high baseline EBV copy number along with high LDH levels, the presence of B symptoms, and EBER positivity predicted a poor OS. In multivariate analysis, only high LDH levels and a high whole-blood EBV copy number predicted a poor outcome (plasma copy number was not predictive).[36] Similar studies have not been conducted in pediatric populations.

Therapy

Frontline Therapy in Adults

The historical treatment for stage I or II nasal-type extranodal NK/T-cell lymphoma is radiation therapy. With doses greater than 50 Gy, this is associated with a complete remission (CR) rate ranging from 52% to 100%, but patients who have localized disease treated with radiation alone have a high recurrence rate (25%-40%).[17] Frontline therapy in adults with early-stage disease moved toward combinations with radiation, although a recent meta-analysis did not support the use of chemotherapy in early-stage disease.[37] Chemotherapy based on what worked for most adult cases of NHL—CHOP or CHOP-like regimens—did not result in satisfactory outcomes.[38] Wang and colleagues described a large retrospective study in which gemcitabine, L-asparaginase, and oxaliplatin were compared with CHOP or etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) followed by involved-field radiation therapy (56 Gy); the 3-year OS and PFS rates were 87% and 72%, respectively, compared with 54% and 50% for EPOCH and 54% and 43%, respectively, for CHOP.[39] Qi and colleagues reported on 37 adult patients treated with a modified SMILE regimen and found a CR rate superior to that of a previously used CHOP-based treatment.[34] NK/T-cell lymphomas express high levels of P-glycoprotein before chemotherapy exposure. This drug resistance mechanism may account for some of the poor results with early attempts at chemotherapy in this disease.[40]

Some regimens use chemotherapy before radiation and some concurrently with radiation. Combination therapy with L-asparaginase, vincristine, and prednisone for 2 cycles, followed by radiation, then 2 to 4 more cycles of chemotherapy ("sandwich" radiation), produced a 2-year OS of 88.5% and a PFS of 80.6%.[41] Concurrent therapy with radiation plus weekly cisplatin for 4 weeks, followed by etoposide, ifosfamide, dexamethasone, and L-asparaginase for 2 cycles, produced an OS of 73% and a PFS of 60% at 5 years.[42] One study added L-asparaginase 3 times a week to cisplatin during radiation therapy and added 3 g of methotrexate per square meter to the 2 cycles of chemotherapy after radiation. The OS rate and PFS rate at 3 years were 81.5% and 74.1%, respectively.[43] The outcome for advanced NK/T-cell lymphoma is poor historically.[44,45] For patients with advanced disease at diagnosis or with recurrent or refractory disease, the SMILE regimen was originally published as a phase 1 study in 2008. Investigators selected the agents based on experience with pediatric EBV-driven hemophagocytic syndrome, in vitro and very early in vivo experience with L-asparaginase, and the drugs not being affected by multidrug resistance genes.[40,46-48] The phase 1 portion of the SMILE regimen, in 6 patients with newly diagnosed stage IV, relapsed, or refractory NK/T-cell lymphoma, produced 3 CRs and 1 partial remission. Toxicity was primarily hematologic, and the protocol was adjusted to include granulocyte colony-stimulating factor (G-CSF).[49] The chemotherapy regimen, which was moved into phase 2 for patients with stage IV, relapsed, or refractory disease based on the promising response rate in phase 1, demonstrated an overall response rate of 79% (90% CI, 65%-89%) and a CR rate of 45% after 2 cycles. In the phase 2 trial, 21 of 28 patients who completed the treatment protocol went on to receive a BMT. There was no statistically significant difference in OS or PFS between those who received transplant and those who did not. The 1-year OS for the 38 patients eligible for the study was 55% (95% CI, 38%-69%). The major toxicities were hematologic toxicity and febrile neutropenia.[50] Other regimens tested replacing L-asparaginase with polyethylene glycol (PEG) asparaginase in sandwich gemcitabine/oxaliplatin and modified SMILE.[51,52] Modified SMILE contains 2 changes: the substitution of PEG asparaginase for L-asparaginase and lower doses of methotrexate, ifosfamide, etoposide, and corticosteroids. Modified SMILE had a 70% overall response rate but a 2-year OS rate of less than 25% in patients with stage IV, relapsed, or refractory disease.[52]

Therapy for Pediatric and Adolescent Patients

In the largest retrospective analysis, conducted by means of a survey of pediatric and adolescent patients registered in EICNHL/I-BFM pediatric oncology centers, the 5-year OS and event-free survival rates of all patients with NK/T-cell lymphoma were 59% (+/–11%) and 34% (+/–11%), respectively. Patients received a variety of regimens, including 3 who received SMILE. There were 8 patients who received radiation and 4 who underwent BMT (1 in CR1, 2 in CR2, and 1 with unknown remission status).[12] The 5-year OS rate was 36% (standard error, 15%) in the BFM patients treated with a variety of regimens and 3 patients undergoing BMT (1 autologous and 2 allogeneic, all in CR2).[10] Treatments in the other reports are variable. Few pediatric patients overall received the SMILE regimen, which is considered the best regimen for adults.

One single-institution retrospective report described patients younger than 21 years of age treated consecutively with standardized treatment. These pediatric and adolescent patients with newly diagnosed disease were treated primarily with radiation therapy or radiation plus chemotherapy (CHOP or CHOP-like) from 1988 to 2008. There were 19 patients with localized disease who received radiation therapy with or without chemotherapy and 14 who received frontline multiagent chemotherapy

followed by radiation. Patients with stage III or IV disease received frontline chemotherapy with radiation to the primary site. The median dose of radiation administered was 50 Gy. The CR rate for frontline radiation (73.7%) was superior to that for chemotherapy (21.4%; *P*=.001). The 5-year OS and PFS rates for all patients were 77.0% and 68.5%, respectively, with a median follow-up of 42 months. Those who achieved a CR had a 5-year OS rate of 84.8%, vs a rate of 30% (*P*=.006) in those who did not achieve a CR. Age, sex, B symptoms, performance status, cervical lymph node involvement, LDH level, and stage were not significant prognostic factors. A Waldeyer's ring primary site was associated with a trend toward improved OS and PFS, but the trend did not reach statistical significance.[4]

Bone Marrow Transplant in Pediatric and Adolescent Patients

No trials in pediatric or adolescent patients incorporate BMT in a uniform fashion. All retrospective pediatric series included patients receiving high-dose therapy followed by autologous or allogeneic BMT, but the selection criteria regarding remission status (first or second) and type of transplant are unclear. No conclusion can be drawn from pediatric reports regarding the appropriate role for BMT, and pediatric oncologists must base their practice on the experience of medical oncology.

Bone Marrow Transplant in Adults With NK/T-Cell Lymphomas

The outcome of NK/T-cell lymphomas in adults, especially those presenting with advanced disease and no clinical nasal involvement and those with relapsed disease, is poor.[44,45] This situation has led investigators to explore the role of consolidation therapy with high-dose chemotherapy followed by either autologous hematopoietic stem cell rescue or allogeneic BMT.

Autologous Hematopoietic Stem Cell Transplant. Au and colleagues published an early retrospective series of autologous hematopoietic stem cell transplant (HSCT) for NK/T-cell lymphoma that included 18 patients who underwent transplant consecutively.[53] Patients with any stage of chemosensitive disease were eligible. Of the patients who received transplant, 8 were in first remission, 5 were in second remission, and 5 had chemosensitive but active disease. The patients who underwent transplant while in remission (first or second) had a superior outcome (disease-free survival rate of 59% [+/–15.4%]) at a median follow-up of 26.2 months. The outcome for patients undergoing autologous BMT was superior to that of patients who fit the eligibility criteria but elected not to have autologous BMT. This prospective series is

limited by several factors: (1) lack of frontline therapy with asparaginase, which is now standard practice and improves outcomes; (2) selection bias among the patients who opted for autologous BMT vs no transplant; and (3) lack of randomization for autologous transplant.[53]

In 2008, Lee and colleagues published a multi-institutional matched controlled study of autologous transplant in NK/T-cell lymphoma. Matching was based on performance status and disease status. The control group was older and had more disseminated disease than the transplant cohort. The 5-year disease-specific survival rates (from date of diagnosis to date of death from disease) were 56.2% for those who received a transplant and 47.6% for those who did not. Disease status was the most important prognostic feature; those who were not in remission had a 7.2-fold (95% CI, 4.4-11.6) increased risk for death. Small numbers of patients, retrospective data analysis, lack of asparaginase in induction therapies, and inconsistent transplant conditioning are limitations of this study.[54] The review by Kwong and colleagues of autologous HSCT for NK/T-cell lymphomas identified 57 patients in the literature, including those in the 2 previously discussed studies. Of the 57 patients, 63% were in stage I/II. Disease status at the time of transplant was the only variable affecting OS with statistical significance.[44] Because the indications for autologous transplant in the patients with early-stage disease were not clear, it is difficult to argue the case for autologous transplant for patients with stage I/II disease in first remission. The results look very similar to those for chemotherapy and radiation therapy.

The outcome of autologous transplant in the face of relapsed, refractory, or primary refractory disease was poor. Kwong and colleagues justified autologous BMT in patients who relapsed and reached remission because of limited alternative options.[44] A large retrospective registry study conducted by the European Society for Blood and Marrow Transplantation (EBMT) examined outcomes for patients who underwent transplant between 2000 and 2010. There were 28 patients who met the criteria for pathologic eligibility or clinical/radiologic findings characteristic of NK/T-cell lymphoma. Half of the patients received cisplatin-based chemotherapy, and 21% received asparaginase in induction. The 2-year PFS and OS rates were 41% (95% CI, 26%-64%) and 52% (95% CI, 36%-75%), respectively. Transplant in first remission showed a trend toward improved PFS, but the trend did not reach statistical significance. The rate of mortality without relapse was 11%. Post-transplant relapses occurred in 36% of patients and were uniformly early, within 1 year after transplant.[55]

Several single-institution studies reported the results of retrospective reviews in patients who underwent both allogeneic and autologous BMT for NK/T-cell disease.

Qi and colleagues reported outcomes for patients treated at Memorial Sloan Kettering Cancer Center from 1996 to 2014. The patients treated early in the series did not receive asparaginase-containing initial therapy, whereas those treated later did. The 2-year OS was 60% (95% CI, 46%-77%) and the PFS was 40% (95% CI, 27%-59%) for all patients. Six out of 14 (43%) of patients who received a transplant were alive and disease-free at last follow-up.[34] A retrospective review of 40 patients who received transplants for various NK-cell malignancies included 22 patients with NK/T-cell lymphoma. The transplant conditioning was uniformly myeloablative, and the patients with NK/T-cell lymphoma who underwent either autologous or allogeneic transplant had a better outcome than did the patients who did not receive a transplant. However, the criteria for those who received a transplant are unclear; the majority of the patients with NK/T-cell lymphoma had nasal-type disease, and 10 had early-stage disease at diagnosis.[56] Limitations of single-institution studies are the following: (1) the prolonged time over which the patients undergo transplant, which means exposure to different frontline therapies and differences in supportive care, tissue-typing resolution, and the availability of unrelated donors; (2) uniformly small numbers; and (3) the inability to conduct comparisons between patients with and without transplants or between those with autologous vs allogeneic transplants.

Allogeneic Bone Marrow Transplant. Allogeneic BMT is used in diseases in which there may be a benefit of a graft-vs-lymphoma effect, and in which the results of autologous transplant indicate a high degree of transplant-related toxicity and a high relapse rate. Many adult patients with NK/T-cell lymphomas have a poor performance status and are elderly, with comorbid conditions that increase the morbidity of myeloablative transplant. The review of Suzuki and colleagues of myeloablative transplant for NK malignancy, which was performed retrospectively, did show less relapse with allogeneic transplant, but with a high rate of transplant-related mortality.[56] With the development of reduced-intensity conditioning for allogeneic BMT, this approach is being re-explored.

Murashige and colleagues conducted a survey of 28 patients in Japan who had undergone allogeneic BMT for NK/T-cell neoplasms from 1990 to 2003. The induction and conditioning therapies were performed per institutional guidelines at multiple centers. Most patients received myeloablative conditioning (n=25) and total-body irradiation (n=20). The donor was matched related for 22 patients, mismatched related for 4 patients, matched unrelated for 1 patient, and mismatched unrelated for 1 patient. Of the 28 patients, 7 had received a prior autologous BMT. Two-thirds of the patients had active disease at transplant. The 2-year PFS and OS rates were 34% (95% CI, 20%-58%) and 40% (95% CI, 24%-64%), respectively.[57] When relapse occurred after BMT, it did so very early (in all cases less than 10 months after BMT). No differences were found in mortality from toxicity and from relapse. There was a trend toward less mortality in the patients receiving reduced-intensity conditioning, but the numbers were too small for any conclusion to be drawn regarding that finding. The numbers also were too small to determine the impact of graft-vs-host disease on outcome.[57]

Two other small series of patients undergoing allogeneic transplant demonstrated the feasibility and possible efficacy of the approach.[58,59] Yokoyama and colleagues reported on 5 patients (4 treated with asparaginase during induction, 2002-2009) undergoing myeloablative allogeneic BMT with cyclophosphamide and total-body irradiation–based conditioning (2 with matched related donors, 2 with matched unrelated donors, and 1 with a cord blood source). Although extensive chronic graft-vs-host disease developed in 3 patients, survival was 100% at a median of 3.3 years (range, 2.4-7.2 years).[58] Ennishi and colleagues reported on 12 patients treated at a single institution from 1995 to 2009. This series included young patients: one 15 years old, two 18 years old, one 21 years old, and one 23 years old. Three patients received a reduced-intensity conditioning regimen; all received total-body irradiation. The actuarial event-free survival and OS rates were 53% and 55%, respectively. One treatment-related death occurred. All 4 cases of relapse and death occurred within 4 months after BMT.[59]

Targeted Therapy for Relapse or the Prevention of Relapse

There is 1 case report in the pediatric literature leveraging STAT3 pathway inhibition, found on a genomics research protocol. The patient had the 6q deletion and mutations in *MAP2KI* and *STAT3*. She received multi-agent chemotherapy and radiation, followed by 1 year of vorinostat (Zolinza, Merck). The effect of vorinostat could not be determined in the setting of combination therapy, but the patient is in continued remission 27 months following diagnosis.[60] Poon and Kwong reported on a patient with relapsed NK/T-cell lymphoma in whom a CR was achieved with a combination of brentuximab vedotin (Adcetris, Seattle Genetics) and bendamustine (Treanda, Teva). The patient underwent a haploidentical transplant, with no evidence of recurrence 5 months after transplant.[61] A pilot study using the histone deacetylase inhibitor romidepsin (Istodax, Celgene) was terminated early owing to reactivation of EBV, causing fever and excessive liver toxicity.[62] Epigenetic modifiers should be used only with careful monitoring of the patient.

Conclusion

Extranodal NK/T-cell lymphomas are rare in the pediatric and adolescent population but must be considered in the differential diagnosis of a nasal/paranasal mass or of systemic lymphomatous disease. The pathologic staining and markers are well defined, although investigators are still learning about the pathways and immunologic phenomena involved in this cancer. Although NK/T-cell lymphoma can occur in very young children, in most pediatric and adolescent patients the disease is diagnosed in the second decade of life. Most pediatric and adolescent patients present with localized disease. Historically, the treatment is radiation to the nose and paranasal area with or without chemotherapy for patients with localized disease, and aggressive systemic multiagent chemotherapy for those with widespread extranodal disease. The role of BMT is unclear in the pediatric literature; however, in the medical oncology literature, BMT is an option for patients with nonlocalized disease that is in remission. The value of reduced-intensity preparative therapy should be studied because of the toxicity associated with BMT.

Owing to the rarity of NK/T-cell lymphomas and the poor outcomes in pediatric and adolescent patients, multi-institutional trials with tumor banking and efforts to address the biology of this disease should be supported. The key to understanding this rare disease and improving outcomes is to perform clinical trials that link biological studies to standardized treatment, including reduced-intensity conditioning for BMT.

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