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Non-anaplastic peripheral T-cell lymphoma in childhood and adolescence: A Children's Oncology Group Study

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Abstract

Background—Peripheral T-cell lymphomas (PTCL) other than anaplastic large cell lymphoma are rare in young patients. While a high proportion of adults with PTCL have poor risk disease, pediatric PTCL is not well characterized. This study examines the outcome of localized and advanced PTCL in pediatric patients treated in standardized fashion.

Procedure—We identified 20 pediatric patients diagnosed with PTCL whose tumor cells did not express CD30 and/or ALK, as determined by immunohistochemistry, between 1992 and 2000 on one of two treatment protocols for localized NHL (POG 9219) or advanced stage large cell lymphoma (POG 9315). All cases were centrally reviewed.

Results and Conclusions—The median age was 12.6 (range 0.7 to 16.9) – 9 male and 11 female. Histological subtypes in the WHO Classification included PTCL, unspecified (12), extra-nodal NK/T-cell lymphoma of nasal type (4), sub-cutaneous panniculitis-like T cell lymphoma (1) and enteropathy-type T-cell lymphoma (1). 2 cases exhibited both T-cell and histiocyte markers and were reclassified as histiocytic sarcoma per the WHO, although T-lineage remains possible. Of 10 patients with localized disease, only 2 relapsed and 9 survive. Of 10 patients with advanced disease, 6 relapsed and 5 (50%) survive. These results suggest that localized PTCL in children and

adolescents is frequently cured with modern therapy, but that advanced stage cases may require novel therapy.

Introduction

The majority of non-Hodgkin lymphomas in childhood and adolescence are comprised of Burkitt, precursor T-lymphoblastic, diffuse large B-cell and anaplastic large cell lymphomas (ALCL). Peripheral T-cell lymphomas (PTCL) other than ALCL are rare in young people but are encountered by pediatric oncologists. (1–7) Incidence and outcome are difficult to estimate due to the rarity of these lymphomas, which precludes specific treatment recommendations, and that they have only been distinguished from ALCL for a little more than 10 years. (5) That was when ALCL was established as a defined entity in the REAL classification and antibodies to identify ALCL-associated markers (i.e. CD30 and ALK) came into widespread use. (8) Outcome data of non-anaplastic PTCL are not available for pediatric patients while outcomes of PTCL in aggregate (excluding mycosis fungoides) have been described as less favorable than ALCL, (9,10) with tendency toward poor prognostic features at diagnosis and short survival. (9–14)

PTCL is categorized in the WHO classification under the general category of mature T-cell and NK-cell neoplasms. (15) This category includes a number of specific entities such as mycosis fungoides/Sézary syndrome (cutaneous T-cell lymphoma – CTCL), HTLV-1 associated adult T-cell leukemia/lymphoma, large granular lymphocyte leukemia, T-cell prolymphocytic leukemia, blastic NK-cell lymphoma and aggressive NK-cell leukemia. All of these are extremely rare in pediatric populations. Another entity, hepatosplenic T-cell lymphoma, is also rare but is most frequently described in adolescents and young adults. (16) It has a generally poor outcome and no cases were treated on these protocols currently described.

Precursor T-lymphoblastic leukemia/lymphoma is categorized separately from mature T-cell and NK-cell neoplasms, and shows outcomes that have improved over the past two decades.

ALCL is a subcategory of mature T-cell and NK-cell neoplasms that occurs relatively frequently in children, adolescents and young adults. (17) It is often noted to have favorable prognosis and our results have shown outcome similar to large B-cell lymphoma. (18,19)

Other PTCL, the subjects of this report, are peripheral T-cell lymphoma unspecified (PTCL-U), extranodal NK/T-cell lymphoma – nasal type (NK/TCL), angio-immunoblastic T-cell lymphoma (AIL), subcutaneous panniculitis-like T-cell lymphoma (SPTCL), and enteropathy type T-cell lymphoma (ETTCL). (20–23)

Methods

Patients

20 pediatric patients diagnosed with PTCL other than ALCL between 1992 and 2000 were treated on one of two treatment protocols of the Pediatric Oncology Group (now of the Children's Oncology Group) for localized NHL (#9219) or advanced stage large cell lymphoma (9315).

Histology

Diagnoses were initially made at the treating institutions and tumors classified according to nomenclatures in use at the time including the Working Formulation, Kiel classification and/or REAL classification. The acceptable diagnoses in these nomenclatures were defined in the protocols. Protocol 9219 included all histologies of localized (stage I and II) NHL while 9315 included advanced (stage III and IV) NHL classified as large cell and mixed small and large cell in the Working Formulation for Clinical Usage, including large B-cell, ALCL, and other peripheral T-cell types. (18) Both protocols included lymphomas of B and T-cell origin. All histologic diagnoses were confirmed by central pathology review and translated into the REAL classification on protocol review, and subsequently into the WHO classification based on histology, immunohistochemistry and clinical findings.

Immunohistochemistry

Immunohistochemical analysis was performed for the protocols with a panel of antibodies effective in paraffin sections: B-lineage antibody L26 (CD20; Dako, Carpinteria, CA); T-lineage antibodies UCHL-1 (CD45Ro), CD3 (Dako), and MT1 (CD43; Biotest, Denville, NJ); Hodgkin and ALCL antibody Ber-H2 (CD30; Biotest), ALCL-associated antibody ALK-1 (Dako), and histiocyte/macrophage-associated antibody KP1 (CD68; Dako). Antibodies were applied in this order in the central review laboratory when material was limited. For cases in which unstained slides were not available, antibody results from treating institutions or reference laboratories of primary diagnosis were accepted if reviewers determined that they were appropriate. T-cell phenotype was determined by positive reactions with anti CD3, CD45Ro and/or CD43 along with negative CD20.

Treatment

Stage was assigned according to the staging system widely accepted for use in children with NHL. (24) Patients with stage III/IV disease on 9315 were treated with a regimen of doxorubicin, vincristine, prednisone, mercaptopurine and methotrexate (APO) with or without alternating intense antimetabolite therapy of intermediate-dose methotrexate (IDM) and high-dose cytarabine (HiDAC). (18) Those with stage I/II disease on 9219 were treated with a modest intensity regimen of vincristine, doxorubicin, cyclophosphamide and prednisone. (19)

Statistical Methods

EFS, defined as time from registration to earliest evidence of relapse, progressive disease, second cancer, or death from any cause (treatment failures), was the major end point of the study. The log-rank test was used in comparative analyses. EFS and OS curves were constructed by the Kaplan-Meier method with SEs of Peto et al. (25,26)

Results

Of the 20 patients, 9 were male and 11 female. The median age was 12.6 (range 0.7 to 16.9). The primary sites of involvement at onset included lymph nodes (5), skin (3), nasal sinuses (3), small intestine (2), soft tissue (2), bone marrow (2), mediastinum (1), breast (1) and liver (1). Histological subtypes included PTCL, unspecified (12), extra-nodal NK/T-cell

lymphoma of nasal type (4), sub-cutaneous panniculitis-like T cell lymphoma (1) and enteropathy-type T-cell lymphoma (1). (Figure 1) The 12 cases of PTCL-U were heterogeneous regarding cell size and composed of diffuse large cells (5), diffuse mixed small and large cells (6) or diffuse small cells (1). 2 cases showed expression of histiocyte marked CD68 as well as T-cell markers and were classified per the WHO as histiocytic sarcoma but included in this analysis since T-lineage was not excluded. Localized cases included 6 PTCL-U and all 4 cases of extra-nodal NK/T-cell lymphoma of nasal type. Advanced stage cases included 6 PTCL-U, 2 histiocytic sarcoma, 1 subcutaneous panniculitis-like T-cell lymphoma and 1 enteropathy associated PTCL. (Table I)

Of 10 patients with localized disease, only 2 relapsed (both were extra-nodal NK/T-cell lymphoma of nasal type) and 9 (90%) survive. Of 10 patients with advanced disease, 6 relapsed (4 PTCL unspecified, 1 enteropathy type and 1 histiocytic sarcoma) and 5 (50%) survive. (Figure 2) The number of PTCL patients on each protocol was insufficient to compare survival with other groups.

Discussion

Lymphoid malignancies, including acute lymphoblastic leukemia (ALL), Hodgkin lymphoma and certain non-Hodgkin lymphomas (NHL), are well-known in pediatric populations. They have been the subjects of intense biologic and clinical investigation for half a century and tremendous progress has been made achieving cures for afflicted children, including those with the usual non-Hodgkin lymphomas of childhood; Burkitt lymphoma (BL), lymphoblastic (LB), large B-cell (LBCL) and anaplastic large cell lymphoma (ALCL). (27) Increasing cure rates have been achieved in large part through systematic use of clinical trials to establish proper therapy for each type.

Outcome of ALCL is frequently noted in the literature to be superior to non-anaplastic PTCL. This may be, at least in part, associated with younger age of incidence of ALCL, since most cases of PTCL occur in adults while ALCL is relatively frequent in young people, and also possibly to biologic factors such as anaplastic lymphoma kinase (ALK) expression. (28) In a previous report, our patients with advanced stage ALCL showed 89% ALK expression and their outcome was not statistically different than those with advanced stage large B-cell lymphoma. (18) ALK-negative ALCL in adults has been reported to show poor outcome, similar to other adult PTCL. (29)

Non-anaplastic PTCL in children are too infrequent for systematic trials and are essentially uncharacterized except as case reports and anecdotes. It has been suggested that a majority tend to be derived from components of the innate immune system including cytotoxic T or NK cells. (30) Their prognosis is not known and their occurrence results in frustration regarding choice of therapy. Histologic types of pediatric PTCL that have been reported as case studies include AIL, NK/TCL, SPLTCL, ETTCL, and, very rarely, CTCL. (2,4,6) Outcomes have been anecdotally mixed.

Many cases of adult PTCL, in contrast, have been reported, including over 500 classified in modern terminology (REAL or WHO). (9–14) Of these, ALCL have constituted

approximately 25% (range, 17–44%), with PTCL-U 48%, T/NK 9%, AIL 11%, ETTCL 6% and others less than 1%. T/NK lymphomas are more frequent in reports from Japan, Korea and Hong Kong.

In the largest series, Rudiger et al, described patients with PTCL, excluding ALCL, from the NHL Classification Project. These constituted 96 of 1378 cases (7%) of NHL. In addition, they saw 33 cases of ALCL (25% of PTCL; 2.4% of NHL). The frequency of non-anaplastic PTCL varied geographically from 1.5–18.3% of NHL (most frequent in Hong Kong). (13)

Overall survivals at four or five years have in most reports varied from 22–38%. Zaja, et al, reported 23 adult patients with PTCL, unspecified (PTCL-U). Response was poor for those treated with chemotherapy alone, but a subset treated with high dose therapy and bone marrow transplantation achieved long-term remission. (14) A small study of 11 patients from Japan, described by Yamazaki, et al, describes long term remissions in patients with SPLTCL and AIL following intensive therapy. (31)

These studies show a stable proportion of ALCL among T-cell lymphomas in adults (about 25%). This is far less than the relative proportion in pediatric lymphoma studies, in which the vast majority of PTCL are ALCL – 90% of advanced (protocol 9315) and 75% of localized PTCL (protocol 9219) in our patients. (18,19) Among the non-anaplastic PTCL in our group, PTCL-U were the most numerous (60%), followed by NK/TCL (20%), SPLTCL (5%) and ETTCL (5%). Although AIL was not represented, the subtypes distributed otherwise similarly to non-anaplastic PTCL occurring in adults.

Our results, however, are very different in terms of outcome from the majority of adult reports. 14 of 20 patients in our group have survived, including 9 of 10 with localized disease. For the group as a whole, we see 5 year EFS of 60% and OS of 70%. Even of those with advanced disease at diagnosis, the outcome appears better than in any adult study of PTCL. This is likely due in part to host factors, with better resilience of children, and to therapies themselves, but may also include biologic differences in tumors of young people versus adults. It is well known that there are age-related differences in outcome among patients with acute lymphoblastic leukemia. (32) The reasons are complex and not completely understood, but include differences in tumor genetics, intensity of therapy, tolerance of therapy, adherence to protocols, presence of caregivers (parents) and other undefined age-related factors. (33) Biologic differences have also been suggested for both anaplastic large cell lymphoma and diffuse large B-cell lymphoma in tumors of children versus adults. (34) We have, for example, recently reported that anti-apoptotic factors expressed in association with STAT3 activation in adult ALCL are not expressed in pediatric ALCL. (35) It is possible that age-related biologic differences also exist in non-anaplastic PTCL. The fact that these tumors are so rare in children suggests that young people may be inherently resistant to their occurrence. PTCL is a heterogenous group of lymphomas rather than a single entity, additionally complicating comparisons.

Two cases were classified as peripheral T-cell lymphoma on entry to protocol 9315 based on expression of CD45Ro and CD43 with absent CD20, but also with expression of monocyte/macrophage marked CD68. These were re-classified as histiocytic sarcoma per the WHO

classification, but included in this report. T-cell receptor gene rearrangement studies were not performed on either case and their true lineage remains ambiguous. In the past, many cases of NHL with histiocyte markers (often ALCL but also non-anaplastic PTCL) have been demonstrated to have clonal T-cell receptor gene rearrangement. (36) Both of the current CD68 positive cases were of advanced stage at diagnosis. One patient is in long-term remission and the other relapsed.

We can conclude that non-anaplastic PTCL in young patients is, in general, responsive to therapy and that patients with localized disease do very well with CHOP type therapy. Even those with advanced disease at diagnosis have an even chance for long-term favorable outcome. Choice of therapy for these advanced patients is not clear, but they can likely be included on protocols designed for other aggressive NHL and, through tracking by rare tumor registries or other mechanisms, optimal therapy may eventually be determined.

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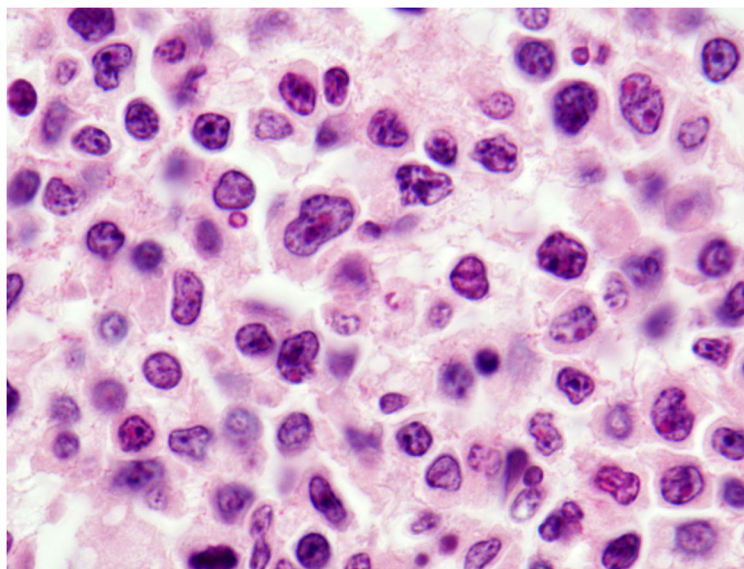


Figure 1.
PTCL, unspecified, with mixed large and small cells (Hematoxylin and eosin, 1000X).

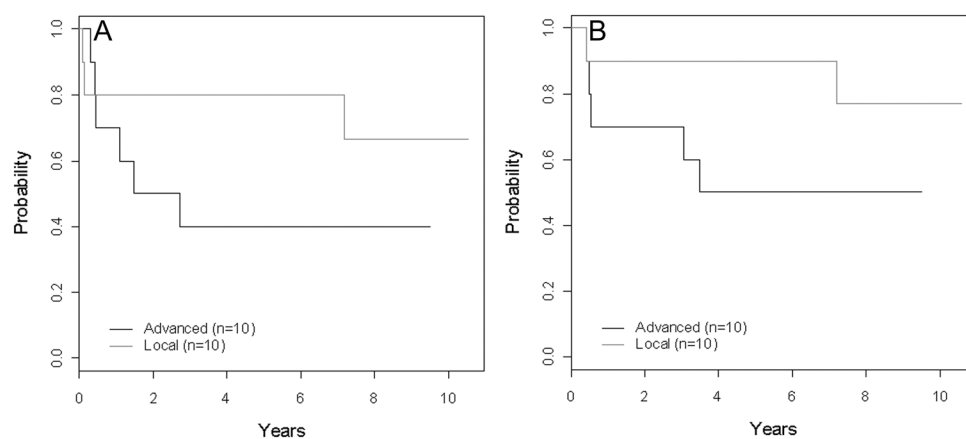


Fig. 2. Survival of patients with non-anaplastic peripheral T-cell lymphoma. A: Event free survival (EFS). B: Overall survival (OS).

Table 1

Patient Characteristics

Protocol	Age	Sex	Histology	Presenting site	Stage	Elevated LDH	Relapsed
9219	0.7	F	Extranodal, NK/T cell, nasal type	Mastoid sinus	1	yes	no
9219	16.3	M	Extranodal, NK/T cell, nasal type	Nasopharynx	1	no	yes
9219	16.3	F	Extranodal, NK/T cell, nasal type	Skin	2	no	no
9219	16.6	M	Extranodal, NK/T cell, nasal type	Nasal sinus	2	no	yes
9219	3.2	F	PTCL, unspecified, large cell	Soft tissue, clavicle	2	yes	no
9219	15.9	M	PTCL, unspecified, large cell	Lymph node	1	no	no
9219	4.4	F	PTCL, unspecified, mixed cell	Skin	1	yes	no
9219	7.9	F	PTCL, unspecified, mixed cell	Breast	1	yes	no
9219	8.6	F	PTCL, unspecified, mixed cell	Skin	1	no	no
9219	11.1	M	PTCL, unspecified, mixed cell	Duodenum	2	no	no
9315	13.5	F	Enteropathy type	Jejunum	3	yes	yes
9315	1.1	M	Histiocytic sarcoma	Mediastinum	4	yes	no
9315	16.9	M	Histiocytic sarcoma	Lymph node	3	yes	yes
9315	8.5	M	PTCL, unspecified, large cell	Mediastinum	3	yes	yes
9315	11.8	F	PTCL, unspecified, large cell	Lymph node	3	yes	yes
9315	16.5	M	PTCL, unspecified, large cell	Bone marrow	4	yes	no
9315	13.6	F	PTCL, unspecified, mixed cell	Bone marrow	4	yes	yes
9315	16.9	M	PTCL, unspecified, mixed cell	Liver	4	yes	yes
9315	13.7	F	PTCL, unspecified, small cell	Lymph node	3	yes	no
9315	5.6	F	Subcutaneous panniculitis-like	Skin	3	yes	no