# Approaches for First-Line Therapy of Peripheral T-Cell Lymphoma

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David Sibon, Christian Gisselbrecht, and Francine Foss

## Introduction

T-cell non-Hodgkin's lymphomas (NHLs) constitute about 10–15% of aggressive lymphomas. The prognostic significance of the immunophenotype has been explored in several studies and results have been reported concerning the outcome of peripheral T-cell lymphoma (PTCL) compared to that of B-cell lymphomas (BCLs). PTCL patients were found to have generally poorer prognoses than patients with BCL. However, PTCL represents a heterogeneous group of lymphomas and a wide variety of different histological subtypes have been recognized.

Patients with PTCL were treated until rituximab era with the same approach used for aggressive BCLs. In GELA prospective studies, LNH 87, LNH 93, and LNH 98, over 900 T-cell lymphoma patients were treated with conventional treatment as well as dose intensive treatments including autologous bone marrow transplantation for patients with adverse prognostic factors. When the outcomes for the T-cell lymphoma patients treated in the LNH 87 protocol with CHOP-like regimens were reviewed, the prognostic value of T-cell phenotype was studied, 5-year overall (OS) and event free survival (EFS) were 41% and 33% respectively [1]. Age, LDH, performance status, BM involvement, and non-anaplastic T-cell NHL were highly independent significant factors affecting OS, and there was no difference in outcome in the different arms of the study. In the subsequent five arm randomized LNH 93 protocol the results were similar. In these studies, the intensive regimen ACVBP was the standard control arm, and for patients less than 60 years; no difference could be seen between ACVBP and m-BACOD or CHOP for low-risk patients [2–4] or stem cell transplantation for high-risk patients or an alternating regimen with ifosfamide and etoposide for patients between 60 and 70 years [5]. Due to the limitation of such subset retrospective analysis it was not possible to determine superiority of any arm, but all regimens included anthracyclines. The retrospective T-cell Lymphoma Project demonstrated similarly that there were no significant differences in the outcomes for patients who received anthracycline-containing regimens as opposed to non-anthracycline-based regimens in the first line [6]. CHOP, therefore, has remained the standard first-line regimen.

D. Sibon
Hématologie Adulte, Hôpital Necker, AP-HP, Université Paris Descartes, Sorbonne Paris Cité, Paris, France

C. Gisselbrecht
Department of Hemato oncology, Saint Louis, Paris, France

F. Foss (✉)
Department of Medical Oncology/Hematology, Yale University School of Medicine, 333 Cedar Street, FMP 130, PO Box 208032, New Haven, CT 06520, USA
e-mail: Francine.foss@yale.edu

F. Foss (ed.), *T-Cell Lymphomas*, Contemporary Hematology,
DOI 10.1007/978-1-62703-170-7_12, © Springer Science+Business Media New York 2013

## Historical Data for CHOP-Based Chemotherapy Regimens in the Different Histological Subtypes

### Peripheral T-Cell Lymphoma, NOS

PTCL, not other specified (PTCLnos) represents the largest PTCL subtype in North America (60–70% of T-cell lymphomas) [6]. In the WHO classification it encompasses all of the PTCLs not classifiable as a specific disease entity in contrast to the rare, but "specified" subtypes [7]. Given the biological heterogeneity encountered in the PTCLnos, it is widely believed that it is made up of more than one disease type. PTCLnos occurs primarily in adults with a median age of 60 years. Despite being classified in as a nodal PTCL in the WHO classification, the majority of patients have extranodal site involvement including the gastrointestinal tract, liver, bone marrow, and skin. The majority of patients present with advanced stage (III–IV) and often with elevated LDH and B symptoms. The 5-year survival of patients with PTCLnos historically has approximately 30% using standard chemotherapy (CHOP and CHOP-like therapy) [6]. In one recent review, outcome has been associated with prognostic score, with patients with low IPI (0–1) having a 5-year OS of 50% vs. 11% for those with 4–5 risk factors [8].

While PTCLnos is a heterogeneous subtype, a number of prognostic markers have been identified. The overexpression of Epstein–Barr virus in 110 nodal NOS T-cell lymphomas was found in 53 patients and was associated with an even poorer prognosis [9]. Additionally for patients with the PTCL-NOS subtype, CD30 expression as well as the expression markers of proliferation such as Ki-67 has been analyzed for their prognostic ability [10]. Two chemokine receptors, CXCR3 and CCR4, were found to be expressed in 63% and 34% of PTCL-NOS cases, respectively [11, 12]. The dominant chemokine expression found in this study was CXCR3-positive/CCR4-negative; this phenotype was shown by multivariate analysis to be an independent adverse prognostic factor.

### Angioimmunoblastic T-Cell Lymphoma

Angioimmunoblastic T-cell lymphoma (AITL) represents a distinct clinicopathological entity, among nodal PTCLs. It generally occurs in elderly patients presenting with generalized lymphadenopathy, hepatosplenomegaly, anemia, and hypergammaglobulinemia. Recent data concerning the identity of the normal cellular counterpart of AITL are emerging. It is now believed that AITL derives from a follicular helper T-cell subset [13, 14]. The tumor cells usually express CD4, CD10, Bcl6, and CXCL13, a phenotype that is unique among T-cell lymphomas.

To evaluate the prognostic significance of clinicobiologic and pathological features in AITL, 157 AITL patients were retrieved from the GELA LNH87-LNH93 randomized clinical trials [15]. One hundred forty-seven patients received a cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-like regimen with intensified courses in half of them. Median age was 62 years, with 81% advanced stage, 72% B symptoms, 65% anemia, 50% hypergammaglobulinemia, and 66% elevated LDH. Overall 7-year survival was 30%. In multivariate analysis, only male sex ($P=0.004$), mediastinal lymphadenopathy ($P=0.041$), and anemia ($P=0.042$) adversely affected overall survival. It was not possible to isolate a group of better prognosis and both IPI and PIT were of limited value. AITL portends a poor prognosis even when treated intensively. However, 30% of patients are long-term survivors, suggesting that there may be a more favorable subset [15].

### Anaplastic Large Lymphoma

Primary systemic anaplastic large cell lymphoma (ALCL) accounts for 2–8% of all lymphomas and 10–15% of all childhood NHLs. Two distinct clinical forms of primary ALCL are now recognized: limited to the skin, not discussed here, and systemic. Clear clinicopathologic differences have been found between AKL-positive (ALK+) and ALK-negative (ALK−) subtypes in most studies. An increased incidence of extranodal

involvement was seen in the AKL-negative group. Skin, bone, and soft tissues were commonly affected extranodal sites. ALK+ ALCL is associated with lower IPI scores than the ALK− group and is the most common ALCL occurring in children. ALK status is the most important prognostic factor in outcome for ALCL, with ALK+ patients having a 5-year overall survival of 70% and progression-free survival of 60% vs. 5-year OS of 49% and FFS of 36% for the ALK− group [16].

In children in most European studies, ALCL is considered to be a separate entity and is treated with either a short and intensive chemotherapy regimen, as for BCL or with more prolonged chemotherapy derived from T-cell lymphoma protocols. The European Intergroup Study of ALCL compared the results and prognoses of 225 children enrolled in trials designed to treat childhood ALCL with short and intensive chemotherapy [17]. Multivariate analysis revealed three significant prognostic factors: (1) mediastinal involvement, (2) visceral involvement, (3) skin lesions. For the good-prognosis group with 0 factors, the 5-years PFS was 89%; for the poor-risk group with at least one factor, the 5-years PFS was 61%.

While no large comparative studies have been published in adults with ALCL, responses to CHOP and CHOP-like regimens range from 60 to 90%. The overall survival of patients with stage I or II disease with low IPI exceeds 90%. According to the GELA study which included 146 adults with T/null- and B-cell ALCL, the 5-year overall-survival rate for patients without adverse IPI was 82%, as compared to 78% for patients with an IPI of 1, 50% for the high-intermediate-IPI group, and 25% for the high-IPI group [18]. Dose-intensive treatments have been used in this study, according to initial stratification based on prognostic factors. However, in that investigation, stratification according to ALK positivity had not been done, and results may also reflect the different percentage of ALK+ lymphomas in adults. In the good-prognosis group of ALK+ lymphomas the 5-year overall-survival rate was 94% for patients with 0–1 risk factor vs. 41% for those with two or more factors [19]. Although ALK positivity is considered a marker of better prognosis, patients with two or more IPI factors still have a poor prognosis, and new approaches are needed.

Considering the response rate and the survival of patients with ALK+ lymphoma, consolidation with ASCT is not recommended if patient achieve a complete remission. The NCCN guidelines does not recommend autologous stem cell transplant in first remission for this group of patients. For ALK− patients the debate is still open for patients with at least two IPI adverse prognostic factors, and the NCCN guidelines would suggest that such patients be consolidated with a stem cell transplant.

## Extranodal Natural Killer/T-Cell Lymphoma, Nasal Type

Extranodal NK/T-cell lymphoma, nasal type, is a rare and severe disease, more frequent in Asia and South America than in Europe and North America. It shows a striking association with Epstein–Barr virus. Usually extranodal NK/T-cell lymphomas primarily involve the nasal cavity or other parts of the upper aerodigestive tract but sometimes occur in extranasal sites without involving the nasal cavity or nasopharynx (gastrointestinal tract, skin, testis, liver, spleen, bone marrow). There is no consensus treatment except that the addition of radiotherapy for early stage nasal cases results in survival benefit and can be used upfront as producing a 83% complete remission rate [20, 21]. Patients with extranodal NK/T-cell lymphoma have a cumulative 5-year survival probability of 40% [21, 22]. The median overall survival is better in nasal compared to the extranasal cases in early (2.96 year vs. 0.36 year) and late stage disease (0.8 year vs. 0.28 year) [23].

For patients with refractory or relapsed extranodal NK/T-cell lymphoma, L-asparaginase-based regimens have been shown to be associated with ORR of 79% with 63% CR [24, 25]. A novel regimen that incorporates L-asparaginase along with ifosfamide, etoposide, dexamethasone, and methotrexate (SMILE) has been developed and shown

to be associated in a Phase I study with a response rate of 67% in refractory patients [26]. A prospective phase II trial has been reported with SMILE regimen in patients with newly diagnosed stage IV or relapsed refractory NK/T-cell lymphomas [27]. Of 39 enrolled patients, 29 (74%) completed the planned treatment. The responses were complete remission (CR) in 15, partial remission in 14, and early death due to infection in 4. Overall response rate and CR were 74% (95% CI, 58–87) and 38%, respectively. The most common grade 3 nonhematologic toxicity was infection (41%).

## Enteropathy-Type T-Cell Lymphoma

EATL is a rare type of T-cell lymphoma, often associated with a history of celiac disease, that usually arises in the jejunum but can involve other gastrointestinal tract sites (e.g., stomach and colon). There are two histological groups of EATL that correlate with clinical and immunophenotypic features. Pleomorphic-anaplastic ETL is usually associated with a history of celiac disease and histologic evidence of enteropathy and is most often CD56–. Monomorphic ETL often occurs without a history of celiac disease, has variable histological evidence of enteropathy, and is usually CD56. The most commonly used regimen for patients with enteropathy-type intestinal T-cell lymphoma is CHOP. However, the use of combination chemotherapy is difficult, and less than 50% of patients can complete their planned courses of chemotherapy, often because of poor nutritional status. Observed complications of treatment are gastrointestinal bleeding, small-bowel perforation, and the development of enterocolic fistulae. Relapses occurred in 79% of patients who respond to initial therapy. Response data are available mainly from study of Gale et al. [28]. Of 24 patients treated with combination chemotherapy, ten (41%) achieved a complete remission and four (16%) a partial response. The regimens included an intensive weekly combination of vincristine, doxorubicin, prednisolone, and high-dose methotrexate ($n=5$); cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) at 21-day intervals ($n=12$); alternating 21-day cycles of CHOP with procarbazine, etoposide, and prednisolone orally on days 3–7, and doxorubicin intravenously on day 1 ($n=1$); cyclophosphamide, vincristine, doxorubicin, and prednisolone ($n=1$); and alternating weekly cycles of prednisolone, doxorubicin, cyclophosphamide, and etoposide with prednisolone, bleomycin, vincristine, and methotrexate (PEACE-BOM; $n=3$). Less than 50% of patients completed their planned chemotherapy courses, largely because of complications of treatment. Poor nutritional status was common, requiring parenteral nutrition during chemotherapy in ten patients and enteral feeding in another two. Gastrointestinal bleeding occurred in one patient 5 days after starting treatment. Four patients suffered small-bowel perforation. In three, this occurred after the first cycle of treatment (at 1, 2, and 4 days) and proved a fatal event. The actuarial 1-year and 5-year overall-survival rates were 39% and 20% respectively.

## Hepatosplenic T-Cell Lymphoma

Hepatosplenic T-cell Lymphoma (HSTCL) is a rare aggressive type of extranodal lymphoma characterized by hepatosplenomegaly, bone marrow involvement, and peripheral blood cytopenias. Most cases express the gamma-delta T-cell receptor, but cases can have an alpha/beta phenotype and are considered to be a variant of the disease. Many patients have a history of immunosuppression. The median age is ~30 years, with a male predominance. Prognosis of HSTCL is poor; response data are available mainly from two studies [29, 30]: median survival time is ~12 months, and almost all patients ultimately die despite consolidative or salvage high-dose therapy. Current treatment modalities appear to be ineffective in most patients. The question of whether aggressive treatment improves the overall survival is unresolved. Possibly transplantation after a short attempt to induce remission might be a suggestion.

## Data with More Intensive Regimens

Given the overall inferiority of CHOP-line BCL regimens in the retrospective studies, more aggressive infusional regimens, including hyper-CVAD and hyper-CHOP, among others, were evaluated in patients with aggressive T-cell lymphomas. A retrospective study from MD Anderson Cancer Center explored alternative higher dose regimens and compared those against CHOP in 135 patients with PTCL. Among those patients with non-ALCL disease, there was no significant difference in outcome between those treated with CHOP and aggressive alternatives (3-year OS: 43% vs. 49%) [31]. However, these results are difficult to interpret, as the study was not randomized.

Mercadal et al. reported results from a study of patients who were treated in the first line with mega CHOP/ESHAP followed by autologous stem cell transplant for patients achieving remission [32]. Forty-one patients were enrolled and received three courses of high-dose cyclophosphamide 2,000 mg/m$^2$/day, adriamycin 90 mg/m$^2$/day, vincristine and prednisone alternating with three courses of etoposide, cisplatin, cytarabine, and prednisone (ESHAP). The histological distribution of the patients included PTCL unspecified, 20 cases (49%); angioimmunoblastic,12 cases (29%); hepatosplenic, 2 cases (5%); extranodal NK nasal type, 2 cases (5%); panniculitis like, 2 cases (5%) and others. Sixty-eight percent of patients received the planned treatment. After chemotherapy, 20 patients reached complete response (CR) and 4 had a partial response, for an overall response rate of 58%. The outcome of the 16 patients who showed primary refractoriness to mega-CHOP/ESHAP was extremely poor, with a median OS of 8 months. Grade 3 or 4 hematologic toxicity occurred in 63 and 68% of patients after CHOP and ESHAP respectively. Thirty-eight and 15% of patients in the CHOP and ESHAP courses respectively required hospitalizations for infections and one patient died of sepsis. Overall, the CR rate in this study (50%) was not better than with CHOP alone in studies done by the same group, suggesting no advantage to this more aggressive approach.

Recently the German High Grade Non-Hodgkin's Lymphoma Study group explored the use of dose intensive CHOP or the addition of etoposide to CHOP for aggressive lymphomas. They reported results for patients with aggressive T-cell lymphomas treated on seven trials with 6–8 courses of CHOP or CHOEP (Hi-CHOEP or MegaCHOEP) [33]. Of 343 T-cell patients enrolled in these studies, 70 had PTCLnos, 28 had AITL, 78 had ALK+ ALCL, and 113 had ALK− ALCL. When analyzed for prognostic factors, B-symptoms were most frequent in AITL patients and bulky disease was seen more often in ALCL, either ALK-positive or -negative, than in other subtypes. Over half of all ALCL (ALK-positive or -negative) patients, 46% of PTCLnos, and 21% of AITL patients were in the low-risk group by IPI.

As an aggregate, the younger patients demonstrated an improvement in EFS for both etoposide containing regimens (75% vs. 51%) compared to the non-etoposide regimen, but there was no overall survival difference. The positive effect of etoposide on EFS was seen even in the favorable ALK+ patients. For the elderly patients, neither shortening of the time interval from 3 to 2 weeks (CHOP-21 vs. CHOP-14), administration of eight instead of six courses of CHOP-14, or the addition of etoposide (CHOEP) significantly improved EFS or OS and increased toxicity was seen with the more intensive regimens. EFS for the different subtypes was 41% for PTCLu, 45% for ALK− ALCL, 50% for AITL, and 76% for ALK+ ALCL. Outcomes in this study were related to IPI for the non-ALK+ patients. Those with IPI 0 and 1 had a favorable 3-year EFS above 50%. Patients with IPI of 2 or greater showed a 3-year EFS below 34%. The conclusions from this study which is one of the largest randomized studies of first-line regimens is that younger patients may benefit from the addition of etoposide in terms of response rate and EFS, which would therefore potentially allow more patients to undergo a consolidation autologous stem cell transplant in first remission. The standard for the elderly based on these data remains six cycles of CHOP at standard doses. Finally, the excellent outcomes in patients with low IPI

suggest that this group may do well and should be distinguished from the intermediate and high IPI patients.

Another more intensive regimen explored in the GELA group was ACVBP (doxorubicin 75 mg/m$^2$ D1, cyclophosphamide 1,200 mg/m$^2$ D1, vindesine 2 mg/m$^2$ D1 and D5, bleomycin 10 mg D1 and D5, and prednisone D1–D5, followed by a sequential consolidation consisting of HD methotrexate (two courses), etoposide + ifosfamide (four courses), and cytarabine (two courses) at 2 weeks intervals). In a randomized study reported by Tilly et al., there was a statistical advantage in patients 60–70 years old for ACVBP (47 T-cell lymphomas) vs. CHOP (49 T-cell lymphomas) [34]. A further study was done adding bortezomib to the regimen (5 mg/m$^2$ was administered at D1 and D5 of each ACVBP cycle, and then at D1, D8, and D15 every 4 weeks during consolidation phase) [35]. Fifty-seven patients were enrolled and were to receive four cycles of bortezomib-ACVBP over 10 weeks; 46 patients responded and received consolidation with high-dose methotrexate, ifosfamide, etoposide, and cytarabine. Only 28 patients completed the consolidation phase of the study and 39% of patients died from lymphoma. There was no overall difference in response rate between the ACVBP-bortezomib regimen and ACVBP alone.

The Groupe Ouest Est d'Etude des Leucemies et Autres Maladies du Sang devised an alternative therapeutic schedule including etoposide, ifosfamide, cisplatin alternating with doxorubicin, bleomycin, vinblastine, dacarbazine (VIP-reinforced-ABVD; VIP-rABVD) and compared it to CHOP/21 as front-line treatment in 88 patients with non-cutaneous PTCL [36]. Patients assigned to VIP-rABVD ($n=43$) received six alternative cycles every 4 weeks (three VIP and three rABVD). VIP cycles (1, 3, and 5) included etoposide 100 mg/m$^2$/day IV days 1–3, ifosfamide 1,000 mg/m$^2$/day days 1–5, and cisplatin 20 mg/m$^2$/day as a continuous infusion on days 1–5. The three cycles of rABVD (cycles 2, 4, and 6) included on days 1 and 15, doxorubicin 50 mg/m$^2$/day, bleomycin 10 mg/m$^2$/day, vinblastine 10 mg/m$^2$/day, and dacarbazine 375 mg/m$^2$/day. Eighty-eight patients were enrolled, including 57 with PTCL-nos, 15 with AITL, and 14 with ALCL. Among the 14 ALCL patients, 10 were ALK+. Grade 3 or 4 neutropenia was higher in the VIP-rABVD arm (23% vs. 8%), but treatment mortality was similar (9% vs. 8%).

The 22-year EFS of 41% vs. 45% for the CHOP-21 arm vs. the intensive regimen was no different despite the more aggressive regimen and median overall survival was 42 months for each of the arms. Outcome in this study was better for patients with ALK+ ALCL and for those with low IPI. Patients with localized disease underwent consolidative involved field radiotherapy.

## New Combination Therapies for PTCL

### CHOP-Based Regimens

A number of studies have investigated chemoimmunotherapy in aggressive T-cell lymphomas. Alemtuzumab is a CD52-targeted monoclonal antibody that has demonstrated activity as a single agent and in combination with CHOP. Up to 40% of PTCL cases have been shown to express CD52 by immunohistochemistry, although expression has been shown to vary by subtype [37]. One phase II study by Kim et al. enrolled 20 patients treated with CHOP combined with intravenous alemtuzumab in 3-week cycles (cycle 1: 10 mg on day 1, 20 mg on day 2; subsequent cycles: 30 mg on day 1) as frontline therapy [38]. Immunohistochemistry for CD52 expression was not required for study entry. Trimethoprim/sulfamethoxazole, twice daily, three times a week, and acyclovir 600 mg, twice daily, were administered starting on day 8 and continued during the study and up to a minimum of 2 months following discontinuation of the alemtuzumab therapy. The overall response rate to this combination was 65% CR and 15% PR. Responses were seen in all ten pts with PTCLnos, one of three with extranodal NK/T-cell lymphoma, two of three with AITL, and one of two with ALK- ALCL and SPTCL respectively. Nearly all patients (90%) experienced grade 4 neutropenia and 5 of 20 experienced CMV-reactivation. Additionally, there were two

treatment-related deaths, including one who died from pseudomonas pneumonial and lung abscess. The high complete response rate of 65.0%, 1-year event-free survival rate of 43.3%, and 1-year overall survival rate of 44.3% in this study was comparable to other studies with CHOP but toxicity was high and the regimen was significantly immunosuppressive in this population.

Gallamini et al. conducted a study of CHOP plus alemtuzumab combination in which alemtuzumab 30 mg was given subcutaneously on day 1 in cycles 1–4 in the first cohort of patients and then for all eight courses in the second cohort [39]. There were 14 patients with PTCLu, 6 with AITL, 3 with ALK− ALCL, and 1 with EATL. Of 24 evaluable patients, 71% had CR, including all 6 with AITL, all 3 with ALK− ALCL, 7 of 14 with PTCLu, and the one with EATL. The ORR was 75%. Neutropenia was seen in 34% of the treatment cycles and CMV reactivation in 9%. There was one patient who had reactivation of Jakob-Creutzfeldt virus and two who developed aspergillosis. At a median follow-up of 16 months at the time of the report (range, 5–42 months), 14 patients were alive, 9 had died from progressive disease, and 1 had died from pneumonia at day 198 while in CR. The overall median duration of response was 11 months. This study demonstrated that subcutaneous alemtuzumab was better tolerated and associated with a lower but still significant incidence of opportunistic infections.

A phase I study evaluated alemtuzumab combined with dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) in PTCL patients [40]. In this study, alemtuzumab was administered at doses of 30, 60, or 90 mg prior to each EPOCH cycle. Significant bone marrow aplasia occurred in two of three patients at both the 60 and 90 mg dose groups; therefore, phase II study accrual is continuing at the 30 mg dose of alemtuzumab. Infections were reported in 11 of 14 patients, including bacterial, fungal, and viral pathogens. Patients underwent ongoing CMV surveillance and received prophylactic therapy with acyclovir and trimethoprim–sulfamethoxazole.

Based on these encouraging data with alemtuzumab and CHOP, the alemtuzumab-CHOP combination is being compared to CHOP-21 in the first line by the Nordic Lymphoma Group and the German High Grade Lymphoma Groups (the ACT Trial). Patients over age 60 will be randomized between the two arms and will then be followed until progression. Patients under age 60 will be randomized to either six cycles of CHOP-14 or four cycles of alemtuzumab-CHOP-14 and two cycles of CHOP-14 without alemtuzumab vs. six cycles of CHOP-14. Patients in remission will then undergo an autolous stem cell transplant.

Another targeted agent that has been combined with CHOP in first-line therapy for PTCL has been the interleukin-2 fusion toxin protein, denileukin diftitox. Denileukin diftitox combines the interleukin-2 receptor-binding domain with diphtheria toxin, and is FDA approved for patients with relapsed or refractory cutaneous T-cell lymphomas whose tumors express the CD25 subunit of the interleukin-2 receptor. In a single center phase II study at MD Anderson Cancer Center, denileukin diftitox was administered to 27 patients with relapsed aggressive T-cell lymphomas at the standard dose of 18 μg/kg/day for 5 days on a 21 day cycle [41]. The overall response rate was 48% in heavily pretreated patients with relapsed PTCL. Responses were seen in four of ten patients with PTCL-NOS, two of three with AITL, and two of two with ALCL. The progression-free survival was 6 months. In this trial, the expression of CD25 by immunohistochemistry was not predictive of response to denileukin diftitox.

Based on these encouraging data in relapsed patients, a multi-center prospective phase II trial evaluated the efficacy and safety of the combination of denileukin diftitox with CHOP in 49 untreated patients with aggressive PTCL subtypes [42]. In this study, denileukin diftitox was administered at a dose of 18 μg/kg/day on days 1 and 2 and CHOP was given on day 3; this was followed by growth factor support on day 4 every 21 days. Histologic subtypes included: ALCL 8, AILT 10, PTCLnos 19, EATL 3, panniculitis-like TCL 5, NK/T 1, hepatosplenic TCL 1. The median cycles was six with seven pts completing only one cycle of therapy; three pts died with PD after cycle one, and four patients were taken off

study for toxicity. The ORR in 47 pts was 68% with 57% CR. In the efficacy-evaluable pts (≥2 cycles completed) the ORR was 86% (CR 75%). All patients with AITL, ALCL, and EATL responded, as did 3 of 5 with SPTCL and 9 of 12 with PTCLnos. Median PFS for the 47 pts was 12 months and 2-year estimated OS was 60%. The median response duration for the 33 responders was 29 months. The most frequent grade 3 or 4 adverse events were bone marrow suppression and febrile neutropenia, which occurred in 12% of patients. Denileukin diftitox-associated toxicities included infusion related rigor in seven pts, hypoalbuminemia in 17, and acute hypersensitivity in 1. There was no prolonged immunosuppression, or opportunistic infections, and a randomized study of CHOP with or without denileukin diftitox is ongoing.

In another study by the GELA, CHOP was combined with rituximab in elderly patients (age 59–79) with AITL in an attempt to target non-neoplastic B lymphocytes which may provide paracrine growth factors to the malignant T cells. Twenty-five patients aged 59–79 years with newly diagnosed AITL were enrolled and treated with a combination of eight cycles of rituximab (375 mg/m$^2$ at day 1 of each cycle) and CHOP chemotherapy delivered every 3 weeks (R-CHOP21). Most of the patients had advanced disease (stage IV: 92% and B symptoms: 68%). Twenty-one patients completed the eight cycles of R-CHOP. The overall response rate was 80%, with 44% achieving a complete response. With a median follow-up of 24 months, the progression free survival was 42 and the 2-year overall survival was 62%. It was concluded that R-CHOP21 did not improve the complete response rate or outcome compared to historical data with CHOP.

CHOP has also been combined with the bevacizumab, the anti-VEGF receptor growth factor monoclonal antibody. Several PTCL subtypes, especially AITL, are characterized by the overexpression of angiogenic factors, such as VEGF. At least one relapsed AITL patient has achieved a CR following treatment with bevacizumab [43]. A combination of CHOP and bevacizumab has been studied in patients with PTCL or NK-cell neoplasms by the Eastern Cooperative Oncology Group. Patients received bevacizumab at a dose of 15 mg/kg on day 1 followed by maintenance bevacizumab. However, this trial has been suspended when a preliminary analysis reported a high incidence of cardiac events related to the therapy, including four cases of congestive heart failure [44].

## Gemcitabine-Based Regimens

Gemcitabine has demonstrated significant activity as a single agent in patients with cutaneous T-cell lymphomas and has been used in a number of combination regimens for PTCL [45]. Zinzani reported results from 19 patients with CTCL and 20 patients with PTCL who received gemcitabine at a dose of 1,200 mg/m$^2$ on days 1, 8, 15 schedule every 28 days. All patients had been heavily pretreated. The overall response rate was 51%; MF patients had a CR rate of 16% and a PR rate of 32%, while PTCL patients had a CR rate of 30% and a PR rate of 25%.

A combination of gemcitabine with cisplatin (GEM-P) was tested in a phase II study [46]. The regimen consisted of gemcitabine given at 1,000 mg/m$^2$ on days 1, 8, 15 with cisplatin 100 mg/m$^2$ on day 8 and methylprednisolone 1,000 mg/m$^2$ on days 1–5 of a 28-day cycle. Of 27 patients treated, the response rate was 73% overall and 80% in first-line patients. Grade 3 or 4 neutropenia occurred in 41% of treated patients.

The combination of gemcitabine with vinorelbine and filgrastim was also found to be active in a pilot study. Patients received vinorelbine 25 mg/m$^2$ and gemcitabine 1,000 mg/m$^2$ on days 1 and 8 of each 21-day cycle [47]. The overall response rate was 70% for the PTCL patients ($n = 10$) treated with this regimen. Febrile neutropenia occurred in 6% of cycles.

In another study, gemcitabine was combined in a CHOP-based regimen (CHOP-EG, CHOP plus etoposide and gemcitabine) as first-line treatment [48]. The regimen consisted of classical CHOP plus etoposide 100 mg/m$^2$ intravenously on day 1 and gemcitabine 600 mg/m$^2$ on day 1 in a 3-week interval. Fourteen of 26 enrolled patients had PTCLnos and 8 had NK/T-cell

lymphomas, 2 had AITL and 2 had ALK– ALCL. Responses were seen in 10 of 14 PTCL, 7 of 8 NK/T, one of two AILT and both ALCL patients. The overall response rate was 76.9%. Median survival has not yet been reached, while median EFS was 7 months at a median follow-up duration of 383 days. Estimated overall survival at 1 year was 69.6%. The most severe adverse event was grade 4 neutropenia in 14 patients (53.8%) and febrile neutropenia in four patients (15.4%). While active, this regimen did not appear to be superior to studies with CHOP-etoposide and incidence of myelosuppression was higher.

The Southwest Oncology Group has recently completed a study of gemcitabine, cisplatin, etoposide, and Solu-Medrol (PEGS) for patients with untreated or relapsed PTCL. The majority of the patients (79%) were untreated at the time of study entry. The 1-year event-free survival was reported to be 38%.

Another regimen incorporating gemcitabine was the GIVOX regimen (gemcitabine, ifosfamide, and oxaliplatin). In a group of high-risk PTCL patients, the response rate was 86% with 67% CR and the 5-year EFS was 49%. Toxicities were primarily hematologic with grade 4 thrombocytopenia and anemia occurring in 38% and 24% of patients respectively.

## Transplantation as a Consolidation Therapy

The role of autologous or allogeneic stem cell transplanation in first remission has been explored in a number of prospective nonrandomized trials. The largest studies are from the Nordic and the German groups, who report overall EFS ranging from 30 to 50% and transplant rates of 40–70% based on intent to treat analysis. The Nordic group reported results from 160 patients treated with CHOEP-14 followed by BEAM conditioning [49]. At a median follow-up of 4 years, the OS was 50% and the PFS was 48%. Outcome results were similar for the nodal subtypes of PTCL. In the German study reported by Reimer et al., 83 patients were treated with CHOP ×4, followed by Dexa BEAM or ESHAP [50]. The conditioning regimen for the transplant was high-dose cyclophosphamide and total body irradiation. In this study, the CR rate to CHOP was 39%, and only 66% of patients were able to be transplanted. At a mean follow-up of 33 months, the OS was 48% and the EFS was 53%.

Based on the poor outcomes for most patients with PTCL, the NCCN guidelines recommends that autologous stem cell transplantation be considered in first remission all but the ALK+ ALCL group. A randomized study comparing outcomes with and without transplantation is underway as is a study comparing outcomes with autologous or allogeneic stem cell transplantation. However, more data is needed to identify prognostic factors which predict which patients will benefit from these approaches.

## Summary of First-Line Treatment Approaches for PTCL

Because of the inferior outcomes with CHOP-based regimens and the paucity of data exploring other regimens in a randomized setting, treatment strategies for patients with aggressive T-cell lymphomas are not clearly defined. In the United States, the NCCN has established evidence-based treatment approaches for T-cell lymphoma and stratifies patients based on stage (Table 12.1). For early stage patients with localized disease, chemotherapy should be followed by involved field radiotherapy. It is recommended that all patients except for those with low IPI be consolidated with autologous stem cell transplant. ALK+ ALCL is identified as the one subtype which has an excellent outcome and should not be transplanted in first remission. Recent data suggest that ALK+ patients with high IPI could be an exception to this rule. In prospective trials where up to 40% of patients do not undergo a complete remission and therefore cannot be consolidated with transplant, new approaches are necessary.

Selection of first-line therapy based on histopathologic features has not yet been widely employed but should be considered. For nodal T-cell lymphomas (PTCL-NOS, AITL, ALCL)

**Table 12.1** Approach to patients with T-cell lymphoma

| Patient population | Induction therapy | Consolidation therapy |
|---|---|---|
| ALK-positive ALCL | CHOP + RT | Not needed if in remission |
| All other subtypes: stage I–II (low/low-intermediate risk) | Clinical trial preferred<br>Multiagent chemotherapy (4–6 cycles) with adjuvant locoregional RT | Consider consolidation with high-dose therapy and stem cell rescue for all patients except low-risk (aaIPI) |
| All other subtypes: stage I–II (high/high-intermediate risk), stage III–IV | Clinical trial preferred<br>Multiagent chemotherapy (6–8 cycles) ± RT | |

**Table 12.2** First-line therapies for T-cell lymphoma

| | |
|---|---|
| First-line therapy | Clinical trial preferred |
| | CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) for ALCL, ALK+ |
| | CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) |
| | CHOP q 2–3 weeks |
| | CHOP followed by ICE (ifosfamide, carboplatin, and etoposide) or IVE (ifosfamide, etoposide, and epirubicin) |
| | HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine |
| First-line consolidation | All patients except low-risk (aaIPI) should be consolidated for high-dose therapy and autologous stem cell transplantation |
| | ALK-1+ ALCL subtype has a good prognosis and does not need consolidative transplant if in remission |

the standard regimen used is a CHOP-based therapy (Table 12.2). For extranodal subtypes, regimens may be individualized. NK/T-cell lymphoma patients have also had inferior outcomes with CHOP-based regimens, and consideration of alternative regimens such as SMILE and asparaginase combinations should be strongly considered for these patients.

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