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First line therapy for peripheral T-cell lymphoma

T-cell non-Hodgkin's lymphomas (NHL) are rare in Europe and the United States, where they 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 PTCL compared to that of B-cell lymphomas (BCL). PTCL patients were found to have generally poorer prognoses than patients with BCL. However, PTCL represent a heterogeneous group of lymphomas and a wide variety of different histological subtypes have been recognized. The most common subtype is an heterogeneous group of PTCL not other specified (PTCL-NOS), followed by anaplastic large cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma (AITL). Some uncommon PTCL subtypes have been included in series and are not always easy to identify in reports.

Patients with peripheral T cell lymphoma (PTCL) were treated until rituximab era with the same approach than B-cell lymphoma patients (BCL). In GELA prospective studies, LNH 87, LNH 93 and LNH 98 which comprised over 900 T cell lymphoma patients, conventional treatment as well as dose intensive treatments including autologous bone marrow transplantation were used for patients with adverse prognostic factors. In the four arms randomized LNH 87 protocol, the prognostic value of T cell phenotype was studied,[1] 5 years overall (OS) and event free survival (EFS) were 41% and 33% for 288 T-cell lymphomas. In Cox's model, age, LDH, performance status (PS), bone marrow (BM) involvement and non-anaplastic T-cell NHL were highly independent significant factors affecting OS. Moreover, it was not possible to find a regimen better than the standard arm. In the subsequent five arms randomized LNH 93 protocol the same findings were described in several reports. Subset analysis of both protocol were made for T cell lymphoma and can be summarized as following: the intensive regimen ACVBP was the standard control arm in most of the studies, except one, for patients less than 60 years; no difference could be seen between ACVBP and m BACOD or CHOP for low risk patients[2,3,4] or stem cell transplantation for high risk patients [5,6,7] or alternating regimen with ifosfamide and etoposide for patients between 60-70 years.[8] Due to the limitation of such subset retrospective analysis it was not possible to find a regimen better than the standard arm, but all regimens included anthracyclines. Data from the International Lymphoma study group failed in the same way to

demonstrate an advantage of any regimen in a heterogenous group of PTCL coming from centres around the world. Moreover, there were no significant differences in the outcomes for patients who received anthracyline-containing regimens as opposed to non-anthracycline-based regimens.[9] However, due to the limitation of such retrospective analysis, CHOP should remain the standard to be compared even if not highly efficient.

What did we learn from the analysis of treatment of the different histological subtypes? Peripheral T-cell lymphoma, not other specified

Peripheral T-cell lymphoma, not other specified (PTCL-NOS) represents the largest PTCL subtype in North America (60-70% of T-cell lymphomas). 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. Given the biological heterogeneity encountered in the PTCL-NOS, it is widely believed that PTCL-NOS is made up of more than one disease type but how to best differentiate these in unknown. PTCL-NOS usually affect adults (M/F ratio 1.5) at a median age of 60 years. Despite being classified in as a nodal PTCL in the WHO, 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 disease often with elevated LDH and B symptoms. Some prognostic factors have been described. The overexpression of Eber in 110 nodal NOS T cell lymphomas was found in 53 patients and was associated with an even poorer prognosis.[10] The 5 year survival of patients with PTCL-NOS is approximately 30% using standard chemotherapy (CHOP and CHOP-like therapy).[9,10]

Angioimmunoblastic T-cell lymphoma

Angioimmunoblastic T-cell lymphoma (AITL) represents a distinct clinicopathological entity, among nodal peripheral T-cell lymphomas. It generally occurs in elderly patients presenting with generalized lymphadenopathy, hepato-splenomegaly, 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 (TFH) subset. 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 angioimmunoblastic T-cell lymphoma (AITL), 157 AITL patients were retrieved from the GELA LNH87-LNH93 randomized clinical trials.[11] 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 or PIT were of limited value. AITL portends a poor prognosis even when treated intensively. However, AITL is not always lethal with 30% of long term survivors.[9, 11]

Anaplastic large lymphoma

Primary systemic anaplastic large cell lymphoma (ALCL) accounts for 2-8% of all lymphomas and 10% to 15% of all childhood non-

Hodgkin's lymphomas. 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 and ALK-negative 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 expression is closely correlated with age and IPI. The ALK-positive group had lower IPI scores than the ALK-négative group and is present in 90% of children. Patients with ALCL-T had significantly better survival than those with non ALCL T-cell lymphoma.[1] However, there is a significant difference in outcome between ALK-positive and ALK-negative ALCL of poor prognosis.[12] 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 B-cell lymphoma or with more prolonged chemotherapy derived from T-cell lymphoma protocols. However, North Americans treated all large-cell lymphomas with the same chemotherapy regimen regardless of the histologic subgroup and immunophenotype. The opportunity to classify a case as either ALK-positive or ALK-negative ALCL according to the criteria of the new WHO classification, and to stratify patients into low- and high-risk categories, according to IPI score or to score described in children, is highly relevant for the design of optimal therapeutic strategies.

The European Intergroup Study of ALCL[13] compared the results and prognoses of 225 children enrolled in trials designed to treat childhood ALCL with short and intensive chemotherapy. Multivariate analysis has brought to light three 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%. Using a risk adapted treatment impressive results have been obtained by the Berlin-Frankfurt-Munster group.[14] With low cumulative doses of critical drugs, such as anthracyclines. It was the basis of the largest international study completed on 352 pediatric and adolescent patients.[15] The overall complete remission rate was 88% with a 2-y EFS 74% and OS 92%. There was no significant difference in efficacy in terms of risk groups as defined by stage according to St Jude and Ann Arbor or adverse factors for high risk group if they had at least one risk factor defined as the presence of skin, and/or mediastinal and/or visceral involvement (defined as lung, liver or spleen involvement) and standard risk if they had no risk factors.

No large comparative studies of adults have been published. Most investigators reported that the ALCL response rate to chemotherapy was good, ranging from 60-90%. Patients generally received the same treatment as that prescribed for diffuse large-cell lymphoma, according to the policy of the institution or in prospective trials. The overall survival of patients with localized stage without adverse IPI factors is known to exceed 90%. As in other adult studies – and in contrast to those in children – patients with more localized stages received radiotherapy. Patients with more advanced-stage disease frequently relapse, and their prognosis, in comparison to that of patients with other large-cell lymphomas, is controversial. Although a few studies have suggested that advanced-stage ALCL may have short disease-free survival and may require more intensive therapy,[16] most investigators consider that ALCLs generally behave like high-grade lymphomas However, several comparative studies on diffuse large-cell lymphomas showed an association between CD30 expression and a favorable outcome[17] when patients were treated with chemotherapy regi-

mens similar to those used for other types of lymphomas (e.g., CHOP). According to the GELA study[18] which included 146 adults T/null- and B-cell ALCL, the 5-year overall-survival rate for patients without adverse IPI factors was 82%, as compared to 78% for patients with one factor, 50% for the high-intermediate-risk group, and 25% for the high-risk group. 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. The age-adjusted IPI within the good-prognosis group of ALK$^+$ lymphomas showed that the 5-year overall-survival rate was 94% for patients with no or one factor versus 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 and comparison with pediatric protocol should be made.

Considering the response rate and the survival of patients with ALK-positive lymphoma, consolidation with ASCT is not recommended if patient achieve a complete remission. For ALK-negative patients the debate is still open for patients with at least two IPI adverse prognostic factors who can be considered for prospective study. Guidelines for the treatment of ALCL in the absence of large prospective studies in adults are not easy. Two factors should be taken in consideration: ALK positivity and adverse prognostic factors. Dose and duration of treatment without radiotherapy have been adjusted in children according to their above-described prognostic factors. The same recommendations can be made for ALK$^+$ adult patients using the IPI as prognosis indicator, although the place of radiotherapy will remain controversial in localized stages. Comparison between CHOP and pediatric regimens could be of interest in the future.

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 (EBV). 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%.[22,23] The median overall survival is better in nasal compared to the extranasal cases in early (2.96 *vs.* 0.36 yrs) and late stage disease (0.8 *vs.* 0.28 yrs).[21] For patients with refractory or relapsed extranodal NK/T-cell lymphoma, L-Asparaginase-based regimens are very effective. In the last report on 20 patients ORR was 79% with 63% CR.[24,25] These results are challenging the 50% complete remission rate observed with chemotherapy alone in first line treatment in 48 patients.[23]

Enteropathy-type T-cell lymphoma

ETL 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 (eg, stomach

and colon). There are 2 histological groups of ETL 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*.[26] Of 24 patients treated with combination chemotherapy, ten (41%) achieved a complete remission and four (16%) a partial response. The actuarial 1-year and 5 year overall-survival rates were 39% and 20% respectively.[26]

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 gammadelta 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 2 studies:[27,28] 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.

Is more intensive conventional treatment better?

A possible impact of more intensive regimen has been described with the addition of etoposide to CHOP, or the use of MACOP-B. Report from the German high grade NHL group reported in two randomized studies a survival benefit of CHOP/14 or CHOEP/ 14 in young patients with a 3 year EFS (71% *vs.* 50%), p=0.01) as well as in patients aged over 60 years when etoposide was added to CHOP.[29,30,31] In only one GELA study there was a statistical advantage in patients between 60-70 years of ACVBP (47 T cell lymphomas) versus CHOP (49 T cell lymphomas).[32]

Comparison of various regimens more or less intensive at the MD Anderson failed to demonstrate a superiority of intensive treatment in 135 patients with a 3 year survival at 43% *vs*. 49% for intensive treatment (30 patients) including hyper CVAD.[33]

In two GELA phase 2 studies the same messages are found 34. Using prospectively an intensive combination regimen of Burkitt's lymphoma on 83 patients <60 years. The response rate was 52% with median EFS at 6 months. Obviously no improvement is seen with dose intense treatment. Moreover, the combination ESHAP in 58 patients >60yrs was associated with a very low CR rate of 33%. According to this study the use of anthracyclines is still recommended.

The most commonly used treatment for PTCL is CHOP or its variations. However, the

results with CHOP are inadequate and new approaches are needed. The activities of new drugs are being described in studies specifically for PTCL, and attempts at novel combinations are beginning.

Based on perceived high single agent activity in T-cell lymphomas, several groups have piloted gemcitabine-based regimens with promising results.[35-37]

Alemtuzumab is a monoclonal anti-CD52 antibody that has shown activity in PTCL. This monoclonal antibody has recently been added to CHOP for PTCL. The GITIL a prospective multicenter trial, combined alemtuzumab with CHOP for newly diagnosed PTCL.[38] Twenty-four consecutive patients were enrolled. CRs were seen in 17 of 24 (71%) patients. At a median follow-up of 16 months, 13 of the 24 patients (54%) were disease-free with an estimated 2-year OS and failure-free survival of 53% and 48%, respectively. Several Phase II with Alemtuzumab alone or in association with chemotherapy gave encouraging results for first line treatment, with manageable toxicities and is now tested in phase III study. Phase II study of CHOP with denileukin diftitox for 37 untreated PTCL showed clinical activity; the response rate was 89% with 78% complete remission, and there was little added toxicity over CHOP.[39]

Incorporation of new agents seems mandatory to make progress proteazome inhibitor (Velcade), Pralatrexate, Zanolimumab anti CD4 are some of the new agents which should be tested in combination with conventional chemotherapy. The addition of Bortezomib to ACVBP or the addition of rituximab to CHOP in AIL are being tested by GELA in phase II. Consequently, in Europe a task force had established different programs among cooperative groups testing new approaches and new drugs in close relation with pathologists.

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