



[haematologica reports]
2006;2(13):12-14

Conventional treatment of peripheral T-cell lymphomas: view from GELA and European perspective

C. GISSELBRECHT

*Hospital Saint Louis, Paris
France*

Patients with peripheral T cell lymphoma (PTCL) were treated until rituximab era with the same approach than B-cell lymphoma patients (BCL). In order to evaluate the impact of different therapeutic approaches, we looked at the results in different GELA prospective studies, which comprised over 900 T cell lymphoma patients since 1984. The reference arm was until now the intensive ACVBP regimen.¹ Patients were subsequently stratified according to age and prognostic factors. Conventional treatment was used for patients without adverse prognostic factors, whereas different dose intensive treatments including autologous bone marrow transplantation were used for patients with adverse prognostic factors. In the first step prognostic significance of immunophenotype was precised, using the LNH 87 study.² From 10/1987 to 3/1993, 1873 pts with aggressive non-Hodgkin's lymphomas (NHL) were eligible for review of both morphology and immunophenotyping. These included 278 pts with peripheral T cell lymphoma (15%) and 1595 (85%) pts with B cell lymphoma. At that time, according to the Kiel classification, T-cell NHL were classified as follow: T-zone, lymphoepithelioid, pleomorphic small cell, and angioimmunoblastic (32%), pleomorphic medium and large T cell (50%), anaplastic T (17%). Using the WHO classification, they were subsequently renamed, angioimmunoblastic, not other specified (NOS) and anaplastic T cell lymphoma. For B and T cell NHL, complete remission rate was respectively 63% and 54% ($p=0.004$). Five years overall (OS) and event free survival (EFS) were 52%, 45% and 42%, 33% for B cell and T cell lymphomas respectively ($p<0.001$, <0.0001). Comparison of the different subtypes of lymphoma was made. Survival of anaplastic T lymphoma was superior to other T and B

large cell NHL. However, survival of other T subtypes NHL was inferior to B lymphoma. In the 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.

Using the WHO classification, different histological subtypes were studied by pooling data from the different protocols LNH 87 and LNH 93. In 158 angioimmunoblastic lymphoma patients, when looking to those with immunoblastic pattern, it was not possible to isolate a group of better prognosis. We then studied the expression of Eber in 110 nodal NOS T-cell lymphomas and found an over expression in 53 patients. This was associated with an even poorer prognosis. In 48 patients with nasal type NK/T cell lymphoma, the CR rate was 50%, but localized stage seems to have a better prognosis when treated with intensive chemotherapy and radiotherapy. Anaplastic large cell lymphomas have a similar or better prognosis than B cell lymphomas and should be separated in prospective studies.³ Nevertheless, alk negative patients are less sensitive to treatment.

Among the different regimens used in protocols, in a subset analysis, ACVBP demonstrated a superiority to CHOP chemotherapy in a randomized study.⁴ A possible impact of more intensive regimen has been described with the addition of etoposide to CHOP,⁵ 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 as well as in patients aged over 60 years 6-7 with a diagnosis of aggressive lymphoma of B or T cell origin.

The role of autologous stem transplantation (ASCT) was studied among the GELA studies in a cohort of 330 CR patients less than 60 years who received

ASCT after induction ACBVP regimen.⁸ The histological slides showed: B aggressive NHL in 249 pts (75%), T NHL in 52 pts (15%) (including 23 T anaplastic) and non classified NHL in 29 pts. With a median follow-up of 6.5 years, the 5 yrs OS was 75±5% and DFS 67±5%. The univariate and multivariate analysis showed that aa-IPI score (0-1 vs. 2-3) had no prognostic value (5 yrs OS 76 vs 74%, p=0.48; DFS 65 vs 66%, p= 0.67) and only the following parameters had a significant (p < 0.05) adverse effect on survival: age, marrow involvement, no of extra-nodal sites ≥1 and histology (non anaplastic T vs. others). A pair-matched analysis from the same GELA data base with control patients treated with sequential chemotherapy only confirmed the poor prognosis of non anaplastic T NHL (5 yrs OS=44% (chemo) vs 49% (ASCT) p=0.87, DFS=38% vs. 45% p=0.89).⁹ Retrospective analysis from Nordic countries or from Spain reported better survival. In the report from GEL-TAMO, the 5 years overall and disease free survival for approximately 100 patients transplanted in first CR were 80% and 79% respectively.¹⁰ More recently, the Nordic group reported a specific PTCL phase II trial; where 6 courses of CHOEP/14 were followed by autologous transplant in first remission patients.¹¹ A lower pre transplant failure rate (30%) and a lower post transplant relapses (12%) was observed.

The main problem in all the studies, when excluding anaplastic lymphoma, was to achieve remission and none of the various regimens was really satisfactory. Analysis of other reports failed to find a better regimen in non-anaplastic lymphoma, even when more specific phase II are designed. In the LNH 98 studies; patients < 60 years were included in a phase II study evaluating an even more dose intense regimen; similar to the one used in children's Burkitt lymphoma. The complete response rate was 52% in 83 patients with median EFS of 6 months. An even more dramatic experience was observed in 58 patients over 60 years treated with ESHAP and cis retinoic acid, with a CR rate of 33%.

A serious need for new approaches or drugs emerged and prospective studies should stratify clearly non-anaplastic PTCL from BCL. Incorporation of new agents seems mandatory to make progress Proteazome inhibitor (Velcade), Gemcitabine (Gemzar), Alemtuzumab (MabCampath), anti-CD4 are some of the new agents which should be tested in combination with conventional chemotherapy. The addition of Bortezomid to ACVBP or the addition of rituximab to CHOP in AIL are being tested by GELA in phase II. Phase II with Alemtuzumab alone or in asso-

ciation with chemotherapy gave encouraging results for first line treatment, with manageable toxicities. A pilot study with alemtuzumab administered 30 mg three times per week in patients with relapsed or refractory PTCL showed that in 14 cases 3 patients achieved CR and 2 PR.¹² However, the infectious and haematological toxicities observed were important, leading to recommend dose reduction and the use in less advanced patients. Recently, data on the combination of CHOP plus 30 mg alemtuzumab were reported in 18 untreated patients with 11 CR. There was 12% CMV reactivation with manageable toxicity; this study demonstrated an acceptable safety profile and feasibility for CHOP-alemtuzumab.¹³

Other development will include in responding patients with initial bone marrow involvement consolidation with allogenic transplant with reduced intensity regimen. Reports from the Italian group were encouraging.¹⁴ All this need prospective studies with a precise identification of histological subtypes. Consequently in Europe a task force had established different programs among cooperative groups testing new approaches and new drugs. Well designed Phase III studies have been proposed. First, a proposal of the Nordic group to evaluate the impact of Alemtuzumab with CHOP through a large randomized study in young patients (< 65 years) and in elderly. For young patients after response they will be submitted to autologous transplantation. This study will start early 2007. Another study organized by the German group will randomize young patients between allograft with reduced intensity regimen and autograft after completion of chemotherapy.

All these efforts for clinical trials are made in close relation with pathologists to better define the characteristics of this difficult heterogeneous group of lymphoma for the discovery of more efficient targeted therapy.

References

1. Coiffier B, Brousse N, Peuchmaur M, et al. Peripheral T-cell lymphomas have a worse prognosis than B-cell lymphomas: a prospective study of 361 immunophenotyped patients treated with the LNH-84 regimen. The GELA (Groupe d'Etude des Lymphomes Aggressives). *Ann Oncol* 1990;1:45-50.
2. Gisselbrecht C, Gaulard P, Lepage E, et al. Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. *Groupe d'Etudes des Lymphomes de l'Adulte (GELA). Blood* 1998;92:76-82.
3. Tilly H, Gaulard P, Lepage E, et al. Primary anaplastic large-cell lymphoma in adults: clinical presentation, immunophenotype, and outcome. *Blood* 1997;90:3727-34.
4. Tilly H, Lepage E, Coiffier B, et al. Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. *Blood* 2003;102:4284-9.
5. Karakas T, Bergmann L, Stutte HJ, et al. Peripheral T-cell

C. Gisselbrecht

- lymphomas respond well to vincristine, adriamycin, cyclophosphamide, prednisone and etoposide (VACPE) and have a similar outcome as high-grade-B-cell lymphomas. *Leuk Lymph* 1996;24:121-9.
6. Pfreundschuh M, Trümper L, Kloess M et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. *Blood* 2004;104:634-41.
 7. Pfreundschuh M, Trümper L, Kloess M et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphoma: results of the NHL-B1 trial of the DSHBHL. *Blood* 2004;104:626-33.
 8. Mounier N, Gisselbrecht C, Briere J, et al. Prognostic factors in patients with aggressive non-Hodgkin's lymphoma treated by front-line autotransplantation after complete remission: a cohort study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 2004;22:2826-34.
 9. Mounier N, Gisselbrecht C, Briere J, et al. All aggressive lymphoma subtypes do not share similar outcome after front-line autotransplantation: a matched-control analysis by the Groupe d'Etude des Lymphomes de l'Adulte (GELA). *Ann Oncol* 2004;15:1790-7.
 10. Rodriguez J, Caballero MD, Gutiérrez A et al. High-dose chemotherapy and autologous stem cell transplantation in patients with peripheral T cell lymphoma: the GEL-TAMO experience. *Ann Oncol* 2003;14:1768-75.
 11. D'Amore F, Lautizen G, Jantunen E et al. High-dose therapy and autologous stem cell transplant as first line treatment in peripheral T cell lymphomas (PTCL). *Ann Oncol* 2005;106:abstr. 71
 12. Enblad G, Hagberg H, Erlanson M et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral-T cell lymphomas. *Blood* 2004; 103:2920-29-24.
 13. Gallamini A, Zaja F, Gargantini L et al. CHOP chemotherapy plus Campath-1H as first-line treatment in peripheral T-cell lymphoma (PTCL). *Blood* 2005;16:3345.
 14. Corradini P, Doderio A, Bregni M et al. Long-term follow-up of patients with peripheral T-cell lymphomas treated upfront with high-dose chemotherapy followed by autologous stem cell transplantation. *Leukemia* 2006; 20:1533-8.