

S-7-4

Treating B cell aggressive lymphomas in clinical trials, present and future: The GELA experience

Christian Gisselbrecht

GELA (Groupe d'Etude des Lymphomes de l'Adulte),
Hôpital Saint Louis, Paris

In the past twenty years, knowledge and treatment of aggressive lymphomas have undergone a continuous progress. In the early eighties our group GELA was already convinced that it was possible to improve the results of standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and run several randomized studies with a dose intensive regimen ACVBP administered every 14 days with a 2.5 fold increase of dose intensity when compared to CHOP.

Chemotherapy regimens for first line treatment

A superiority of ACVBP against m-BACOD was first observed in patient with high LDH level or disseminated stages (Tilly *et al* 2000). In patients with poor-risk aggressive lymphoma we conducted a randomized trial in which we compared the ACVBP chemotherapy regimen with standard CHOP (Tilly *et al* 2003). At three years, the event-free survival was 45 percent in the ACVBP group and 33 percent in the CHOP group ($p=0.004$). The conclusion was that ACVBP is obviously a more toxic regimen than CHOP but it prolongs survival in patients with poor-risk aggressive lymphoma. However, it should be restricted to patients in good performance status and under the age of 65 yr. The standard treatment for elderly patients with diffuse large-B-cell lymphoma was until recently still CHOP. Monoclonal antibodies an especially the anti CD 20 Rituximab did change the approach of treatment of diffuse large-B-cell lymphoma (Coiffier *et al* 2002). Previously untreated patients with diffuse large-B-cell lymphoma, 60 to 80 years old, were randomly assigned

to receive either eight cycles of CHOP every three weeks (197 patients) or eight cycles of CHOP plus rituximab given on day 1 of each cycle (202 patients). The rate of complete response was significantly higher in the group that received CHOP plus rituximab than in the group that received CHOP alone (76 percent vs. 63 percent, $P=0.005$). With a median follow-up of four years, event-free and overall survival times were significantly higher in the CHOP-plus rituximab group ($P<0.001$ and $P=0.007$, respectively). The addition of rituximab to standard CHOP chemotherapy significantly reduced the risk of treatment failure and death. The magnitude of the effect was especially observed in lymphoma patients overexpressing Bcl2 oncoprotein. (Mounier *et al* 2003). Clinically relevant toxicity was not significantly greater with CHOP plus rituximab. Updated results with a 4-year median follow-up confirm this benefit on EFS 53% vs. 35% and OS 62% vs 51% $p=0.008$.

Autologous stem cell transplantation

Four randomized trials (Haioun *et al* 1997, Gianni *et al* 1997, Santini *et al.* 1998 Milpied *et al.* 2004) provide positive information on the role of HDT in patients with adverse prognostic factors. In the GELA, LNH87-2 study, 1043 patients with various adverse prognostic factors were enrolled (Haioun *et al* 2000). Complete remission was achieved in 614 patients, who were then randomized to receive either intensive consolidation with HDT or sequential chemotherapy. There was no difference in overall survival or disease-free survival between the two consolidation arms. However, for the subgroup of 236 patients

with at least two adverse IPI factors, HDT had a significant advantage in terms of 8-year disease-free survival (55 % vs. 39 %, $p=0.01$) and in survival (64% vs. 39% respectively, $p=0.04$). Similar results have been reported recently by Milpied et al.

The absence of consensus on prognostic factors for patient treated with consolidate ASCT increases the difficulty to compare studies or to design clinical trials on maintenance therapy. We aimed to estimate the prognostic effect of clinical and biological variables by pooling the data from GELA trials on up-front ASCT (Mounier *et al* 2004).

Between 9/1987 and 9/1998, 330 CR patients less than 60 years received ASCT after induction ACBVP regimen, in 84 pts doxorubicin had been randomly substituted by mitoxantrone. There were 197 male and 133 female. Median age was similar at 43 years range [16;60]. Aa-IPI score was equal to 0 in 11%; 1 in 23%, 2 in 51% and 3 in 15%. 140 pts (43%) had more than one extra-nodal site and 69 pts had marrow involvement. The histological slides (centrally reviewed in 80%) showed: B aggressive NHL in 249 pts (75%), T NHL in 52 pts (including 23 T anaplastic) and non classified NHL in 29 pts. With a median follow-up of 6.5 yrs range [0.5; 12.1], the 5yr OS was $75 \pm 5\%$ and EFS $67 \pm 5\%$. The univariate analysis showed that aa-IPI (0-1 vs. 2-3) had no prognostic value (5yr OS 76 vs 74%, $p=0.48$; EFS 65 vs 66%, $p= 0.67$) and only the following parameters had a significant ($p < 0.05$) adverse effect: age ≥ 35 years old, marrow involvement, no of extra-nodal sites ≥ 1 , type of anthracyclin (mitoxantrone vs. doxorubicin), anthracycline dose-intensity below 85%, cyclophosphamide dose-intensity below 85% and histology (non Anaplastic T vs others).

A complementary pair-matched analysis from the same GELA data base (on histology, phenotype, extranodal sites, marrow and anthracycline) with control patients treated with ACVBP induction and sequential consolidation chemotherapy confirmed that consolidation with ASCT in patients with B cell lymphoma and at least 2 adverse prognostic factors is able to prevent relapses.

However, it did have an effect for the poor prognosis non anaplastic T NHL (5 years OS=44% (chemo) vs 49% (ASCT) $p=0.87$, EFS=38% vs 45% $p=0.89$).

More recently, we reported that ASCT was able to overcome the adverse prognostic factor of Bcl2 oncoprotein expression in 151 patients with B cell lymphoma with only one adverse IPI factor.(Morel *et al* 2004)

It seems probable that a group of poor prognostic patients exists which would benefit from HDT in first remission. For patients who fall into the IPI categories 'high -or 'high -intermediate' risk. improving the CR rate remains the major goal for these high risk patients. Incorporating new agents such, as anti-CD 20 is the natural trend and the easiest way to improve the results obtained with chemotherapy followed or not by consolidation with HDT. The use of maintenance therapy with rituximab is in debate for patients having already being exposed to this drug during induction and is presently under investigation. Entry into on-going trials should be encouraged, but patients in first remission should be offered the option of HDT.

Salvage treatment of aggressive lymphomas

What is clear from the available data is that patients who are not in complete remission at the beginning of the preparative regimen fare less well than those who have responded to conventional chemotherapy and are disease free (or nearly so) at that time. Furthermore, it is now evident that the procedure is not indicated for patients who have disease refractory to conventional salvage treatment. It is still unclear whether variations of the standard preparative regimen or bone-marrow purging can have a significant impact on outcome (Mounier and Gisselbrecht 1998). Recently several alternatives such as tandem transplants (Fitoussi et al. 1999) or early transplant (Bosly et al. 2001) have been explored without success by our group. There is no doubt that monoclonal antibodies integrated in the strategies of ASCT will open for the coming years new opportunities of improving the cure rate of lymphomas.

The best salvage chemotherapy regimen is still in debate. In the past years, the combination of ifosfamide, carboplatin and etoposide (ICE) was widely used by the MSKCC in 220 patients with relapse or refractory lymphomas (Moskowitz et al 1999). After three cycles and collection of peripheral blood stem cells they received an intensification followed by stem cell rescue. The response rate was 72%, and 81% of relapsed patients responded. The CR rate was 26% with 16% CR for patients with primary refractory disease. Cumulative 4 years survival was 40%. The addition of Rituximab to ICE regimen was evaluated in 45 patients with an 81% of response rate, complete remission in 55% including 31% CR in refractory patients. As there is no defining chemotherapy standard for relapsing patients and considering that the addition of Rituximab is likely to increase the response rate as in first line treatment, a comparison in clinical practice will be important for decision making. An international study CORAL, will first evaluate the efficacy and mobilization capacity of R-ICE when compared to R-DHAP and in responding patients submitted to transplant the impact of randomized maintenance treatment with Rituximab for one year.

From these experiences, it is clear that NHL remain sensitive to chemotherapy after relapses. However, the duration of response will depend not only on the quality of salvage regimen but on several factors: time to relapse, on/off therapy, prior treatment, stage, biological factors. Results should be interpreted with these parameters. In NHL large prospective studies with new combination chemotherapy with rituximab are necessary to establish some standard for salvage chemotherapy.

REFERENCES

Bosly A, *et al.* (1992). Bone marrow transplantation prolongs survival after relapse in aggressive lymphoma patients treated with the LNH84 regimen. *Journal of Clinical Oncology*, 10:1615-23.

Bosly A, *et al.* (2001). High-dose treatment with autologous stem cell transplantation versus sequential chemotherapy: the GELA experience. *European Journal of Haematology*, 66 : 3-7.

B. Coiffier *et al.* (1989). LNH84 regimen: a multicenter study of intensive chemotherapy in 737 patients with aggressive malignant lymphoma. *J. Clin. Oncol.*, Vol 7, n°8, 1018-26

B Coiffier *et al.* (2002). CHOP plus Rituximab with CHOP chemotherapy in elderly patients with diffuse large B-Cell lymphoma. A Groupe d'Etude des Lymphomes de l'Adulte study. *N Engl J Med*, 346 : 235-42.

Fitoussi O, *et al* (1999). Tandem Transplant of peripheral blood stem cells for patients with poor-prognosis Hodgkin's disease or non-Hodgkin's lymphoma. *Bone Marrow Transplantation*, 24:747-755.

Gisselbrecht C, *et al* (1994). Placebo controlled phase III trial of lenograstim in bone marrow transplantation. *The Lancet*, vol 343, 696-700.

Haïoun C, *et al.* (1997). Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor risk aggressive non Hodgkin's lymphoma: updated results of the prospective study LNH87-2. *J. Clin. Oncol*, 15:1131-37.

Haïoun C, *et al* (1998). High-dose therapy followed by stem cell transplantation in partial response after first-line induction therapy for aggressive non-Hodgkin's lymphoma. *Annals of Oncology*, 9 :S5-S8.

C Haïoun, *et al.* (2000). Survival benefit of high dose therapy in poor risk aggressive non-Hodgkin's lymphoma : Final analysis of the prospective LNH87-2 protocol – A Groupe d'Etude des Lymphomes de l'Adulte study. *J. Clin. Oncol*, 18 : 3025-3030.

Milpied NJ, *et al.* (2002). Frontline High-Dose Chemotherapy (HDC) with Autologous Stem Cell Transplantation vs Standard CHOP Regimen for Patients (PTS) (\leq 60 yo) with Non IPI High-Risk Intermediate or High-Grade Lymphomas (NHL). Final Results of a Randomized Trial by the GOELAMS. *Blood*, Vol 100, (11), November 16, abstract 675, 2002.

Moskowitz CH. *et al.* (1999). Ifosfamide, Carboplatin, and Etoposide: A Highly Effective Cytoreduction and Peripheral-Blood

- Progenitor-Cell Mobilization Regimen for Transplant-Eligible Patients With Non-Hodgkin's Lymphoma. *J. Clin. Oncol* : 17:3776-3785.
- Mounier N, *et al.* (1998). Conditioning regimens before transplantation in patients with aggressive non-Hodgkin's lymphoma. *Annals of Oncology*, 9:S15-S21.
- Mounier N, *et al.* (2000). Quality of life-adjusted survival analysis of high-dose therapy with autologous bone marrow transplantation versus sequential chemotherapy for patients with aggressive lymphoma in first complete remission. *Blood* 95:3687-3692.
- Mounier N, *et al.* (2004). Up-front auto transplantation (ASCT) in aggressive lymphomas overcomes the adverse predictive value of the IPI but not of the immuno-phenotype. *J. Clin Oncol*: in press
- Morel P, *et al.* (2004): Autologous stem cell transplantation as consolidation therapy for patients with low-intermediate risk large B-cell lymphoma and overexpression of bcl2 protein. Results of the GELA trial LNH 98-B2 Proc Am Soc Clin Oncol.
- Reyes F, *et al.* (2002). For the GELA. Superiority of Chemotherapy Alone with the ACVBP Regimen over Treatment with Three Cycles of CHOP Plus Radiotherapy in Low Risk Localized Aggressive Lymphoma: The LNH93-1 GELA Study. *Blood*, Vol 100, (11), November 16, abstract 343.
- Shipp AM, *et al.* (1999). International consensus conference on high-dose therapy with hematopoietic stem cell transplantation in aggressive non-Hodgkin's lymphomas: report of the jury. *Journal of Clinical Oncology*, 17:423-29.
- Tilly H, *et al.* (2000). For the Groupe d'Etude des Lymphomes de l'Adulte. Randomized comparison of ACVBP and m-BACOD in the treatment of patients with low-risk aggressive lymphoma : the LNH87-1 study. *J Clin Oncol*, 18 : 1309-1315.
- Tilly *et al.* (2003). Superiority of intensive conventional chemotherapy (ACVBP regimen) over standard CHOP for poor-prognosis aggressive non-Hodgkin's lymphoma, in press *Blood*.
- Velasquez WS, *et al.* (1988). Effective salvage therapy for lymphoma with cisplatin in combination with high-dose ara-C and dexamethasone (DHAP). *Blood*, 71:117-22.