Survival impact of rituximab combined with ACVBP and upfront consolidation autotransplantation in high-risk diffuse large B-cell lymphoma for GELA

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ABSTRACT

Background

As rituximab combined with CHOP improves complete remission and overall survival in diffuse large B-cell lymphoma, intensified chemotherapy followed by autologous stem-cell transplantation has also been advocated for high-risk patients. The aim of this study was to establish whether or not combining rituximab with high-dose chemotherapy and auto-transplantation also benefits patient survival.

Design and Methods

The LNH2003-3 study was a phase II trial including diffuse large B-cell lymphoma patients with 2 or 3 International Prognostic Index factors. They received four cycles of intensive biweekly chemotherapy with rituximab, doxorubicine, cyclophosphamide, vindesine, bleomycine, prednisolone (R-ACVBP) followed by auto-transplantation in responding patients. Two hundred and nine patients under 60 years of age were included in the study and 155 responding patients underwent auto-transplantation. In addition, a case-control study was performed by matching (1:1) 181 patients treated with R-ACVBP with ACVBP patients not given rituximab but submitted to auto-transplantation from the previous LNH1998-3 trial.

Results

With a median follow up of 45 months, 4-year progression-free survival and overall survival were estimated at 76% (CI: 69-81) and 78% (CI: 72-83), respectively. There was no difference between patients with 2 or 3 International Prognostic Index factors. Four year progression-free survival was significantly higher in R-ACVBP than ACVBP patients (74% *vs.* 58%; P=0.0005). There was also a significant increase in 4-year overall survival (76% *vs.* 68%; P=0.0494).

Conclusions

In high-risk diffuse large B-cell lymphoma patients, treatment with R-ACVBP followed by auto-transplantation results in a 78% 4-year overall survival which should be compared to other approaches. *(ClinicalTrials.gov identifier: NCT00144807)*

Key words: follicular lymphoma, autologous stem cell transplantation, rituximab.

Citation: Fitoussi O, Belhadj K, Mounier N, Parrens M, Tilly H, Salles G, Feugier P, Ferme C, Ysebaert L, Gabarre J, Herbrecht R, Janvier M, Van Den Neste E, Morschhauser F, Casasnovas O, Ghesquieres H, Anglaret B, Brechignac S, Haioun C, and Gisselbrecht C. Survival impact of rituximab combined with ACVBP and upfront consolidation autotransplantation in high risk diffuse large B-cell lymphoma for GELA. Haematologica 2011;96(8):1136-1143. doi:10.3324/haematol.2010.038109

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This work was presented in oral sessions at the American Society of Hematology annual meeting in San Francisco, California, December 5-12, 2008 and at the American Society of Clinical Oncology annual meeting in Orlando, Florida, May 29-June, 2, 2009.

Acknowledgments: the authors would like to thank all the pathologists involved in the study for pathological review, especially J Brière, T Molina, C Copie-Bergman and Philippe Gaulard. They also thank GELARC (Groupe d'Etude des Lymphomes de l'Adulte – Recherche Clinique) for the clinical management of this work, M. Fournier for statistical analysis and Mathilde Dreyfus for English Language use.

Funding: this work was supported by Programme Hospitalier de Recherche Clinique [PHRC-AOM 98-117], Ministry of Health. The study was also supported by grants from Roche and Amgen.

Manuscript received on December 1, 2010. Revised version arrived on April 4, 2011. Manuscript accepted on April 28, 2011.

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Introduction

Diffuse large B-cell lymphomas (DLBCL) are the most common lymphoid neoplasms. Although DLBCL patients can be cured with current chemotherapy regimens, this disease is heterogeneous and long-term survival is estimated at only 50% for high-risk patients.[1]

Before the rituximab era, high-dose therapy followed by autologous stem cell transplantation (ASCT) was a promising option for front-line therapy. Several randomized phase III studies have shown that this approach is beneficial for event-free survival (EFS), and is better than consolidation chemotherapy for high-risk patients under 60 years of age with 2 or 3 age-adjusted International Prognostic Index (aa-IPI) factors.[2] However, the benefit of consolidation ASCT has been the subject of intense controversy and has mostly been verified for good responders after induction chemotherapy.[3-9] At the present time, in the rituximab era, the addition of rituximab to various CHOP-like chemotherapies in phase III trials has been shown to improve patient outcome.[10-13] Data for patients with 3 or more IPI factors treated with R-CHOP from the British Columbia registry suggest a 4-year progression-free survival (PFS) at 53%,[1] in agreement with the 58% 3-year PFS seen in several German randomized studies.[14] However, very few prospective studies have been reported on large series focusing on DLBCL with 2 or 3 aa-IPI factors with a long follow up[15,16] in a population under 60 years of age.

In 2003, the Groupe d'Etude des Lymphomes de l'Adulte (GELA) initiated the LNH2003-3 study to evaluate the efficacy of rituximab combined with high-dose CHOP-like chemotherapy (R-ACVBP) followed by consolidation ASCT in an approach similar to prior studies.[7,17] ACVBP was described in our previous studies as being superior to the CHOP regimen.[18,19] The present case-control study aims to establish whether combining rituximab with the ACVBP regimen also benefits patient outcome. Cases were part of the LNH2003-3 study population and controls were chosen from the population of our previous LNH1998-3 study, in which we evaluated the same ACVBP regimen but without rituximab.[17] The aim of this non-randomized phase II study was to set a baseline for subsequent study in poor prognosis DLBCL.

Design and Methods

Cases (n=210) included in the present LNH2003-3 study included the participants in a prospective multicenter phase II trial conducted by the GELA between January 2004 and December 2005. One patient dropped out of the study leaving 209 active participants (Table 1). Approval for these trials was obtained from our institutional review board. Participants gave written informed consent in accordance with the declaration of Helsinki. The trial was entered on the National Institutes of Health website (NCT00144807).

LNH-2003-3 study design

The LNH-2003-3B trial was an open label, multicenter phase II trial. The primary end point was the rate of complete response (CR) plus the unconfirmed complete response (CRu) rate (i.e. CR^+CRu) after completion of R-ACVBP treatment.[20] Calculation of sample size was based on this end point. We expected a CR^+CRu rate of 70% with R-ACVBP, and calculated that to detect a rate of more than 60% a total of at least 150 patients would provide 80% power, at an overall 5% two-sided significance level. Sixty patients were added in a subsidiary study conducted to evaluate the effectiveness of R-ACVBP combined with pegfilgrastim instead of the filgrastim given in LNH-2003-3B. The secondary end points were toxicity, overall survival (OS) and progression-free survival (PFS).

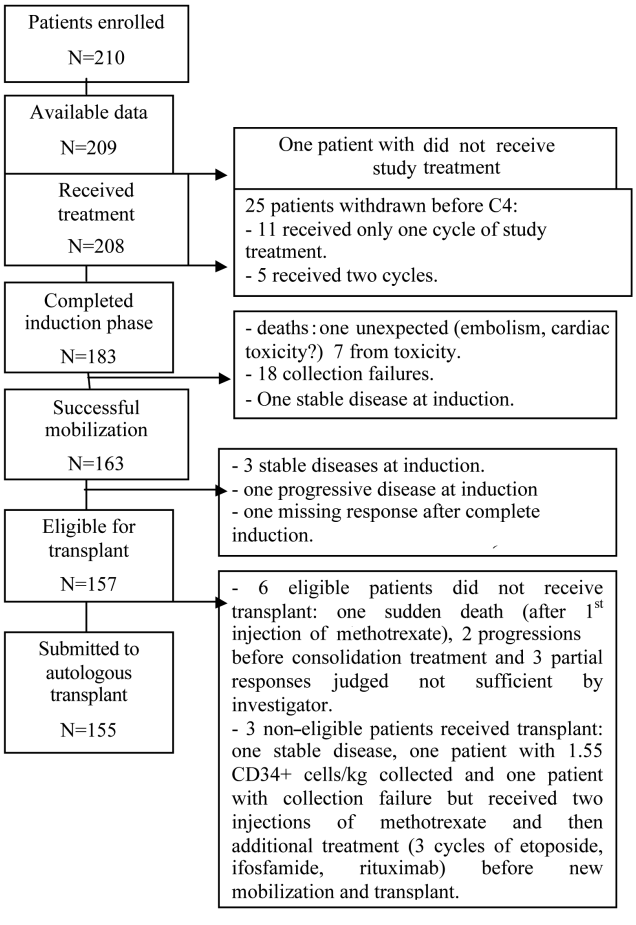
Patient selection

Patients eligible for the present LNH2003-3 study were 18-60 years old and had newly diagnosed $CD20^+$ diffuse large B-cell lymphomas (DLBCL), diagnosed according to the World Health Organization (WHO) classification. Patients were also required to have an age-adjusted International Prognostic Index (aa-IPI) score of 2 or 3. Exclusion criteria included: other lymphoma diagnoses (e.g. Burkitt's lymphoma or transformed previously diagnosed low-grade lymphoma), central nervous system or meningeal involvement by lymphoma, contraindication to anthracyclines (i.e. cardiac insufficiency, left ventricular ejection fraction <50% or recent myocardial infarct), corticosteroid treatment, serious psychosis, sepsis, uncontrolled diabetes, neutrophils less than 1.5×10^9/L, platelets less than 100×10^9/L considered unrelated to lymphoma, renal insufficiency (serum creatinine greater than 150 μM/L), hepatic disorders (total bilirubin greater than 30 mM/L or transaminases greater than 2.5 UNL), positive serology for HIV or hepatitis B, previous organ transplant, and pregnancy.

Treatment

Patients underwent induction chemotherapy consisting of four

Table 1. Consort diagram of the whole cohort.



cycles of the following R-ACVBP regimen: rituximab (375 mg/m^2), doxorubicin (75 mg/m^2) and cyclophosphamide (1,200 mg/m^2) given intravenously (IV) on day 1, vindesine (2 mg/m^2) given on days 1 and 5, bleomycin (10 mg) given IV on days 1 and 5, prednisone (60 mg/m^2) given orally on days 1 through to 5, and intrathecal methotrexate (15 mg) on day 2. There was an interval of 14 days between each of the four cycles, with systematic G-CSF (filgrastim support from days 6 to 13 or pegfilgrastim (6 mg) at day 3). The patients were also given prophylactic treatment with cotrimoxazole and acyclovir. Leukapheresis was performed after the 3rd and/or 4th cycle (weeks 6 and/or 8). The target dose of collected CD34$^+$ cells was 2×10^6 cells/kg. Patient disease status was then re-assessed and those who experienced a 50% response or more (i.e. at least a partial response) were given two courses of high-dose methotrexate (3g/m^2) followed by leucovorin rescue treatment. There was an interval of 14 days between each of the two cycles. Patients then received the BEAM conditioning regimen, followed by ASCT (week 13). BEAM consisted of carmustine (300 mg/m^2) day 1, etoposide (200 mg/m^2) days 1-4, aracytine (continuous infusion of 200 mg/m^2) days 1-4, melphalan (140 mg/m^2) day 5.

Radiotherapy was not part of the treatment plan for any patient and this includes those with mediastinal bulky involvement.

Staging and follow up

Morphology and immunophenotype were reviewed by 2 independent pathologists from the GELA team and lymphoma subtypes were classified according to the WHO classification.[21] Disagreement over individual cases was resolved using a two-headed microscope.

The stage of the disease was evaluated by physical examination, computerized tomography (CT) scan of the chest and abdomen, cerebrospinal fluid examination, bone marrow biopsy, and other investigations, depending on the clinical symptoms. Patients were staged according to the Ann Arbor classification. Eastern Cooperative Oncology Group (ECOG) performance status was assessed and lactate dehydrogenase (LDH) was expressed as the maximum/normal value ratio. No routine molecular biology procedures or dynamic imaging methods, such as PET scan, were used.

Tumor responses were assessed after the four cycles of R-ACVBP. Response to treatment was classified according to International Workshop Criteria (IWC1999).[20] After response classification, patients had a complete clinical examination every three months for the first year and every six months for the next five years. A CT scan was performed twice a year.

Patient-control matching

Cases, i.e. the present R-ACVBP LNH2003-3 study population, were matched with ACVBP patients selected from our previous LNH1998-3 trial. Details regarding the design and results of the latter trial have already been published.[17] Briefly, in this phase III trial, patients (n=476) were randomized for induction chemotherapy with either ACE (adriamycin, cyclophosphamide and etoposide) or ACVBP, followed by consolidation with ASCT. In a second randomization, the effects of maintenance rituximab post ASCT were compared with observation. To obtain a homogeneous control group for the present case-control analysis, we only selected LNH1998-3 patients who were in the ACVBP arm without rituximab post ASCT. They were fully matched (1:1) with the LNH2003-3 study population for aa-IPI factors, gender, and age, and were all adjusted for duration of follow up.

Statistical methods

Case report forms collected in the participating centers were sent to the GELA centralized database and keyed-in twice for verification. Outliers and erroneous values were routinely checked. Queries and on-site monitoring were used for final validation.

Patients' results were analyzed on an intent-to-treat basis. Progression-free survival was defined as the time from randomization to first progression, relapse and either death from any cause or last follow up. Overall survival was defined as the time from randomization to either the last follow up or death from any cause. Estimates of survival were calculated according to the Kaplan-Meier method and tested with the log rank test. Categorical covariates were compared by the χ^2 test or Fisher's exact test. Differences between the results of comparative tests were considered significant if the two-sided P value was less than 0.05. All statistical analyses were performed using the Statistical Application System software (SAS, version 9.1.3, SAS Institute, Cary, NC, USA).

Results

Clinical characteristics

Two hundred and ten eligible patients were enrolled in the study between January 2004 and December 2005. Their clinical characteristics were confirmed by pathological review in 194 patients (92%). One patient had a subtype of Burkitt's lymphoma.

No data were available for one patient who was, therefore, excluded and present results concern 209 patients. Median age was 49 years (range 18-60). Forty-six patients (22%) presented with an aa-IPI of 3 and 120 (58%) with an aa-IPI of 3-5. One hundred and ninety-four (93%) had elevated LDH and 112 (54%) more than one extranodal site. Patients' demographic and baseline disease characteristics are listed in Table 2. Among patients with bulky disease, 31 had mediastinal involvement.

Treatment delivery and toxicity

As one patient died of septic shock before beginning treatment, only 208 patients had induction chemotherapy

Table 2. Patients' characteristics (n=209).

	N (%)
Age median, (range)	49 (18-60)
Sex male/female	107/102
Ann Arbor stage,	
II bulky	6 (3)
III	35(17)
IV	168 (80)
B symptoms	112 (54)
LDH >1N,	194 (93)
>1 extranodal localization	112 (54)
Bulky disease >10 cm	83 (40)
Mediastinal bulky	31(15)
Bone marrow involvement	40 (19)
aa-IPI score	
1 (low-intermediate)	6 (3)
2 (high-intermediate)	157 (75)
3 (high)	46 (22)
Revised IPI score	
1-2 (good)	88(42)
3-5 (poor)	120 (58)

LDH: lactate dehydrogenase; 1N: normal level; aa-IPI: age-adjusted International Prognostic Index.

(Table 1). In all, 780 cycles of R-ACVBP were administered to the 208 patients. The median dose intensity of doxorubicin and cyclophosphamide was 90% (range [41%; 114%]) and 90% (range [41%; 105%]), respectively. Only 4 patients with mediastinal involvement received radiotherapy on a residual mass, apart from those who experienced progression.

One hundred and eighty-three patients (87%) were given all four planned cycles. Of the 25 patients who withdrew before the 4th cycle, 11 only completed one cycle, 5 completed two cycles, and 9 completed three cycles. In most cases (n=18), chemotherapy was stopped due to lymphoma progression. There were 9 deaths (4.3%) during therapy. Five deaths (3 from sepsis, one from hemorrhage, and one from heart failure) may have been treatment related. For the remaining 4, causes of death were: sudden death at home (n=2), cardiac infraction (n=1) and multiorgan failure (n=1). The toxicity profile during induction is shown by the worst grade reported *per* patient in Table 3. Toxicities were mainly hematologic and infectious.

Overall, 162 patients experienced successful stem cell mobilization. However, only 155 received ASCT due to an insufficient tumor response in 6 patients and sudden death in one patient. There were no transplant-related deaths during aplasia. During the total treatment period, investigators reported 151 infectious adverse events. Most of these were due to bacterial sepsis, but 3 cases of oral herpes, 3 of extensive herpes, and 4 of *pneumocystis* were also recorded.

Table 3. Frequency of grade 3-4 toxicities (all cycles, n=208 patients).

	N. of patients	(%)
Leukopenia	198	(95)
Anemia	123	(59)
Thrombopenia	91	(44)
Mucositis	63	(30)
Infection	129	(62)
Heart	3	(1)
Vascular	8	(4)
Digestive	7	(3)
Pulmonary	9	(4)
Treatment - related mortality	9	(4.3)

Table 4. Responses to treatment (n=208).

Response	Response after R-ACVBP N	(%)	Response after ASCT N	(%)
CR	37	(18)	84	(40)
CRu	89	(43)	69	(33)
PR	50	(24)	22	(11)
SD	4	(2)	4	(2)
PD	1	(0)	6	(3)
Death	9	(4)	9	(4)
Premature withdrawal/ not evaluated	18	(9)	14	(7)

CR: complete response; CRu: unconfirmed CR; PR: partial response; SD: stable disease; PD: progressive disease.

Outcome

Of the 208 patients who underwent induction therapy, 126 (60%) showed a complete response (CR+CRu) to induction with R-ACVBP. Fifty (24%) showed a partial response, leading to an overall response rate of 84% (176 patients). Table 4 shows that CR+CRu increased to 73% after ASCT.

With a median follow up of 45 months, 31 patients experienced progression or relapse. Overall, 44 patients died. Of these, 20 died without documented progression, including patients in partial response, 9 died from toxicity during initial treatment, and 11 died thereafter not directly related to lymphoma (4 with infections, 2 from another cancer, and 5 from concurrent illness, other treatments or other unspecified reasons).

Four-year progression-free and overall survival were estimated at 76% (CI: 69-81) and 78% (CI: 72-83), respectively.

Figure 1 shows no significant difference between aa-IPI score 2 or 3 for progression-free survival (77% and 73%) or overall survival (82% and 74%), respectively. There was no difference between revised-IPI in 88 low- *vs.* 120 high-risk patients. In the latter subset, defined by 3-5 adverse prognostic factors, 4-year progression-free survival and overall survival were estimated at 72% (CI 63-79) and 75% (CI 66-82), respectively. Neither dose intensity nor pre-transplant status (CR *vs.* Cru *vs.* PR) had a significant effect on progression-free and overall survival; there was no difference for mediastinal lymphoma (P=0.1). For patients who underwent ASCT, 3-year progression-free survival was 85% with no difference between aa-IPI score 2 or 3.

Pair-matched analysis

A case-control study was performed by matching the present R-ACVBP patients (n=208) with ACVBP patients selected from the LNH1998-3 trial (n=241). The CR+CRu rate was 63%. Due to control factors, 181 controls treated with ACVBP were fully matched (1:1) with 181 cases treated with R-ACVBP in the present LNH2003-3B study.

As expected from the matching method, there was no significant difference in main clinical characteristics between the case and control groups of patients (Table 5). However, with the same median follow up of 45 months, the 4-year progression-free survival estimate was higher for the R-ACVBP-treated patients: 74% (CI 67-80) *vs.* 58% for the controls (CI 51-65); P=0.0005. Four-year overall survival was estimated at 76% (CI 69-82) *vs.* 68% (CI 60-74) (P=0.0494). The increase in 4-year overall survival was significant for the whole population but especially for patients who underwent ASCT (88% *vs.* 77%; P=0.0264) (Figure 2).

Discussion

Despite the striking advances in the treatment of diffuse large B-cell lymphoma, some patients still have a poor prognosis and long-term survival is only estimated to be 50% for high-risk patients.[1] Biomarkers are currently being investigated to improve understanding of the biological basis of treatment outcome. For the moment, the clinical factors included in the IPI will probably prove to be surrogate markers of the intrinsic molecular heterogeneity of the disease. Our main objective here was to determine

whether or not rituximab, delivered with first-line high-dose chemotherapy and followed by ASCT, could improve outcome in young patients presenting with 2 or 3 aa-IPI factors.

These results for R-ACVBP induction and consolidation ASCT suggest that this treatment has a major impact, as the complete remission rate increased to 73%, and 4-year survival estimates were impressive (76% for PFS and 78% for OS). The incidence of acute toxicity was as expected, with less than 5% of treatment-related mortality.[6] However, with intensive chemotherapy and ASCT, late toxicities may compromise results in a long-term follow up. Selection of patients who may benefit from this approach is crucial. Compared to retrospective data, the present results suggest that the impact of treatment increases with the severity of the disease: thus, in low-risk patients, 4-year overall survival was estimated at 82% in the present study but (the most important present finding) these good results persisted for high-risk patients with a 4-year overall survival estimated at 75%. More recent data from the addition of 1,062 patients, representing a general population aged between 19-80 years treated in randomized German studies, found that standard IPI could still be used. In their studies using R-CHOP, a challenging 79% 3-year progression-free survival was observed for patients with only 2 IPI factors and who were older than in our study.[14] Nevertheless, in our younger population, there

Table 5. Pair-matched analysis: characteristics of the case and control populations.

	LNH1998-3B (control)		LNH2003-3B (case)		All	
	N	(%)	N	(%)	N	(%)
Sex						
Female	81	(45)	81	(45)	162	(45)
Male	100	(55)	100	(55)	200	(55)
Age (years)						
≤45 yr	75	(41)	75	(41)	150	(41)
>45 yr	106	(59)	106	(59)	212	(59)
Performance status (ECOG)						
0-1	126	(70)	126	(70)	252	(70)
2-4	55	(30)	55	(30)	110	(30)
Ann Arbor Stage						
I-II	5	(3)	5	(3)	10	(3)
III-IV	176	(97)	176	(97)	352	(97)
Bulky disease > 10 cm	76	(42)	80	(47)	156	(43)
LDH	5	(3)	5	(3)	10	(3)
≤normal						
>normal	176	(97)	176	(97)	352	(97)
Age - adjusted IPI	136	(75)	136	(75)	272	(75)
2						
3	45	(25)	45	(25)	90	(25)
Total	181	(100)	181	(100)	362	(100)

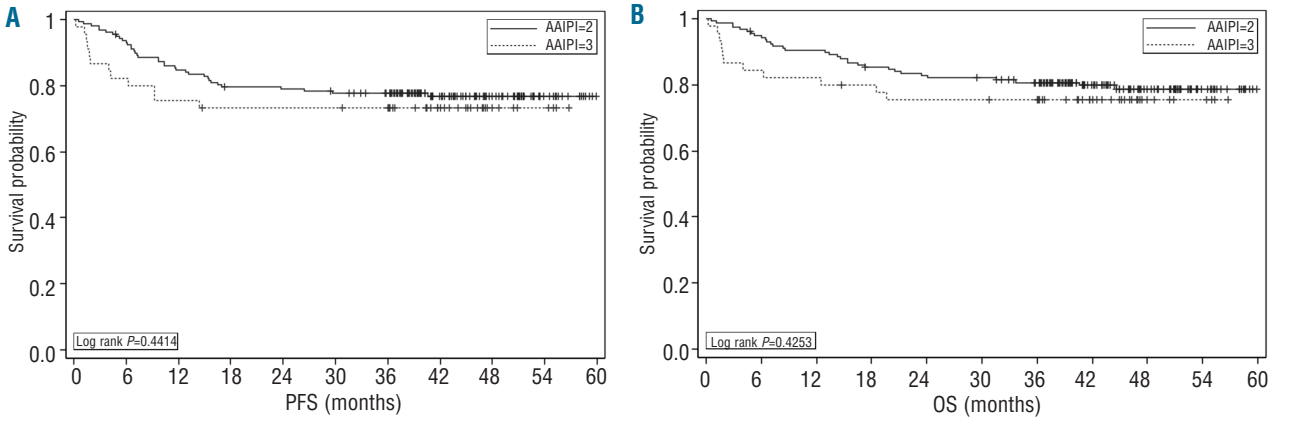


Figure 1. PFS (A) and OS (B) according to the age-adjusted International Prognostic Index (aa-IPI).

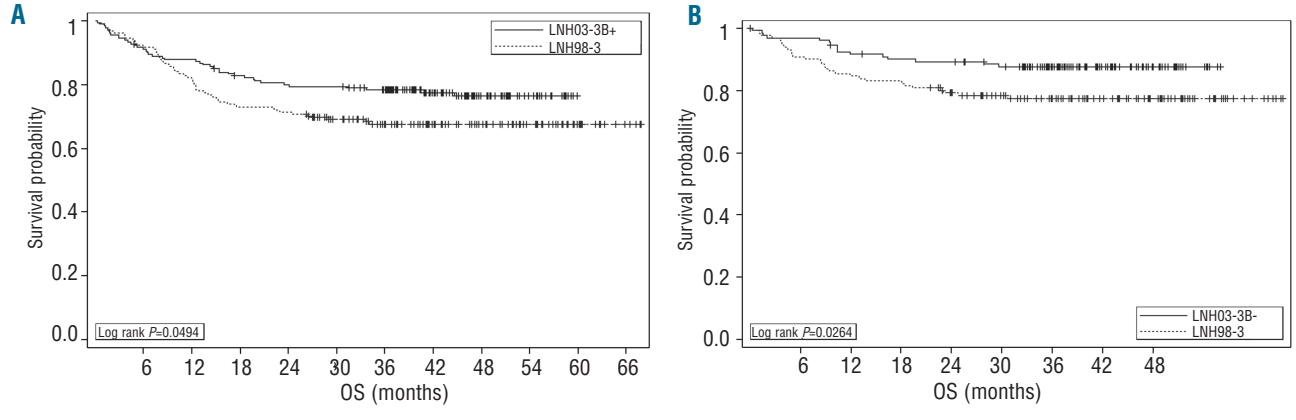


Figure 2. OS for R-ACVBP *vs.* ACVBP. (A) Whole population. (B) Patients given ASCT.

Table 6. Treatment of diffuse large B-cell lymphoma with 2-3 aaIPI factors with high-dose therapy and rituximab.

	N	Median age in years (range)	aa IPI score	Treatment	TRM (%)	4 yr OS	4 yr PFS
Tarella 2007[15]	112	48 (18-65)	all score	R-HDS maps ASCT ± RT	4.5%	76% (CI 68-85%)	73% (CI 64-81%)
			2 = 74 (66%)			82%	68%
			3 = 38 (34%)			67%	78%
Vitolo 2009[16]	97	47 (19-60)	all score	R-HDC ASCT BEAM	5%	80% (CI 71-88%)	73% (CI 63-82%)
			2 = 50 (53%)	± RT		87%	80%
			3 = 44 (47%)			73%	64%
Present Study	209	49 (18-60)	all score	R-ACVBP BEAM ASCT	4.3%	78% (CI 72-83%)	76% (CI 69-81%)
			2 = 157 (75%)	No RT		82%	77%
			3 = 46 (22%)			74%	73%

Rituximab – HDC: high-dose chemotherapy – R-HDS: rituximab, high-dose sequential - BEAM: carmustine, etoposide, cytarabin, melphalan – ASCT: autologous stem cell transplantation – aa IPI : age-adjusted International Prognostic Index – RT: radiotherapy.

was a high progression-free survival rate without any difference between patients with 2 or 3 IPI factors whether or not the revised IPI formulation was used.[1] In addition, the present case-control study showed an estimated increase in survival of at least 15% compared to the previous study of ACVBP induction without rituximab. Similar findings in the same young population were reported by Vitolo *et al.* who compared the results for rituximab plus HDT to those for a historical cohort treated with the same HDT but without rituximab: 4-year overall survival was 80% for R-HDT *vs*. 54% for HDT alone (P=0.002)[16] (Table 6). However, for the 44 score 3 aa-IPI patients, 4-year failure free survival was 64% compared with 80% for score 2. Similar results were observed with high-dose sequential chemotherapy with a 62% 5-year event free survival for 38 patients with 3 aa-IPI factors.[15]

Intensification of chemotherapy is still a matter of debate in the rituximab era. Cunningham *et al.* recently reported the interim results of a phase III trial including 1,080 patients aged under or over 60 years of age, in which they compared the effects of standard R-CHOP given every three weeks (R-CHOP21) to those of R-CHOP intensification, i.e. R-CHOP14 every two weeks.[22] The complete remission rate was disappointing; only 47% in both treatment arms. Similar findings were reported by the GELA for R-CHOP21 *vs*. R-CHOP14 in an interim analysis of the phase III LNH 2003-6 trial. Delarue *et al.* reported 2-year event-free survival estimates of 61% *vs.* 48% (P=0.11) in patients over 60 years of age with aa-IPI 2 or 3.[23] Nevertheless, R-ACVBP was recently compared to R-CHOP21 in a population of DLCBL under 60 years of age with one adverse prognostic factor. The authors reported a superiority of R-ACVBP over R-CHOP for progression-free and overall survival.[24] This intensive regimen is obviously a part of the strategy and should play a key role in the reported results. Other authors published encouraging results for more intensified chemotherapy plus rituximab, using the same approach as ours (i.e. ASCT support)[15,16] or infusional chemotherapy.[25] In a series of 112 DLBCL patients, Tarella *et al.* reported impressive results for the combination of rituximab and high-dose sequential chemotherapy delivered with multiple ASCT support: a complete remission rate of 80% and an estimated 4-year overall survival of 76%[15] (Table 6). Within the framework of rituximab and intensified chemotherapy, Wilson *et al.* did not use ASCT but administered rituximab and infusional dose-adjusted chemotherapy to 72 patients[25] including, however, 20 patients over 60 years of age. They reported a complete remission rate of 94% but an estimated 5-year overall survival of only 55% in high-risk patients, in accordance with these patients' R-IPI. Whether or not more intensive treatment is still of benefit in the rituximab era remains a subject of debate, but considering these good results a more precise definition of criteria of patients eligible for such an approach should be put forward.

In particular, the end point criteria used make all these results questionable. Given the need to further refine the quality of tumor response, positron emission tomography (PET) using [18F]-Fluoro-2-Deoxy-D-Glucose, which was first introduced for the management of lymphomas in the early 1990s, is now recognized as a standard tool for the staging and assessment of response to treatment of Hodgkin's and non-Hodgkin's lymphomas.[26,27] Significant benefit was reported in patients who achieved a true complete remission after chemotherapy and before ASCT compared with those who experienced a less satisfactory response, thus showing the importance of the quality of response after induction treatment for long-term prognosis.[28] However, neither the present study nor previous control trials used PET imaging, making it extremely difficult to generalize results.

As salvage treatment is difficult to administer to patients pre-treated with rituximab, whose global response rate was only 50%,[29] recent studies investigated residual PET avidity after two cycles of front-line chemotherapy. Retrospective studies have shown the predictive value of tumor response assessed by PET imaging for early identification of patients at high risk of treatment failure.[30-32] However, this predictive value is still controversial and other authors found a high probability of false positives.[33] In contrast, there is some agreement for considering that PET-negative patients are at less risk of relapse after initial treatment. Whether or not the criteria used to interpret PET imaging are a reliable guide to therapy, especially for decision-making concerning transplant, is currently being

evaluated in our ongoing trial of R-ACVBP *vs.* R-CHOP for poor prognosis DLBCL patients.[34,35]

While we await the availability of microarray genome-wide approaches to predict non-Hodgkin's lymphoma treatment outcome, and the introduction of new drugs,[36] the challenge today is to increase the efficacy of the induction regimen. On the one hand, the impact of rituximab combined with high-dose chemotherapy regimens needs confirmation by a prospective randomized study comparing R-CHOP. On the other, the strict evaluation of response by PET imaging as a guide to subsequent therapeutic decisions deserves further investigation. We believe that the present R-ACVBP regimen constitutes a good basis for further trials based on a risk-adapted strategy.

Appendix

The following clinicians were active participants in the LNH 2003-03 study:

C Allard, M Andre, B Audhuy, M Azagury, F Bauduer, M Blanc, D Bordessoule, A Bosly, K Bouabdallah, F Boue, D Bron, S Castaigne, B Christian, B Coiffier, J Collignon, B De Prijck, R Delarue, A Delmer, H Demuynck, P Fenaux, M Fleck, C Fruchart, I Galliard, S Glaisner, F Jardin, E Jourdan, A Kentos, N Ketterer, C Kulekci, S Lampertz, P Lederlin, S Lepretre, G Lepeu, M Macro, M Maerevoet, C Martin, F Offner, H Orfeuvre, P Pierre, C Recher, C Salanoubat, R Schots, C Sebban, A Stamatoullas, C Thieblemont, A Thyss, X Vallantin, A Van Hoof.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

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