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Background: Overexpression of B-cell lymphoma 2 (bcl-2) protein is a simple biological adverse prognostic factor that could delimit the poor prognosis population candidate for improvement with high-dose therapy and autologous stem-cell transplantation (ASCT) in diffuse large B-cell lymphoma (DLBCL). Therefore, we conducted a risk-adapted phase II study with ASCT as consolidation therapy in low-intermediate risk (LIR) International Prognostic Index patients aged ≤60 years with bcl-2 overexpression (bcl-2+).

Patients and methods: Induction chemotherapy consisted of four courses of adriamycin, cyclophosphamide, vindesine, bleomycin, prednisone, once every 2 weeks. Responding bcl-2+ patients received ASCT as consolidation, and those without bcl-2 overexpression (bcl-2−) conventional chemotherapy. Three hundred and sixteen LIR patients with DLBCL, aged between 18 and 60 years, were included. Of these, 177 (56%) were bcl-2+ and 139 (44%) bcl-2−.

Results: Complete response rates after induction chemotherapy were similar in bcl-2+ and bcl-2− patients (74% versus 78%). Estimated 2-year event-free survival and disease-free survival for the bcl-2+ subgroup were 79% and 87%, for bcl-2− 84% and 92% and for the whole series 81% and 90%, respectively.

Conclusions: These results demonstrate that taking into account biological characteristics in prospective multicenter trials allow successful adjustment of treatment and indicate that ASCT may counteract the adverse prognostic value of bcl-2 overexpression in responding LIR patients.

Key words: autologous stem-cell transplantation, bcl-2, high-dose chemotherapy, lymphoma
to improve event-free survival (EFS) or overall survival (OS) by using autologous stem-cell transplantation (ASCT) as an intensive consolidation therapy in the first-line treatment [10]. The impact of ASCT in these trials is still debated, but improved outcome was observed in the most severe patients, defined by the presence of at least two adverse aa-IPI prognostic factors [11, 12]. Therefore, the assessment of a simple biological prognostic factor in patients with one adverse IPI factor could delimit the poor prognosis population candidate for improvement with high-dose therapy and ASCT.

We designed in 1998 the LNH98-2 trial for LIR patients with DLBCL to assess prospectively the efficacy of risk-adapted ASCT as consolidation therapy, only in patients with bcl-2 overexpression. bcl-2 expression was centrally determined in patients with DLBCL histology was confirmed by the pathology review for improvement with high-dose therapy and ASCT.

It was designed with a two-sided test, a type I error of 0.05 and a type II error of 0.10. The induction regimen consisted of four courses of ACVBP (75 mg doxorubicin/m² of body surface and 1200 mg cyclophosphamide/m² on day 1, 2 mg vindesine/m² and 10 mg bleomycin on days 1 and 5, given i.v. and 60 mg oral prednisone/m² on days 1–5) given at 2-week intervals [14] with granulocyte colony-stimulating factor. bcl-2 patients underwent peripheral blood stem-cell collection after the fourth cycle of ACVBP. In case of complete or partial response ≥50%, ASCT was carried out between days 80 and 90. The conditioning regimen (N-CBV) comprised the following given i.v.: 45 mg mitoxantrone/m² on day −7, 1.5 g cyclophosphamide/m² and 250 mg etoposide/m² on days −6 to −4 and 300 mg carmustine/m² on day −3. bcl-2 patients received sequential consolidation consisting of two cycles of melphalan (3 g/m²) plus leucovorin rescue, four cycles of etoposide (300 mg/m²) and ifosfamide (1500 mg/m²) and two cycles of cytarabine (100 mg/m²) s.c. for 4 days given at 2-week intervals.

patients and methods

study design

This trial was a nonrandomized study. Its main objective was to establish whether or not ASCT significantly improves by 15% the 2-year EFS rate reported in the LNH932 trial for bcl-2− patients with DLBCL at LIR treated with adriamycin, cyclophosphamide, vindesine, bleomycin, prednisone, (ACVBP) followed by conventional consolidation. If this goal was reached, the EFS between bcl-2− and bcl-2+ patients should not be different. At the time of the design of the study, retrospective analyses of patients treated in Groupe d’Etude des Lymphomes de l’Adulte (GELA) protocols with bcl-2 overexpression had shown for LIR a 71% 2-year EFS rate which was different from the 82% 2-year EFS rate of LIR bcl-2+ patients. The trial was designed with a two-sided test, a type I error of 0.05 and a type II error of 0.10. It required the inclusion of 110 LIR patients with bcl-2 overexpression who had received ASCT and therefore of 300 patients, followed at least 1 year.

patients

Patients aged 18–60 years were required to have newly diagnosed DLBCL and to present with only one of the following adverse prognostic factors: elevated LDH level, performance status of more than 1 and Ann Arbor stage III/IV. Inclusion criteria: positive serology for human immunodeficiency virus and human T lymphotropic virus type I, transformation of previous indolent lymphoma, primary cerebral cancer, previous organ transplantation, concomitant or previous cancer (except in situ cervical carcinoma), liver or kidney failure and cardiac contraindication to doxorubicin. The trial was approved by our institution’s Ethics Committee and all patients gave written informed consent to participate. From October 1999 to May 2003, 354 patients aged 18–60 years with newly diagnosed DLBCL were registered before treatment at the central office of the GELA by 107 participating centers (see Appendix 1). After pathology review, 316 patients were eligible for the analysis. Initial staging procedures included physical examination, computed tomography scan of chest, abdomen and pelvis, bone marrow biopsy and cerebrospinal fluid examination.

histology and bcl-2 staining

Immediately after patient central registration at the GELA office, preprinted express mail package was sent to each patient’s initial pathologist, and paraffin blocks or slides were collected at the GELA Institute of Pathology. An independent review of each case by two pathologists as well as the score for bcl-2 were obtained within 40 days of registration to allow stem-cell harvest before the end of the induction regimen in bcl-2− patients. The diagnosis of DLBCL was based on the presence of at least two adverse aa-IPI prognostic factors [11, 12]. Therefore, the assessment of a simple biological prognostic factor in patients with one adverse IPI factor could delimit the poor prognosis population candidate for improvement with high-dose therapy and ASCT.

We designed in 1998 the LNH98-2 trial for LIR patients with DLBCL to assess prospectively the efficacy of risk-adapted ASCT as consolidation therapy, only in patients with bcl-2 overexpression. bcl-2 expression was centrally determined in patients with DLBCL histology was not confirmed by the pathology review for improvement with high-dose therapy and ASCT.

bcl-2 immunostaining was carried out as previously described [4]. Briefly, after microwave pretreatment (three cycles of 5 min in 0.01 M citrate buffer, pH 7.6), deparaffinized tissue sections were stained with the bcl-2-124 mAb (Dako), using an indirect immunoperoxidase method and an automated immunostainer (Ventana Medical Systems, Tucson, AZ). Expression of bcl-2 was evaluated independently by two observers (PG and JB). The few disagreements were resolved by joint review using a multiheaded microscope. Cases were considered positive (bcl-2+) if 50% or more of the tumor cells were stained according to previous series [3, 7] which showed a significant association between outcome and bcl-2 expression. Cases with a lower percentage of bcl-2-stained tumor cells were classified as bcl-2−. Tumors without any staining including that of small reactive lymphocytes which normally act as internal positive control were scored as noninformative. Finally, 38 of 354 patients were not eligible because bcl-2 staining was not available for 11 patients, not informative for five, and DLBCL histology was not confirmed by the pathology review for 22 patients with the following: follicular lymphoma: seven cases, Hodgkin’s lymphoma: three cases, mantle cell lymphoma and Burkitt’s lymphoma: two cases each and marginal zone lymphoma, lymphoblastic lymphoma, peripheral T-cell lymphoma: one case each and five cases unclassifiable.

treatment

The induction regimen consisted of four courses of ACVBP (75 mg doxorubicin/m² of body surface and 1200 mg cyclophosphamide/m² on day 1, 2 mg vindesine/m² and 10 mg bleomycin on days 1 and 5, given i.v. and 60 mg oral prednisone/m² on days 1–5) given at 2-week intervals [14] with granulocyte colony-stimulating factor. bcl-2 patients underwent peripheral blood stem-cell collection after the fourth cycle of ACVBP. In case of complete or partial response ≥50%, ASCT was carried out between days 80 and 90. The conditioning regimen (N-CBV) comprised the following given i.v.: 45 mg mitoxantrone/m² on day −7, 1.5 g cyclophosphamide/m² and 250 mg etoposide/m² on days −6 to −4 and 300 mg carmustine/m² on day −3. bcl-2 patients received sequential consolidation consisting of two cycles of melphalan (3 g/m²) plus leucovorin rescue, four cycles of etoposide (300 mg/m²) and ifosfamide (1500 mg/m²) and two cycles of cytarabine (100 mg/m²) s.c. for 4 days given at 2-week intervals.

patient management

No dose adjustment of chemotherapy was planned according to toxicity but the courses were postponed until white blood cell and platelet counts increased to >1 x 10⁹/L and 100 x 10⁹/L, respectively. ASCT was carried out in a single isolated room, according to the protocol for supportive care at each participating center. At least 2 x 10⁹ CD34+ cells/kg were reinfused.

evaluation of responses

Responses were evaluated 1 month after completion of four cycles of ACVBP and at the end of treatment according to the International Workshop criteria [15]. A complete response was defined as the disappearance of all clinical evidence of disease and of the radiologic abnormalities observed at diagnosis. An unconfirmed complete response was defined as a complete response with some persistent radiologic...
abnormalities, which had to have regressed in size by at least 75% the sum of the products with the greatest diameters of each tumor. A partial response was defined as the regression of tumor sizes of ≥50% and stable disease as regression of <50%. Stable disease and progressive disease (growth of the initial lesion by ≥25% or appearance of a new lesion during treatment) were considered as primary failure. Follow-up procedures included physical examination every 3 months for the first 2 years after the end of therapy, then every 6 months for 3 years and then annually.

statistical analyses
Analyses were all conducted on an intention-to-treat basis. Patient characteristics and CR rates were compared with the chi-square and Fisher's exact tests [16]. EFS was measured from the date of inclusion to disease progression or relapse or death from any cause. Disease-free survival (DFS) was measured from the date of remission to either relapse or death from any cause. OS was measured from the date of inclusion to death from any cause. Survival functions were estimated by the Kaplan–Meier method [17] and compared with log-rank test. Differences were considered significant if the two-sided P value was <0.05. Analyses were carried out with SAS software (version 8.0; SAS Institute, Cary, NC).

results
initial characteristics
Patient's characteristics are described in Table 1. Immunostaining disclosed high bcl-2 expression in 177 patients (56%, bcl-2+) and low expression in 139 patients (44%, bcl-2−). There was no difference between the initial characteristics of bcl-2+ and bcl-2− patients, except for more advanced age in the bcl-2+ group (Table 1).

induction treatment and response
At the end of the induction regimen, the rates of complete response (complete or complete unconfirmed response) were 74% in bcl-2− patients and 78% in bcl-2+ patients. Overall response rates to the ACVBP regimen were 93% and 97%, respectively (Table 1). Fourteen of the 177 bcl-2− patients (7%) and 5 of the 139 bcl-2− patients (3%) were failures. Two deaths of toxicity occurred among bcl-2− patients (Table 1). Hematologic toxicity was mainly grade 4 neutropenia of short duration similar to that previously described [18] with a 9% incidence of infections graded >2.

consolidation with ASCT and outcome of bcl-2− patients
Among the 163 patients who responded to treatment, 24 (14%) did not undergo ASCT. Two of these patients progressed, and three died of toxicity before ASCT (two of pneumocystis carinii pneumonia and one patient of cytomegalovirus pneumonia). Five others could not undergo ASCT because of severe toxicity [cardiac and hepatic (1), pulmonary and hepatic (one each) and hematologic (2)]. For the remaining 14 patients, ASCT could not be carried out because of failure of mobilization in seven patients and refusal by seven. By the stopping date, 9 of those 24 patients had progressed and five of them died after progression. ASCT was delivered to 139 patients. The median count of CD34+ positive cells obtained from mobilized peripheral blood after the last cycle of induction chemotherapy was 6.6 × 10⁶ CD34+ cells/kg. The median times to absolute neutrophil count recovery were 12 days to >0.5 × 10⁹/l (range 8–49) and 13 days to >1.0 × 10⁹/l (range 9–110). The median time to absolute platelet count recovery to >50 × 10⁹/l was 11 days (range 4–54). The median hospital stay was 23 days. One patient died of multiorgan failure. There were 32 cases of grade 3 or 4 infection. The other cases of grade 3 or 4 toxicity were as follows: liver (two), lung (one), gastrointestinal (five) and mucositis (61). One patient developed shingles. One month after the completion of treatment, the rate of complete response was 87%.

consolidation with chemotherapy and outcome of bcl-2− patients
Consolidation chemotherapy was not completed in 24 (17%) of the 134 patients who responded because of the physician's decision (six), patient refusal (one), severe toxicity (11, one

Table 1. Initial characteristics and response at the end of induction chemotherapy for the 316 diffuse large B-cell lymphoma patients with low-intermediate risk

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>bcl-2+ (177 patients)</th>
<th>bcl-2− (139 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>68 (38)</td>
<td>67 (48)</td>
</tr>
<tr>
<td>Male</td>
<td>109 (62)</td>
<td>72 (52)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>95 (53)</td>
<td>99 (71)</td>
</tr>
<tr>
<td>≥50 years</td>
<td>82 (47)</td>
<td>40 (29)</td>
</tr>
<tr>
<td>Adverse characteristic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance status (WHO)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>3 (2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Ann Arbor stage III or IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>120 (71)</td>
<td>101 (74)</td>
</tr>
<tr>
<td>LDH above normal value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>120 (71)</td>
<td>101 (74)</td>
</tr>
<tr>
<td>2 or more</td>
<td>50 (39)</td>
<td>37 (26)</td>
</tr>
<tr>
<td>Number of extranodal sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>136 (80)</td>
<td>119 (87)</td>
</tr>
<tr>
<td>2 or more</td>
<td>34 (20)</td>
<td>19 (13)</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>144 (84)</td>
<td>116 (85)</td>
</tr>
<tr>
<td>Present</td>
<td>27 (16)</td>
<td>20 (15)</td>
</tr>
<tr>
<td>Bulky disease (&gt;10 cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>119 (73)</td>
<td>101 (76)</td>
</tr>
<tr>
<td>Present</td>
<td>43 (27)</td>
<td>32 (24)</td>
</tr>
<tr>
<td>Response at the end of induction chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>53 (30)</td>
<td>42 (30)</td>
</tr>
<tr>
<td>Complete unconfirmed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial &gt;50%</td>
<td>77 (44)</td>
<td>66 (48)</td>
</tr>
<tr>
<td>Stable</td>
<td>33 (19)</td>
<td>26 (19)</td>
</tr>
<tr>
<td>Disease progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

The difference was significant, P = 0.001.

*Data were missing for some patients with Ann Arbor stage III or IV disease.

bcl-2, B-cell lymphoma 2; WHO, World Health Organization; LDH, lactate dehydrogenase.
patient died at 2 months) or disease progression (six). Five additional patients progressed later. Four of the 11 patients who progressed without completing consolidation had died at the stopping date. One hundred and ten patients received conventional consolidation. At the end of treatment, the rate of complete response for the 134 patients was 96%.

**survival**

Analyses were carried out with a median follow-up of 34 months for surviving patients (range 10–57 months). Estimated 2-year EFS, DFS and OS were 81%, 89% and 90%, respectively, for the 316 patients. In bcl-2+ patients, 2-year EFS, DFS and OS were 79% ± 3%, 87% ± 3% and 84% ± 3%, respectively. In bcl-2- patients, the corresponding estimates were 84% ± 3%, 92% ± 2% and 96% ± 2% (Figures 1 and 2). There was no difference for EFS and DFS for the two groups.

At the time of the analysis, disease progression was observed in 23 bcl-2+ patients who received ASCT between 5 and 38 months after the initiation of treatment (median 10 months). Despite salvage therapy including rituximab (15 patients) or allogeneic stem-cell transplantation (one patient), 13 patients died. In addition to the patient who died of multiorgan failure, three other patients died without lymphoma progression, two of them of cancer at 27 and 34 months and one died of an unknown cause at 55 months. Twelve bcl-2- patients relapsed after consolidation, and four had died.

**discussion**

The present analysis indicates that it is feasible, in a large-scale multicenter trial, to take prospectively into account a biological characteristic to modulate the treatment. Thus, we report here 81% and 90% 2-year EFS and OS estimates, respectively. Such results have never been achieved with chemotherapy either alone [1, 19] or combined with rituximab [20] in all LIR patients. As far as we know, the LNH98-B2 trial was the first study in which a treatment strategy based on a biological characteristic of the tumor, determined in a central place, was prospectively evaluated in a multicenter setting. The number of patients and the diversity of the 107 study centers provide a broadly representative population. bcl-2 staining was carried out here in a single institution to prevent heterogeneous results due to different immunohistochemical procedures. In addition, bcl-2 expression was scored independently by two expert hematopathologists to avoid a possible lack of interobserver reproducibility during this large trial. Tumors were considered positive when at least 50% of tumor cells expressed bcl-2 because bcl-2 protein expression defined by this cut-off point retained a prognostic value independent of the IPI [4, 8] and germinal center B-cell (GCB) phenotype [8]. Furthermore, this threshold was easy to use as most of the bcl-2+ cases exhibited strong cytoplasmic staining in virtually all tumor cells [3, 4]. Thus, we observed an overexpression of the bcl-2 protein in 56% of LIR DLBCL patients. This finding agreed with the 52%–66% frequencies previously reported with appropriate antigen retrieval procedures and a similar cut-off value of 50% [4, 8]. Expected difficulties in getting rapidly a centrally determined bcl-2 expression and the high number of bcl-2- favorable patients unnecessary for the objective of the trial lead us to design a nonrandomized study.

The LIR subgroup defined by the IPI is not a narrow population because it accounts for one-third of all aggressive non-Hodgkin’s lymphoma aged 60 years or less. Pooling LIR and high-intermediate risk patients, Barrans et al. assessed the prognosis uncertainty of these patients. bcl-2 expression and the GCB phenotype among bcl-2- patients significantly improve risk stratification. Despite controversies [7, 20–24], it has been reported that high bcl-2 protein expression was more frequently observed in the GCB subgroup than in the non-GCB subgroup of DLBCL [8, 24], with various molecular mechanisms in the two subgroups [22, 24]. The optimal combination of IPI and molecular characteristics for predicting the outcome of DLBCL patients is still controversial because of conflicting results [7, 8, 23, 25, 26]. For LIR DLBCL, our present study confirmed that bcl-2 protein expression is a useful and simple tool in a large multicenter trial, despite the heterogeneity of the mechanisms underlying this expression [27].

The previously reported difference of EFS between bcl-2+ and bcl-2- patients was not observed in the present series. Primary failures before the time of ASCT were more frequent in bcl-2+ patients.
patients compared with bcl-2− patients. Biological studies should now focus on the identification of patients who require additional early treatment intervention. The response rate after induction treatment was, however, similar in both groups; thus, early intensive chemotherapy with ASCT as consolidation therapy may, at least in part, counteract some biological mechanisms of drug resistance associated with bcl-2 expression. Although only 16% of bcl-2− patients relapsed after ASCT, 56% of these relapsing patients had died at the time of analysis with a poor efficacy of salvage treatment after ASCT. Thus, the difference in OS between bcl-2− and bcl-2+ patients was still observed. Since the present median follow-up was 34 months, it is unlikely that a longer follow-up would alter our 2-year estimates. Before the rituximab era, several reports indicated that chemotherapy dose rate could have important implications in the treatment of curable lymphomas. Moreover, a dose-adjustment strategy resulted in dose escalations of the adaptable etoposide, prednisone, oncovin, cyclophosphamide, adriamycin, regimen [dose-adjusted (DA)-etoposide, prednisone, oncovin, cyclophosphamide, adriamycin (EPOCH)] in most patients. The lack of association between the IPI and outcome indicated that DA-EPOCH has a cell-kill profile that is different from that of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-based regimens [9], bcl-2+ patients treated with DA-EPOCH, however, retained a lower progression-free survival (50%) compared with bcl-2− patients (82%).

Previous reports showed that bcl-2 overexpression was no more a prognostic marker in patients 60 years of age or older with any IPI risk, treated with rituximab, cyclophosphamide, adriamycin, oncovin, prednisone [28]. This observation supports a down-regulation of bcl-2 through an inhibition of the NF-kB and extracellular signal-regulated kinase1/2–mitogen-activated protein kinase pathways by rituximab [2]. Given the favorable safety profile of rituximab, the relevance of any results from high-dose chemotherapy in patients with high bcl-2 protein expression may be considered questionable. However, 3-year EFS of LIR DLBCL patients aged <60 years (either bcl-2− or bl-2+, since the expression was not addressed in this study) and treated with rituximab in combination with CHOP-like regimen was estimated 74%–76% only [20]. This outcome emphasizes the presence of a subpopulation of patients who do not respond to rituximab or acquire resistance [2]. The 79% 2-year EFS reported in bcl-2+ patients may support a role for intensive chemotherapy regimen with ASCT beside rituximab. The effectiveness of the combination of rituximab and high-dose chemotherapy has been debated. On one hand, the coadministration of rituximab and high-dose chemotherapy may compromise the participation of the host immune system in killing rituximab-treated cells [29]. On the other hand, Haioun et al. [30] have shown recently that early and brief rituximab maintenance outperforms the period of ASCT may prolong remission status in high-risk patients treated with rituximab and the comparative advantages of ASCT and rituximab for counteracting molecular mechanisms of drug resistance [31], in order to ascertain whether rituximab avoids the need for ASCT or improves its results.

In summary, for clinical practice, the present report demonstrates that in a large multicenter study, it is feasible to take biological knowledge into account to adjust treatment. It indicates that ASCT, in combination with a better identification of high-risk patients, may be useful in bcl-2+ patients at LIR for reducing relapse rate.

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Appendix 1


The following members of the GELA carried out the pathologic review: J. Brière, J. Bosq, J. F. Emile, B. Fabiani, P. Gaulard and T. Petrella.


