Malignant Lymphomas

Estimating the impact of rituximab on bcl-2-associated resistance to CHOP in elderly patients with diffuse large B-cell lymphoma

Rituximab plus CHOP (R-CHOP) has been proven to increase overall survival in aggressive bcl-2-positive lymphoma patients. Using competing risk analysis, we studied the long-term impact of this treatment in patients from a GELA trial: R-CHOP prevented from progression or relapse in both bcl-2-positive and bcl-2-negative patients without increasing the risk of death in complete remission.

Haematologica 2006; 91:715-716
(*http://www.haematologica.org/journal/2006/05/715.html*)

Although rituximab is widely used in the treatment of B-cell non-Hodgkin's lymphomas, the mechanism of action of this chimeric anti-CD20 IgG1 remain unclear. Rituximab modulates cellular and molecular signal transduction pathways, in particular, the downregulation of Bcl-2 and Bcl-xl expression, leading to chemosensitization.[1-3] However, information regarding the long-term impact of bcl-2 expression is scarce and does not take into account the competing risk between relapse and age-associated mortality. We investigated whether rituximab reduces bcl-2-associated CHOP treatment failure, by comparing bcl-2 expression to long-term clinical outcome in 292 patients with diffuse large B-cell lymphoma.[4,5] The 292 patients included in this analysis had confirmed DLBCL with suitable slides for Bcl-2 immunostaining and came from the previously published LNH-98-5 trial. The LNH-98-5 trial showed that the combination of eight cycles of rituximab and CHOP (R-CHOP) was more effective than eight cycles of CHOP in 399 DLBCL patients aged 60-80 years old.[5] Cases were considered bcl-2-positive when at least 50% of tumor cells expressed the protein.

To allow direct comparison with the data published by Feugier *et al*. from the 5-year update of the LNH-98-5 trial, the stopping date of the present analysis was set at April 1, 2004.[6] We controlled for the effects of prognostic factors on outcome using the competing risk formulation of Cox model regression which investigates the effect of the explanatory variables on different competing events, such as progression, relapse, or death, during course of a disease.[7]

With a median follow-up of 5 years (range [3.9-5.7]), 140 patients had died. The 5-year survival estimate for all patients was 52±6%. Survival outcomes were significantly better for the 155 patients treated with R-CHOP than for the 132 patients treated with CHOP (overall survival): 57±8% vs. 45±9%, p=0.02; event-free survival: 47±9% vs. 25±8%, p<0.0001).

As shown in Figure 1, among the 193 bcl-2-positive patients R-CHOP treatment was associated with a significantly better overall survival than CHOP (56±9% vs. 42±11%, p=0.01), whereas in the 99 bcl-2-negative patients there was no difference according to treatment (58±14% vs. 52±15%, p=0.6). Likewise, the effect on event-free survival of adding rituximab to CHOP treatment was marked among bcl-2-positive patients but limited in the smaller group of bcl-2-negative patients (bcl-2-positive: 46±11% vs. 21 ± 9%, p=0.0001; bcl-2-negative: 49±13% vs. 31±13%, p=0.06). These results suggest that rituximab prevents bcl-2-associated CHOP failure in bcl-2-positive patients. However, during this long follow-up, some deaths could have been due to age-associated morbidity and the apparent lack of treatment effects in bcl-2-negative patients aged 60-80 may be due to the return of the underlying mortality hazard (e.g. cardio-vascular events).

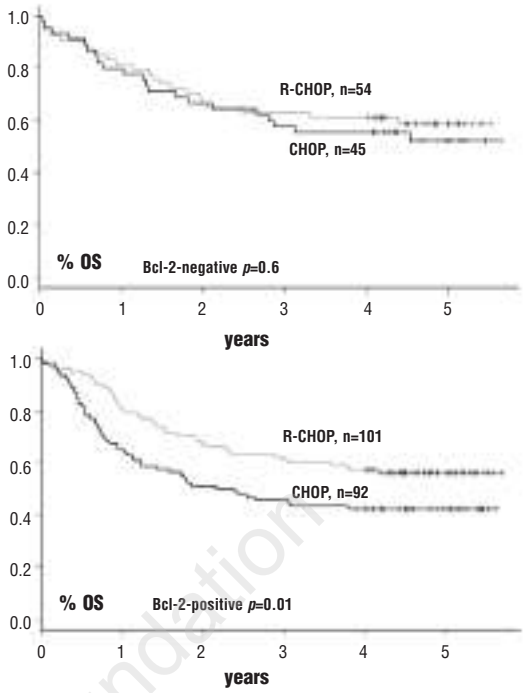

Figure 1. Kaplan-Meier survival estimates according to treatment and bcl-2 protein expression in 292 lymphoma patients. Overall, 140 patients have died: 43 bcl-2-negative patients (22/54 treated with R-CHOP and 21/45 treated with CHOP) and 97 bcl-2-positive patients (44/101 treated with R-CHOP and 53/92 treated with CHOP).

To further analyze this possibly confounding factor, the impact of rituximab on patients' outcome was evaluated by analyzing the competing risks between progression or relapse (n=141) and death without progression or relapse (n=40). Multivariate analysis (Table 1) demonstrated that age-adjusted International Prognostic Index (aa-IPI) did not have a predictive value in bcl-2-negative patients. Moreover, in this subset of patients with a good prognosis, age above 70 played the major role in predicting the risk of death (relative risk, RR=1.8, p=0.002). On the other hand, in bcl-2-positive patients, the impact of aa-IPI on the risk of death was highly significant but age had no prognostic value. Of particular interest, rituximab significantly decreased the risk of progression or relapse in both bcl-2-positive (RR=2.6, p=0.001) and bcl-2 negative (RR=2.2, p=0.01) patients, leading to a major difference in progression-free survival (bcl-2-positive: 56±9% vs. 25±8%, p=0.0001; bcl-2-negative: 59±13% vs. 33±13%, p=0.02). After relapse, aa-IPI 2-3 (RR= 2.9, p<0.0001) and bcl-2 overexpression (RR= 1.5, p=0.03) still had significant effects on the risk of death whereas front-line rituximab and age above 70 did not.

The present updated analysis adds details to our previ-

Table 1. Relative risk estimates (95% confidence interval) for competing risks according to bcl-2 expression in 292 lymphoma patients. Significant relative risks are shown in bold.

	Progression or relapse (n=141)	*Death without progression or relapse (n=40)*
bcl-2-negative (n=99)	n=42/99	n=16/99
aa-IPI 2-3 vs. 0-1	1.2, [0.7;2.2] *p*=0.6	1.3, [0.5;3.4] *p*=0.4
Age >70 yrs vs. ≤70 yrs	0.9, [0.7;1.2] *p*=0.4	**1.8, [1.2;2.5] *p*=0.002**
CHOP vs. R-CHOP	**2.2, [1.2;4.0] *p*=0.01**	0.6, [0.2;1.8] *p*=0.4
bcl-2-positive (n=193)	n=99/193	n=24/193
aa-IPI 2-3 vs. 0-1	**1.5, [1.1;2.3] *p*=0.03**	**3.1, [1.1;8.3] *p*=0.02**
Age >70 yrs vs. ≤70 yrs	1.0, [0.8;1.2] *p*=0.9	1.3, [0.9;1.9] *p*=0.07
CHOP vs. R-CHOP	**2.6, [1.7;3.7] *p*<0.001**	0.9, [0.4;2.0] *p*=0.8

aa-IPI: age-adjusted International Prognostic Index.

ous work.[4] In terms of progression/relapse both bcl-2-positive and negative patients benefit from rituximab but the benefit is greater in the bcl-2-positive ones. As regards mortality, bcl-2-positive patients fail to respond to salvage treatment after relapse. For these two reasons, the impact of rituximab on overall survival is greater in bcl-2-positive patients than in bcl-2-negative ones. In addition, the competing risks analysis failed to demonstrate that rituximab had an impact on the risk of death without progression or relapse but confirmed the significant impact of age (i.e. return of the underlying mortality hazard), suggesting that the long-term toxicity of R-CHOP is no greater than that of CHOP.[6,8]

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Funding: this study was supported in part by research funding from Hoffmann-La Roche to the GELA.

Acknowledgments: the authors thank Olive Eccleston for editing the English.

Key words: lymphoma, rituximab, bcl-2, survival analysis.

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