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Prognostic role of gender in diffuse large B-cell lymphoma treated with rituximab containing regimens: a Fondazione Italiana Linfomi/Grupo de Estudos em Moléstias Onco-Hematológicas retrospective study

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Abstract

Male gender was recently reported as an adverse prognostic factor in patients with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). We conducted a retrospective study of adult patients with DLBCL initially treated with rituximab containing regimens between 2001 and 2007. Patients were identified from the clinical archives of 43 Italian and Brazilian institutions. The principal endpoint was overall survival (OS). One thousand seven hundred and ninety-three patients were fully eligible for the study. Thirty-eight percent, 27%, 22% and 12% of patients had an International Prognostic Index (IPI) score of 0–1, 2, 3 and 4–5, respectively; 53% were males. After a median follow-up of 36 months (1–106), the 5-year OS was 76% (95% confidence interval 74–78%). In univariate analysis, male gender was an adverse prognostic factor with a hazard ratio of 1.52. In multivariate analysis, when adjusted by IPI, again gender maintained its prognostic relevance, showing an independent additive effect. In conclusion, in patients with DLBCL treated with rituximab containing regimens, gender may increase the predictive power of the IPI. Based on these results, given possible differences in blood clearance of rituximab between males and females, the benefit of higher doses of rituximab in males should be explored.

Keywords: Gender, IPI prognosis, diffuse large B-cell lymphoma, overall survival, retrospective study

Introduction

Diffuse large B-cell lymphoma (DLBCL) represents the most common subtype of non-Hodgkin lymphoma (NHL), accounting for approximately 35% of all newly diagnosed cases and more than 80% of aggressive lymphomas [1].

Based on the improved efficacy of rituximab containing regimens compared with conventional chemotherapy alone, immunochemotherapy (ICT) currently represents the standard of care for most patients with DLBCL. This has resulted in an overall improvement of patient outcome that is confirmed for all ages and risk groups [2–4]. While the efficacy of ICT is largely acknowledged, patients with DLBCL still have a variable clinical course, and the creation of more sensitive prognostic tools is warranted.

The International Prognostic Index (IPI) score is currently used to assess individual risk and to define treatment strategy [5]. Although developed and largely validated for defining prognosis in patients with DLBCL who were treated in the pre-rituximab era, the IPI has been recently confirmed as a valid prognostic tool also for

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patients treated with ICT [6,7]. In particular, Ziepert *et al.* demonstrated that the addition of rituximab to chemotherapy could improve treatment outcome for all patients as a whole and within each IPI group, keeping unchanged the relative risk estimates of single IPI factors and their rank in patients treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) [6].

Research is currently ongoing to define novel prognostic factors that may improve individual risk estimates. These studies include both clinical and biological factors. There is clear evidence that DLBCL subtypes are different diseases with distinct oncogenic pathways. Gene expression profiling models have defined molecular subgroups of DLBCL, termed germinal B cell (GB) and activated B cell (ABC), with different prognoses [8–10].

Although frequently neglected, gender is emerging as a relevant prognostic factor [11]. In particular, some data suggest that male gender is associated with a poorer outcome in patients with Hodgkin lymphoma [12], follicular lymphoma [13], chronic lymphocytic leukemia [14] and aggressive lymphoma [11,15]. Of note, male gender has been postulated as an adverse prognostic factor in patients with DLBCL who receive rituximab [16–18]. More recently, a subset analysis of the CORAL study (Collaborative Trial in Relapsed Aggressive Lymphoma) showed that maintenance treatment with rituximab after autologous stem cell transplant had a more beneficial role in terms of event-free survival in females than in males [19]. If the role of gender were to be confirmed as independent from the IPI, this could be extremely useful for planning new therapeutic strategies, taking into account the necessity of establishing the optimal dosage of rituximab in males with DLBCL. For this reason, we decided to conduct a retrospective study of a large series of patients with DLBCL who were treated upfront with R-CHOP or R-CHOP-like regimens.

Design and methods

This observational, retrospective and multicenter study was conducted in compliance with the Declaration of Helsinki and was accepted by the appropriate research ethics committees. Histologically confirmed cases of newly diagnosed DLBCL according to the World Health Organization classification were identified from the clinical archives of centers participating in the FIL (Fondazione Italiana Linfomi) and the Brazilian GEMOH (Grupo de Estudos em Moléstias Onco-Hematológicas) groups.

Patient selection was based on the following criteria: diagnosis of DLBCL was made between 1 January 2001 and 31 December 2007; age was between 18 years and 80 years; all stages of disease and all IPI risk groups were allowed; and human immunodeficiency virus (HIV) positive patients were excluded. To be included in the study, patients should have been treated with frontline R-CHOP or R-CHOP-like regimens (i.e. anthracycline containing regimens); also included were patients who were treated with frontline high-dose regimens followed by autologous stem cell support if they received ICT as part of their initial debulking treatment.

For each eligible case, a chart review was performed to collect additional data on disease stage and sites of involvement, patient characteristics (performance status and demographics) together with response assessment, and patient outcome. The stage of disease was defined according to the Ann Arbor staging system. Bulky disease was defined as a nodal or extranodal lesion larger than 10 cm in maximum transverse measurement on computed tomography (CT) scan. The IPI was calculated for all eligible patients and subjects grouped as originally reported [5].

With respect to therapies, treatment data were collected with details on administered regimen, number of cycles and administration of radiation treatment. Inclusion in a clinical trial was also retained as a study detail.

Statistical analysis

The principal endpoint of this study was overall survival (OS), defined as the time from diagnosis of DLBCL to the date of death from any cause or date of last follow-up for censored patients. OS was estimated by the Kaplan-Meier method [20]; survival curves were compared using the log-rank test. A Cox proportional hazards (PH) model was used to estimate the hazard ratio (HR), with the low-risk group as the reference group [21]. Univariate and multivariable analyses were performed by means of Cox PH regression.

The relationship between the variables of IPI and gender was evaluated using explorative multidimensional scaling analysis (MDS) for dissimilarities (Pearson measure).

The impact of covariates in the multivariable model was assessed by means of the percentage coefficient change:

$$[(\mathrm{Coeff}_{\mathrm{multivariable}} - \mathrm{Coeff}_{\mathrm{univariable}})/\mathrm{Coeff}_{\mathrm{univariable}} \times 100]$$

Moreover, to determine the stability of gender in the Cox PH model, we used a bootstrapping method with 1000 replications and with a backward selection cut-off = 0.01; stability was evaluated in terms of percentage of replications in which gender was included as an independent prognostic factor in addition to IPI [22]. Performance of indices was compared by measuring global fit of the model using Bayesian information criteria (BIC) as proposed by Raftery and Volinsky [23] and by measuring index discrimination using the concordance probability estimate (CPE) [24]. Low values of BIC mean better fit, and high values of CPE indicate better discrimination. The stability of BIC and CPE indices was determined by means of 250 bootstrap resamples.

Statistical analyses were performed with Stata 10.1/SE and R version 2.10.0 packages. The χ^2 test or Fisher's exact test was used to compare categorical variables. Associations between variables were measured by means of Spearman correlation. All performed tests were two-sided. We did not plan a sample size; however, as a recommended rule, in order to avoid the problem of over-fitting a model in a multivariable analysis, we assumed a factor to event ratio of 1/20. Continuous biologic covariates were dichotomized according to usual clinical thresholds.

Results

One thousand nine hundred and twenty-seven cases of DLBCL were retrieved from 43 different centers and considered eligible for the study. Overall, 134 cases were excluded due to missing data for calculating the IPI. The remaining 1793 (93%) cases represented the final study population. The main clinical characteristics of patients are summarized in Table I. Clinical features were similar between males and females (data not shown). One thousand four hundred and forty-three subjects (80%) were initially treated with R-CHOP, whereas 191 patients (11%) were treated with other, different rituximab containing regimens, and 159 patients (9%) received high-dose chemotherapy followed by autologous stem cell transplant with rituximab as part of their upfront therapy. After a median follow-up time of 36 months (range 1–106) (45 months for patients still alive), 380 deaths were recorded, and 78 patients (4%) were lost to follow-up. Hence the 5-year OS rate was 76% (95% confidence interval [CI] 74–78). No difference was observed between patients included in the study population and those initially excluded (data not shown; $p = 0.948$).

The majority of patients had none or one adverse prognostic factor (38%) according to the IPI, while 35% had three or more adverse prognostic factors. When the IPI was tested to evaluate OS, it was confirmed as a good prognostic tool, with the estimated HR ranging from 2.6 to 7.7, when intermediate and high risk groups (2, 3, 4–5) were compared with the low risk level (0 or 1) (Table II).

Prognostic role of gender

In univariate analysis, male gender showed an adverse effect on OS, with a HR of 1.52 (Table II and Figure 1). Gender did not show any correlation with IPI (Spearman's rho = − 0.02, $p = 0.32$), and its position in MDS analysis did not suggest any correlation with the other studied variables (Figure 2).

Then, gender was added to IPI as an additional factor and evaluated in multivariable analysis, and gender was confirmed as an additive prognostic factor (Table III). The model with IPI and gender was internally validated with bootstrapping, and results confirmed a good performance, the frequency of inclusion of gender in the final model being 98.6% (Table III).

Compared to IPI alone, the addition of gender resulted in an increase in the discrimination ability (CPE 0.684 and 0.698 for IPI alone and IPI plus gender, respectively). The addition of gender to IPI also resulted in a greater improvement in model "fitness" (BIC − 184 and − 198 for IPI alone and IPI plus gender, respectively), and was confirmed by bootstrapping analysis.

Table I. Baseline characteristics of assessable patients ($n = 1793$).

Characteristic	n (%)
Gender	
Male	943 (53)
Female	850 (47)
Age	
>60 years	970 (54)
Median (range)	62 (18–80)
Ann Arbor stage	
I	302 (17)
II	452 (25)
III	297 (17)
IV	742 (41)
Serum LDH >UNL	906 (50)
ECOG PS >1	381 (21)
>1 extranodal site	246 (14)
Serum β2M* >UNL	614 (51)
Bone marrow involvement	437 (20)
Hemoglobin* < 11 g/dL	314 (18)
Serum albumin* < 3.5 g/dL	357 (26)
IPI	
0–1	472 (39)
2	324 (27)
3	271 (23)
4–5	131 (11)

*Missing data: β2M ($n = 595$), hemoglobin ($n = 38$) and albumin ($n = 405$).
LDH, lactate dehydrogenase; UNL, upper normal limit; ECOG, Eastern Cooperative Oncology Group; PS, performance status; β2M, β_2-microglobulin; IPI, International Prognostic Index.

Table II. Overall survival (OS) stratified by IPI index and gender for any level of prognostic index in univariate analysis ($n = 1793$).

Factor	%*	5-year OS (%)	OS 95% CI	HR	HR 95% CI	Wald p
IPI						
0–1	38	91	88–93	1.00		
2	27	80	75–83	2.56	1.82–3.59	< 0.001
3	22	61	54–66	5.44	3.97–7.47	< 0.001
4–5	12	49	40–58	7.69	5.50–10.8	< 0.001
Gender						
F	47	81	77–84	1.00		
M	53	72	69–75	1.52	1.24–1.87	< 0.001

*Because of rounding, percentages may not total 100.
IPI, International Prognostic Index; CI, confidence interval; HR, hazard ratio.

Discussion

Despite the improved outcome since the acceptance of ICT as standard treatment for DLBCL, affected patients continue to have highly variable clinical courses. The IPI has been the primary clinical tool used to predict outcome for patients with DLBCL since it was first published in 1993. Also with the use of ICT, IPI still represents the best available prognostic tool for this type of lymphoma.

In recent years, several attempts have been made to identify more accurate prognostic parameters. Among these, the predictive value of gene expression profiling is currently being explored, but has not been adequately validated in this setting. In addition, early or late restaging

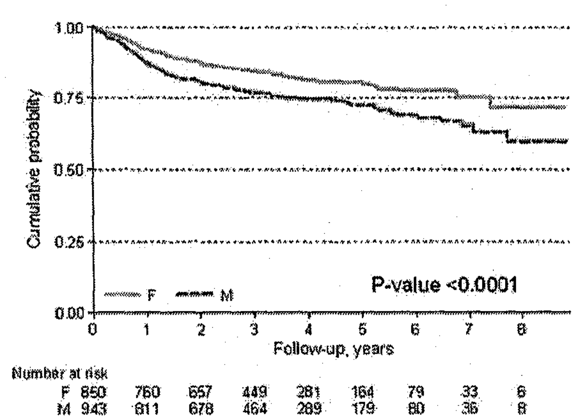

Figure 1. OS stratified by gender.

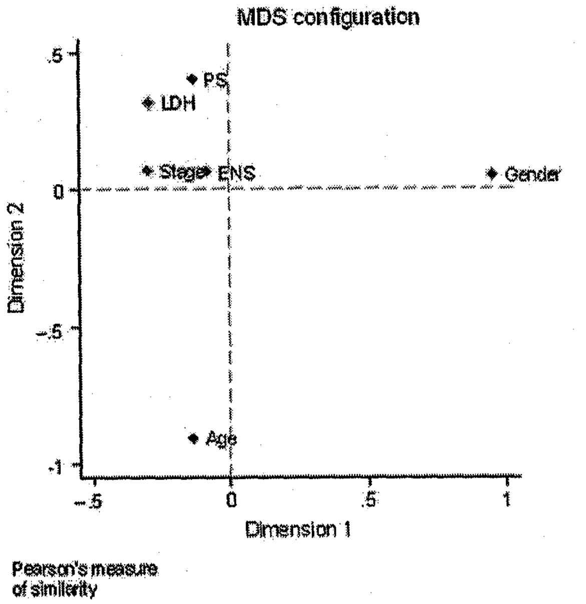

Figure 2. Multidimensional scaling (MDS) with variables included in IPI related to gender. LDH, lactate dehydrogenase; ENS, extranodal sites; PS, performance status.

with PET scanning has shown promising results, but requires further investigation. Also with the use of ICT, clinical models such as IPI or the revised IPI (R-IPI) remain the only reliable tools for predicting outcome and planning risk-adapted treatment. The classic IPI has recently been analyzed by Ziepert *et al.* [6], who have confirmed the index as still valid and up-to-date.

In our study of 1793 patients with DLBCL homogeneously treated with ICT, we focused on the possibility of improving the ability of the IPI to predict outcome. To achieve this goal, we decided to investigate the prognostic role of gender, which emerged from literature data as a powerful factor in several types of lymphoma. With a similar approach, the significance of bone marrow involvement in patients with DLBCL treated with ICT was considered in a retrospective study by Sehn *et al.* [25], which demonstrated the negative prognostic impact of this factor and emphasized again the need for new, more accurate tools.

A survival advantage for women is already known, and has been demonstrated to be significant in different kinds of tumors, including Hodgkin- and non-Hodgkin lymphoma [26]. The inferior survival of males versus females was confirmed also in the present study when the analysis was corrected for competing causes of death by analyzing the excess mortality rate (versus a healthy Italian population, data not shown).

In recent studies, gender has emerged as a prognostic factor in patients with DLBCL treated with ICT, with a better outcome for females [16–18,27]. More recently, gender was also shown to be an independent prognostic factor for patients with relapsed/refractory DLBCL receiving rituximab as maintenance therapy after autologous stem cell transplant [19]. The mechanism that can explain these data is unclear; however, pharmacokinetic studies suggest that the difference could be due to higher rituximab serum levels in females, due to a lower intrinsic drug clearance [18,27]. Considering existing data to justify the prognostic role of gender, a different pharmacology of rituximab between males and females can be a likely explanation. Ng and colleagues reported faster rituximab clearance in men treated for rheumatoid arthritis compared with women, leading to a decrease in rituximab exposure of 30% in men [28]. The influence of gender on antibody pharmacokinetics has also been described in studies with infliximab [29] and bevacizumab [30]. However, the influence of gender on rituximab clearance rates or therapeutic response remains to be shown in the context of lymphoproliferative disorders [31]. If the prognostic role of gender is confirmed, and studies of rituximab pharmacokinetics provide convincing results, an attempt to correct the poorer outcome of males could be made by modifying rituximab dosing or schedules in men.

Based on the results of our study, we confirm that gender can add prognostic information to the IPI. Finally, some limitations of our study must be acknowledged. First, this is a retrospective analysis with all the biases usually seen in such an analysis, but the large number of cases decreases the risk of misinterpretation of the results. Second, considering OS, we observed that the 5-year survival was slightly better than expected for an unselected population of patients with DLBCL, and this can be confirmed by the smaller proportion of high-risk patients. Selection of a better patient population could be suggested, but would have only minimally affected the results of our study. Actually, this study was conducted to validate the relative role of different prognostic parameters within a huge series of patients rather than to define the absolute role of new prognostic factors. The aim of our study was simply to provide data for better interpretation of the prognostic role of gender in patients with DLBCL treated with current regimens. It was not one of the aims of this analysis to define a new prognostic index, as we agree that the IPI still remains the best available prognostic score.

In conclusion, our results support the adverse effect of male gender on the outcome of patients with DLBCL, although this effect could most likely be overcome by increasing the rituximab dosage in males. Obviously well designed prospective controlled trials are warranted to test this hypothesis.

Table III. Multivariable analysis of IPI index adjusted for gender.

Factor	HR	HR 95% CI	Wald *p*	% CC	% BS
Multivariable analysis					
IPI					
0–1	1.00				
2	2.62	1.87–3.68	< 0.001	+ 2.1	
3	5.50	4.01–7.55	< 0.001	+ 0.6	
4–5	7.91	5.66–11.1	< 0.001	+ 1.4	
Gender					
F	1.00				98.6%
M	1.60	1.30–1.96	< 0.001	+ 11.9	

IPI, International Prognostic Index; HR, hazard ratio; CI, confidence interval; % CC, percentage of coefficient change from univariate to adjusted multivariable model; % BS, percentage of selection (cut-off = 0.01) over 1000 bootstrap resamples, locked IPI index in Cox proportional hazards model.

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Supplementary Appendix available online at http://informahealthcare.com/doi/abs/10.3109/10428194.2012.691482