

Prognostic models for diffuse large B-cell lymphoma in the rituximab era: a never-ending story

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Background: Improved treatment have modified survival outcome in patients with diffuse large B-cell lymphoma (DLBCL) and altered the importance of previously recognized prognostic markers.

Design and methods: To evaluate International Prognostic Index (IPI) score before and after rituximab introduction and to validate the absolute lymphocyte count (ALC)/revised International Prognostic Index (R-IPI) model, we carried out a retrospective analysis on a total of 831 patients with DLBCL.

Results: Our results show that IPI lost its discriminating power with the introduction of rituximab. The analysis of our second set allowed us to validate the ALC/R-IPI model. The R-IPI and ALC/R-IPI could still be used for designing clinical trials, but both have difficulty recognizing a high percentage of poor prognosis patients, though it remains an important goal of a good prognostic model considering the modest impact of salvage treatments on survival.

Conclusions: A new model on the basis of significant variables in the rituximab era and built on a large database of patients treated with rituximab is urgently needed. As prognostic models are changing with the efficacy and mechanisms of action of treatment utilized, looking for a new prognostic score is a never-ending story in which researchers are trying to hit a continuously moving target.

Key words: clinical trials, DLBCL, innovative treatments, NHL, prognostic models, rituximab

introduction

The introduction of rituximab in combination with various chemotherapies has improved survival outcomes [1, 2] in patients with diffuse large B-cell lymphoma (DLBCL) and has altered the importance of previously recognized prognostic markers [3]. In the last few years, most work has concentrated on the use of molecular markers to define new prognostic scores. A number of variables have been identified but they require validation in the rituximab era [4]. Several other markers appear to no longer retain prognostic significance, including Bcl-2 [5] and Bcl-6 [6], whereas the predictive value of gene expression profiling has not yet been adequately explored. Early restaging with positron emission tomography appears promising [7] but requires further investigation. Until now, no prognostically relevant molecular markers have been validated and no molecularly based prognostic model has been built. Thus, in the clinical setting, the International Prognostic Index (IPI) introduced in early 1990 [8] remains one of the most utilized prognostic scores. However, in the rituximab era,

the IPI identifies only two risk groups [3], both with an overall survival (OS) at 3 years of >55%. The revised International Prognostic Index (R-IPI) [3], which is on the basis of the same parameters but grouped differently, is capable of identifying three risk categories but does not identify patients with a <60% chance of survival at 3 years [3]. The recently published absolute lymphocyte count (ALC)/R-IPI score [9] combines R-IPI with the ALC and seems to be able to better discriminate between patients with different survival outcomes. The aims of our research are (i) to evaluate the significance of the IPI model after rituximab introduction; (ii) to apply R-IPI criteria to our series of patients; and (iii) to validate the ALC/R-IPI model on a larger, independent dataset represented by a series of 271 patients.

design and methods

patients

This study is a retrospective analysis of previously untreated DLBCL patients. Cases were retrieved either from Gruppo Italiano Studio Linfomi (GISL) archive or from the Modena Cancer Registry (MCR), which collects detailed clinical and survival data on subjects with lymphoma who are residents in the province of Modena. Patients were included in this study if they fulfilled the following criteria: histologically confirmed diagnosis of

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DLBCL CD 20+, previously untreated; age >18 years; no primary central nervous system involvement; no human immunodeficiency virus, hepatitis B virus, or hepatitis C virus infection; no severe coincident illness; and the availability of data on clinical and laboratory characteristics, treatments, outcome, and follow-up. Patients were treated with combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), CHOP-like, or third-generation anthracycline-containing regimens with or without rituximab. A total of 831 patients treated from 1988 to 2007 were identified.

The cases registered in GISL archive had been enrolled in clinical trials [10–18] that complied with the requirements of the Declaration of Helsinki and its amendments and conducted in accordance with Good Clinical Practice guidelines, including obtaining written informed consent. For cases retrieved from the Cancer Registry archives [19], formal approval from its ethical board was obtained. Final approval for the present study was obtained from the GISL review board. From 1988 to 2006, 560 patients were treated with chemotherapy alone; in particular, 143 received CHOP, 97 CHOP-like, and 320 third-generation anthracycline-containing regimens, of which 446 enrolled in clinical trials [10–18] and 114 were identified in the MCR [19]. From 2003 to 2007, 271 patients were treated with immunochemotherapy: 263 with CHOP, 4 with CHOP-like, and 4 with third-generation anthracycline-containing regimens all in combination with rituximab. Of these patients, 196 were enrolled in clinical trials [14–18] and 75 were identified in the MCR [19].

At the end of chemotherapy, involved-field radiotherapy (IF-RT) was allowed at the physician's discretion to irradiate residual masses or sites of previous bulky or extranodal disease. The radiotherapy consisted of 3500 Gy.

statistical methods

The analysis was on the basis of follow-up through 15 October 2008. The end points utilized to validate the proposed ALC/R-IPI score [9] were OS and progression-free survival (PFS). The OS was measured from the date of diagnosis until last follow-up or death from any cause. The PFS was defined from the date of diagnosis to last follow-up or to one of the following events: documented progression during or after chemotherapy, relapse for patients in complete remission at the end of therapy, or death from any cause.

Comparisons between categorical variables were made by means of Fisher's exact test when appropriate or chi-square test. Comparisons between continuous variables were made by means of the Mann–Whitney test. Survival functions were assessed by the Kaplan–Meier method [20] and compared by risk groups using the log-rank test and Cox proportional hazard (PH) regression [21].

To check if the ALC/R-IPI score is consistent with our dataset, we utilized discrimination and calibration procedures for OS [22]. Discrimination was evaluated by calculating the scores for each patient and constructing Kaplan–Meier curves using the score as defined previously [9]. This evaluation provided a visual idea of the discriminative capacity and preservation of the correct ordering of patient groups. Calibration was carried out to check the reproducibility of the hazard ratio (HR). We carried out a Cox PH regression on our dataset with the prognostic index (PI) obtained when applying ALC/R-IPI over the dataset as the only covariate. Given the linear relationship $H(t) = \beta \times PI$ (where $H(t)$ is the cumulative hazard function), if nonsignificant results are obtained when testing the null hypothesis that $\beta = 1$, the HR is reproducible, whereas if $\beta \neq 1$ adjustment should be necessary. Furthermore, we evaluated the concordance measure *c*-Harrell [23] that estimates the proportion of patient pairs in which the highest ALC/R-IPI implies the shortest OS.

Finally, statistical validation was carried out by means of reevaluated weights for the individual prognostic variables as calculated in the reference population. The predictive power improvement resulting from the

inclusion of new prognostic factors was checked and judged from the *P* value generated by Wald's test. Also, the PHs risk assumption was verified.

We did not plan a sample size for this study, and in all analyses, a two-sided $P < 0.05$ was considered to demonstrate a moderate strength of evidence against the null hypothesis. This level of probability was helpful for detecting clinically useful findings. All analyses were carried out using Stata Statistical Software SE/8.2 (StataCorp, College Station, TX).

The IPI for aggressive non-Hodgkin lymphoma (NHL), which takes into account an age >60 years, lactate dehydrogenase level greater than the upper limit of normality (ULN), Eastern Cooperative Oncology Group score >1, clinical stage III or IV disease, and more than one extranodal site of disease, was calculated for all patients in the cohort [8].

results

patients

A total of 831 patients with DLBCL, of which 560 were treated with CHOP, CHOP-like, or third-generation anthracycline-based chemotherapy alone (from 1988 to 2006) and 271 with the same chemotherapy in combination with rituximab (from 2003 to 2007), fulfilled all eligibility requirements and entered this study. The median age of patients treated with chemotherapy alone was 61 years (range 18–90 years), 50% were male and 35% were treated with IF-RT (maximum dose 3500 Gy) after induction chemotherapy. The median follow-up was 41 months (range 1–215 months) and 271 deaths had been recorded by the time of the last follow-up. The median age of patients treated with rituximab was 69 years (range 21–89 years), 51% were male and 20% were treated with IF-RT (maximum dose 3500 Gy) after induction chemoimmunotherapy. The median follow-up was 23 months (range 1–74 months) and 67 deaths had been recorded by the time of the last follow-up. Clinical characteristics at diagnosis, including the distribution of the individual IPI factors in the three series of patients treated with chemotherapy and rituximab (Sehn et al. [3], Cox et al. [9], and our series) and the ALC in our patients compared with the series of Cox et al. [9] are listed in Table 1. Our series had a higher percentage of patients with advanced age and a better performance status, probably in relation to the inclusion of several patients in trials designed for elderly patients.

survival outcomes before and after the introduction of rituximab

The survival of the 560 patients treated with chemotherapy alone, compared with the 271 patients treated with chemotherapy in combination with rituximab, is reported in Figure 1A and B. As expected, patients who received chemoimmunotherapy had better outcomes in comparison to those who were treated only with chemotherapy. These results confirm that the high efficacy of rituximab has changed the outcomes in DLBCL patients. The PFS and OS curves are similar, demonstrating the weak impact of salvage therapy in patients not cured with front-line therapy.

patient outcomes by IPI score

The OS of the 831 patients broken down by IPI score is reported in Figure 2A and B. In the 560 patients treated with

chemotherapy alone (Figure 2A), the IPI score is highly predictive of outcome and discriminates well between the four expected risk groups. In the 271 patients treated with chemotherapy plus rituximab (Figure 2B), the IPI score separates only high-intermediate- and high-risk curves but it no longer discriminates well between low- and low-intermediate-risk groups that show clearly overlapping curves. These results demonstrate that the introduction of rituximab has improved the outcome of all IPI groups and highlight that its high efficacy has changed the value of prognostic parameters in patients with DLBCL. Indeed, the HR between patients treated with chemoimmunotherapy and patients treated only with chemotherapy for IPI scores of 0–1, 2, 3, and 4–5 were 0.3 ($P = 0.003$), 0.3 ($P < 0.001$), 0.6 ($P = 0.009$), and 0.6 ($P = 0.045$), respectively.

Table 1. Characteristics of the three series of patients: R-IPI study [3], ALC/R-IPI study [9], and validation dataset. Our series had a higher percentage of patients with advanced age and better performance status

Factor	R-IPI study (<i>n</i> = 365), %	ALC/R-IPI study (<i>n</i> = 101), %	Validation dataset (<i>n</i> = 271), %	<i>P</i>
Age >60 years	51	54	74	<0.001
PS >1	41	31	16	<0.001
LDH > ULN	55	51	49	0.400
ENS >1	34	34	26	0.070
Stage III/IV	59	57	62	0.589
ALC <0.84 × 10 ⁹ /l	–	23	20	0.563
β2M > ULN	–	–	61	
β2M >1.5 ULN	–	–	27	

R-IPI, revised International Prognostic Index; ALC, absolute lymphocyte count; PS, performance status; LDH, lactate dehydrogenase; ULN, upper limit of normality; ENS, extranodal sites; β2M, β2-microglobulin.

patient outcomes by R-IPI score

In the original R-IPI [3], patients are divided into three groups with 0, 1–2, and 3–5 risk factors. This redistribution allows for a more simplified model, distinguishing between three prognostic groups, very good (VG), good (G), and poor (P), with a 3-year OS ranging from 63% to 94%. Grouping variables for our 271 patients treated with rituximab following the indications of R-IPI, we observed three clear-cut curves representing prognostic groups with an OS ranging from 54% to 100% at 3 years (Figure 3A and Table 2). These data confirm the results obtained in the 365 patients treated in British Columbia [3], which showed three risk groups with similar survival outcomes.

patient outcomes by ALC/R-IPI

In the original ALC/R-IPI score model [9], when considering an ALC cut-off of $0.84 \times 10^9/l$ and R-IPI VG, G, or P, patients are divided into three risk groups: low risk with R-IPI VG or G and $ALC \geq 0.84 \times 10^9/l$; intermediate risk with R-IPI P or $ALC < 0.84 \times 10^9/l$; and high risk with R-IPI P and $ALC < 0.84 \times 10^9/l$. This model allows the identification of three prognostic groups with an OS ranging from 52% to 90% at 3 years (Table 2). When this model was applied to the validation sample of the 271 patients, we obtained an equally predictive model with the identification of three risk groups (log rank $P < 0.01$; Figure 3B). The three risk groups show an OS varying from 39% to 88% at 3 years (Table 2).

validation of the ALC/R-IPI model on our dataset

In Figure 3B, the OS of our patients is reported and stratified by ALC/R-IPI prognostic score. We observed that the model was capable of discriminating between the three risk groups. The HR between intermediate and low risk and high and intermediate risk were 3.7 ($P < 0.001$) and 2.1 ($P = 0.012$),

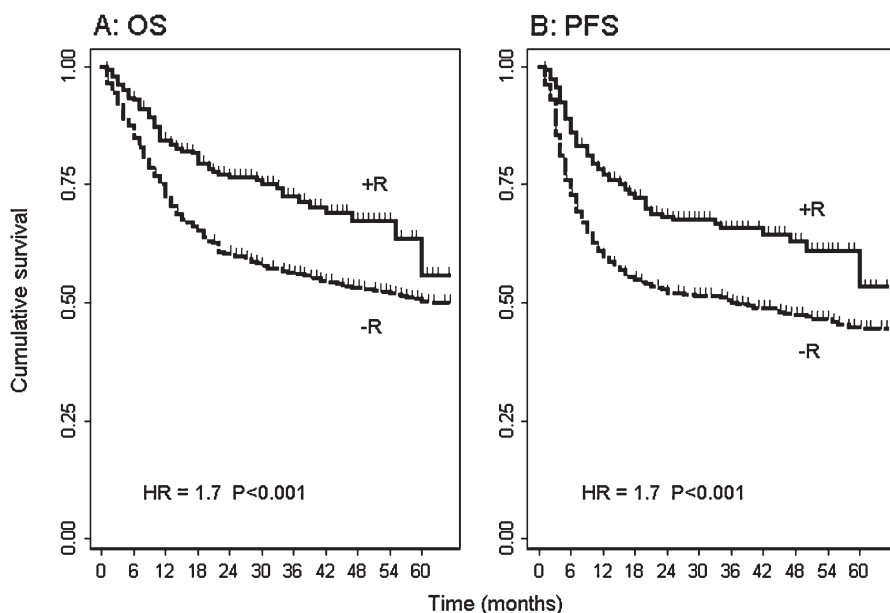


Figure 1. Comparison between survival outcomes of the 560 patients treated with chemotherapy alone (–R) and those of 271 patients treated with chemotherapy combined with rituximab (+R). (A) Overall survival (OS). (B) Progression-free survival (PFS).

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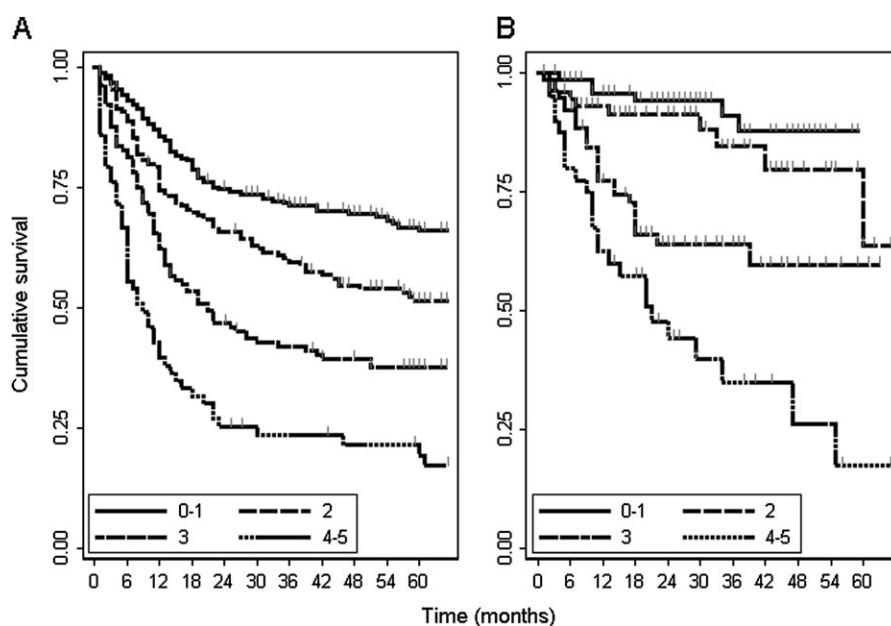


Figure 2. Overall survival stratified by International Prognostic Index score: (A) 560 patients treated with chemotherapy alone; (B) 271 patients treated with rituximab-containing regimens.

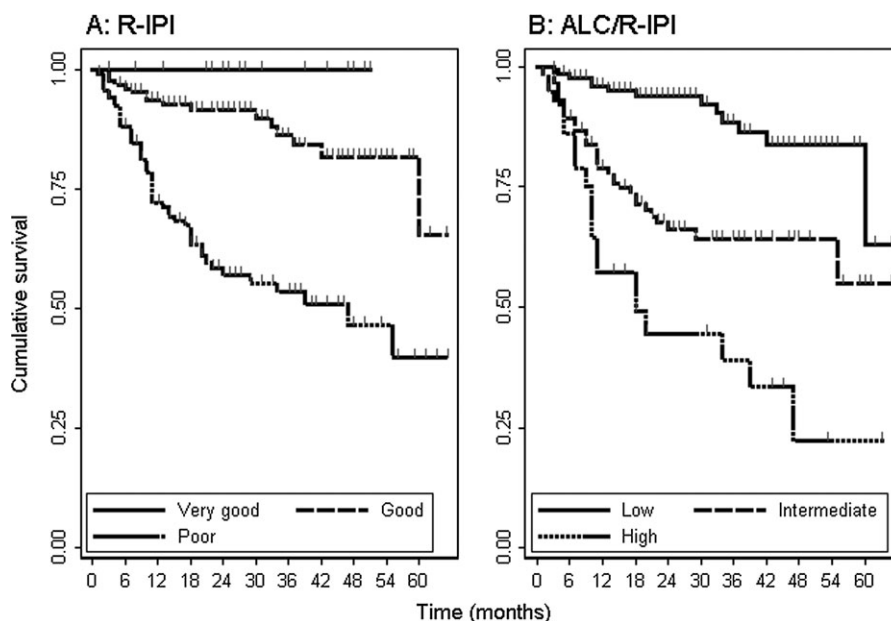


Figure 3. Overall survival of the 271 patients treated with chemotherapy plus rituximab, stratified by criteria of revised prognostic models. (A) Revised International Prognostic Index (R-IPI) and absolute lymphocyte count (ALC)/R-IPI. B: R-IPI: very good = International Prognostic Index (IPI) 0; good = IPI 1–2; and poor = IPI 3–5. ALC/R-IPI: low risk = R-IPI very good or good and $ALC \geq 0.84 \times 10^9/l$; intermediate risk = R-IPI poor or $ALC < 0.84 \times 10^9/l$; and high risk = R-IPI poor and $ALC < 0.84 \times 10^9/l$.

respectively. The ALC/R-IPI also maintained a good performance (HR intermediate versus low = 2.8, $P < 0.001$; high versus intermediate = 1.9, $P = 0.026$) in the evaluation of PFS. Furthermore, the prognostic score showed a good concordance index (c -Harrell = 0.71, 95% confidence interval 0.65–0.76), and the HR was reproducible with our data ($\beta = 0.86$, $P = 0.297$). In the univariate analysis, the prognostic factors showed their relevance, and in multivariate analysis, the two factors were used to build-up the ALC/R-IPI score

maintained their prognostic value. Finally, it is worth noting that $ALC < 0.84 \times 10^9/l$ is a significant prognostic factor only in patients treated with rituximab.

distribution of patients inside risk groups

The distribution of the 365 British Columbia patients [3] according to standard IPI shows that ~25% of the cases were attributed to each of the four risk groups. By R-IPI, the distribution of patients was 10%, 45%, and 45% in the VG, G,

Table 2. Distribution of patients inside risk groups and OS by standard IPI [8], R-IPI [3], and ALC/R-IPI [9]

Risk group	N factors	Patients(%)			3-Year OS (%)		
		R-IPI study	ALC/R-IPI study	Validation dataset	R-IPI study	ALC/R-IPI study	Validation dataset
Standard IPI							
Low	0–1	28	–	28	82	–	91
Low–intermediate	2	27	–	27	81	–	85
Intermediate–high	3	21	–	29	59	–	64
High	4–5	24	–	15	55	–	35
R-IPI							
Very Good	0	10	14	7	94	100	100
Good	1–2	45	39	48	81	87	86
Poor	3–5	45	48	45	63	58	54
ALC/R-IPI ^a							
Low		–	45	47	–	90	88
Intermediate		–	35	42	–	66	64
High		–	20	11	–	52	39

Because of rounding, percentages may not be total 100.

^aALC/R-IPI: low risk = R-IPI very good or good and ALC $\geq 0.84 \times 10^9/l$; intermediate risk = R-IPI poor or ALC $< 0.84 \times 10^9/l$; high risk = R-IPI poor and ALC $< 0.84 \times 10^9/l$.

OS, overall survival; IPI, International Prognostic Index; R-IPI, revised International Prognostic Index; ALC, absolute lymphocyte count.

and P prognosis groups, respectively, and the distribution of the original ALC/R-IPI 101 patients [9] was 45%, 35%, and 20% in risk groups low, intermediate, and high, respectively (Table 2). Also, the distributions of our 271 patients by standard IPI, R-IPI, and ALC/R-IPI are reported in Table 2. The percentage of our patients who fell into the high-risk group was lower but with a worse OS compared with that observed in the other series. In conclusion, when utilizing ALC/R-IPI model, not >11% of high-risk patients can be recognized at diagnosis and presented with an OS of 39% at 3 years.

recognizing more high-risk patients at diagnosis

In our series of rituximab-treated patients, $\beta 2$ -microglobulin ($\beta 2M$) showed a prognostic value independent from R-IPI and ALC/R-IPI in univariate and multivariate analyses when dichotomized at $\beta 2M > 1.5$ ULN. Thus, we tried to utilize the variable to recognize a higher number of high-risk patients at diagnosis by adding this variable to the ALC/R-IPI model. Patients falling into the high-risk group increased from 11% to 23% with an OS at 3 years of roughly 41%.

discussion

Since its publication in 1993, the IPI, which is on the basis of the number of negative prognostic factors present at the time of diagnosis, has become the primary prognostic tool for patients with aggressive NHL. The use of more effective treatments can alter the significance of previously recognized risk factors, and it is likely that the introduction of rituximab, having improved patient outcomes, has changed the predictive capacity of IPI. Thus, it appears justified to look for more accurate prognostic models. Indeed, in the rituximab era, the R-IPI distinguishes between three different prognostic groupings with significantly different outcomes at 3 years: the VG subset, including roughly 10% of patients with an OS of 94%; the G subset, including

roughly 45% of cases with an OS of 81%; and the P group, including roughly 45% of patients with an OS of 63%. Applying the R-IPI criteria on our series of 271 patients, we observed a similar distribution of patients in the three risk groups and similar OS, ranging from 54% to 100% at 3 years. More recently, Cox et al. [9] showed that the ALC at diagnosis has a strong prognostic impact and is independent from the R-IPI, although there were several limitations to the study, including the number of patients utilized in the training dataset and the lack of lymphocyte subset analysis. Thus, they have built up a new score, termed ALC/R-IPI, that incorporates both parameters and shows in multivariate analysis that it is the most powerful predictor for OS. The analysis of our validation set of 271 patients allowed us to validate the ALC/R-IPI model. We noted that the strong prognostic value of ALC is not observed in patients treated with chemotherapy without rituximab. Thus, we suppose that ALC may play a key role in rituximab's mechanisms of action. The distribution of patients of the various series in the different risk groups and the corresponding OS at 3 years according to IPI, R-IPI and ALC/R-IPI are summarized in Table 2. It was observed, when utilizing the ALC/R-IPI prognostic score, that not >20% of patients had fallen into the high-risk group with an OS of 52% at 3 years, whereas the other two groups, which represent 80% of patients, had an OS of >66% at 3 years. Therefore, regardless of the model utilized, we observed a very good prognostic subset with >88% chance of survival at 3 years. For this group of patients, rituximab plus chemotherapy represents an excellent treatment, and it is difficult to imagine a clinical trial with an experimental arm to compare with standard treatment as a very high number of patients will be necessary to demonstrate advantages compared with the standard arm and toxicity could increase. It would be of more interest to look for a noninferiority arm that is less toxic but with the same efficacy. A second group is represented by good prognosis with >64%

chance of survival at 3 years. Certainly, we could improve the outcomes of these patients and randomized trials are needed. However, we have to pay particular attention to not cause excessive toxicity considering the good results obtained with rituximab plus chemotherapy. The poor prognosis group have an almost 39% chance of survival at 3 years. These are the typical patients that should be addressed in clinical trials for treatments with innovative approaches. However, the percentage of patients who fall into the high-risk group is highly variable, ranging from 11% to 48%, with an OS ranging from 39% to 63% depending on the prognostic model and series of cases utilized. This breakdown highlights the difficulty in identifying patients with poor prognosis at the time of diagnosis. However, considering the poor impact of salvage treatment on OS, it remains one of the most important goals of a valid prognostic model and every attempt has to be made to recognize the patients with the poorest prognosis. With this aim, we have added the variable $\beta 2M$ to the ALC/R-IPI model, obtaining a high-risk group of 23% of patients with an OS of 41% at 3 years. Obviously, this finding deserves further confirmation and validation.

In conclusion, the standard IPI lost its discriminatory power with the introduction of rituximab. New prognostic models, such as R-IPI and ALC/R-IPI, could be used for designing clinical trials but both have difficulties clearly discriminating a high percentage of poor prognosis patients. Thus, while waiting for molecular-based prognostic scores, a new model on the basis of variables with significance in the rituximab era and built on a large database of patients treated with chemotherapy plus rituximab is urgently needed. Indeed, as prognostic models are changing in relation to type, efficacy, and mechanism of action for the utilized treatment, looking for new and better prognostic scores is a never-ending story in which researchers are trying to hit a continuously moving target.

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disclosure

None of the authors has conflict of interest to declare.

references

- Coiffier B, Lepage E, Briere J et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002; 346: 235–242.
- Pfreundschuh M, Trümper L, Osterborg A et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol* 2006; 7: 379–391.
- Sehn LH, Berry B, Chhanabhai M et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood* 2007; 109: 1857–1861.
- Lossos IS, Morgensztern D. Prognostic biomarkers in diffuse large B-cell lymphoma. *J Clin Oncol* 2006; 24: 995–1007.
- Mounier N, Briere J, Gisselbrecht C et al. Rituximab plus CHOP (R-CHOP) overcomes bcl-2—associated resistance to chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL). *Blood* 2003; 101: 4279–4284.
- Winter JN, Weller EA, Horning SJ et al. Prognostic significance of Bcl-6 protein expression in DLBCL treated with CHOP or R-CHOP: a prospective correlative study. *Blood* 2006; 107: 4207–4213.
- Haioun C, Itti E, Rahmouni A et al. [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. *Blood* 2005; 106: 1376–1381.
- A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 1993; 329: 987–994.
- Cox MC, Nofroni I, Ruco L et al. Low absolute lymphocyte count is a poor prognostic factor in diffuse-large-B-cell-lymphoma. *Leuk Lymphoma* 2008; 49: 1745–1751.
- Silingardi V, Federico M, Cavanna L et al. ProMECE-CytaBOM vs MACOP-B in advanced aggressive non-Hodgkin's lymphoma: long term results of a multicenter study of the Italian Lymphoma Study Group (GISL). *Leuk Lymphoma* 1995; 17: 313–320.
- Federico M, Luminari S, Gobbi PG et al. The length of treatment of aggressive non-Hodgkin's lymphomas established according to the international prognostic index score: long-term results of the GISL LA03 study. *Eur J Haematol* 2006; 76: 217–229.
- Gobbi PG, Ghirardelli ML, Avanzini P et al. A variant of ProMACE-CytaBOM chemotherapy for non-Hodgkin's lymphoma with threefold higher drug dose size but identical cumulative dose intensity. A pilot study of the Italian lymphoma study group (GISL). *Haematologica* 2000; 85: 263–268.
- Gobbi PG, Brogna C, Valentino F et al. The role of dose size in a chemotherapy regimen (ProMECE-CytaBOM) for the first-line treatment of large B-cell lymphomas: a randomized trial by the Gruppo Italiano Studio Linfomi (GISL). *Ann Oncol* 2006; 17: 676–682.
- Di Renzo N, Luminari S, Montanini A et al. Early response to a short course of induction chemotherapy overcomes the prognostic role of IPI in patients with aggressive NHL. Preliminary results of the GISL LA05 Trial. *Blood* 2006; 108: 689a (Abstr 2434).
- Gobbi PG, Ghirardelli ML, Cavalli C et al. The role of surgery in the treatment of gastrointestinal lymphomas other than low-grade MALT lymphomas. *Haematologica* 2000; 85: 372–80.
- Merli F, Bertini M, Luminari S et al. Long term results of a randomized study performed by Intergruppo Italiano Linfomi comparing Mini-CEOP vs P-VEBEC in elderly patients with diffuse large B-cell lymphoma. *Leuk Lymphoma* 2007; 48: 367–373.
- Merli F, Bertini M, Sacchi S et al. A pilot study with an oral chemotherapy regimen (CIEP) in the treatment of diffuse large cell lymphoma (DLCL) in elderly patients: an interim report from Italian Lymphoma Intergroup (ILI). *Ann Oncol* 2002; 13 (Suppl 2): 156 (Abstr 554).
- Merli F, Vitolo U, Luminari S et al. R-CHOP vs R-mini-CEOP in elderly patients with diffuse large B cell lymphoma: an interim report from Intergruppo Italiano Linfomi (ILI). *Blood* 2005; 106: 262b (Abstr 4729).
- Luminari S, Cesaretti M, Rashid I et al. Incidence, clinical characteristics and survival of malignant lymphomas: a population-based study from a cancer registry in northern Italy. *Hematol Oncol* 2007; 25: 189–97.
- Kaplan EL, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53: 457–481.
- Cox D. Regression models and life tables. *J R Stat Soc B* 1972; 34: 187–220.
- Van Houwelingen HC. Validation, calibration, revision and combination of prognostic survival models. *Stat Med* 2000; 19: 3401–3415.
- Harrell FE Jr, Lee KL, Mark DB. Multivariate prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; 15: 361–387.