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Malignant Lymphomas

Validation of the International Prognostic Index in Working Formulation group A low-grade non-Hodgkin's lymphoma: retrospective analysis of 137 patients from the *Gruppo Italiano per lo Studio dei Linfomi* registry

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ABSTRACT

Background and Objectives. **The subset of non-follicular non-Hodgkin's lymphoma (NHL) includes patients with varied prognoses, thus suitable for different therapeutic approaches. The International Prognostic Index (IPI), originally proposed for aggressive NHL, has been demonstrated to be of prognostic relevance also in follicular NHL. The main aim of the study was to validate the IPI in this histologic category; in addition, the specific prognostic classification, currently employed in the *Gruppo Italiano per lo Studio dei Linfomi* (GISL) prospective therapeutic trials and based on different features, more similar to those applied to chronic lymphocytic leukemia, was analyzed.**

Design and Methods. **The present series consists of 137 evaluable patients affected by Working Formulation group A NHL out of 256 cases referred to the GISL Registry. The retrospective prognostic study included the evaluation by both univariate and multivariate analyses of overall survival, response to therapy and response duration. The IPI was applied as originally proposed. The GISL definition of indolent and aggressive disease at diagnosis was based on the presence of B symptoms, bulky disease, anemia and thrombocytopenia.**

Results. **The distribution of patients in IPI risk groups was rather unbalanced with 18%, 47%, 28% and 7% of cases classified as low (L), intermediate-low (IL), intermediate-high (IH) and high (H) risk, respectively. The median overall survival was not reached in either L or IL risk groups, and was 84.1 and 7.4 months for IH and H risk groups, respectively (p=0.0005). A simplified IPI model was designed merging patients in both intermediate risk groups and the statistical difference of survival retained its significance. GISL prognostic stratification was demonstrated to have a significant association with survival, with a median survival of 71.3 months in aggressive disease and a median survival not reached at 152 months in indolent disease. Both the simplified IPI model and the GISL risk definition retained their significance in multivariate analysis for overall survival, while for response to therapy only the simplified IPI model resulted to be of statistical significance. In addition, the GISL prognostic stratification identified patients with different outcomes within the IPI intermediate risk group, with a median survival of 70.2 months for patients with aggressive disease wheras the median survival for those with indolent disease was not reached. Finally, a prognostic score resulting from the integration of the simplified IPI and the GISL system was statistically validated.**

Interpretation and Conclusions**. The retrospective analysis of this series demonstrates the validity of the IPI in non-follicular indolent NHL and the usefulness of integrating the IPI parameters with disease specific prognostic variables.**

Key words: non-Hodgkin's lymphoma, prognosis, International Prognostic Index, survival

Low-grade non-Hodgkin's lymphoma (NHL) includes different histologic and clinical entities, all characterized by a median overall survival measurable in years, high sensitivity to radio and chemotherapy accompanied by a constant tendency to relapse which makes it almost impossible to achieve disease eradication.[1] In this context, it has been well demonstrated that the clinical course can be extremely variable with survival ranging from a few months to more than a decade. This observation justifies the application of totally different therapeutic approaches ranging from a *watch-and-wait* pol-

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icy to high dose chemotherapy with stem cell rescue. Consequently, it would be of great importance to design a prognostic system able to guide the choice of the appropriate therapeutic strategy in individual patients.

Before the extended use of the REAL classification, which lists each recognized histologic entity,[2] low-grade NHL were grouped into A, B and C categories of the Working Formulation (WF).[3] From the prognostic point of view, many clinical and biological parameters were reported as influencing the outcome of these patients and, to some extent, prognostic systems were proposed.[4-6] In addition, the International Prognostic Index (IPI), originally conceived for high-grade NHL,[7] has been validated in patients with low-grade histologies.[8-11] The above mentioned experiences dealt either specifically with follicular NHL or with low-grade NHL as a whole category, while few prognostic studies were addressed at non-follicular low-grade NHL,[12-14] and none analyzed the possibility of validating the IPI in this NHL category.

So far, in prospective therapeutic studies the *Gruppo Italiano per lo Studio dei Linfomi* (GISL) has stratified patients affected with low-grade NHL, WF group A, according to a definition of indolent or aggressive disease specifically designed for this histotype, mainly based on parameters commonly used for the prognostic evaluation of patients with chronic lymphocytic leukemia patients.

The present retrospective study was aimed at evaluating the prognostic power of the IPI in the specific subset of low-grade non-follicular NHL (WF group A) in terms of survival, response to therapy and response duration. In addition, the accuracy of the prognostic criteria previously employed in GISL therapeutic studies with regards to the final outcome of these patients is reported.

Design and Methods

From 1988 to 1995 256 patients affected by low-grade NHL, WF group A, were reported to the GISL Lymphoma Registry from 15 co-operative Institutions. A proportion of these patients was included in current prospective therapeutic GISL trials. In 137 (55.7%) and 122 (47.6%) cases the clinical information available at diagnosis allowed classification according to the IPI and the GISL definition of indolent or aggressive presentation, respectively. The median age of the evaluable cases was 65.8 years (range 26-84) and 79 cases were males. At the time of the present evaluation (May 1998) the median observation was 44.9 months, the median overall survival of the evaluable cases was 117 months with 45% of patients alive at 10 years.

The IPI system was applied according to the original scheme which takes into account four unfavorable parameters (age over 60, high LDH, performance status >1, number of extranodal sites >1) and stratifies patients in four risk groups, low (L), intermediate-low (IL), intermediate-high (IH) and high (H) risk.

Patients were also stratified into three IPI risk groups, by pooling the data of cases classified as IL and IH risk in the original scheme into a single group.

According to the GISL prognostic classification, patients were defined as presenting with aggressive disease if they had at least one of the following features: B symptoms, bulky lesion (> 5 cm), Hb < 10 g/dL, platelet count $< 100\times10^9$/L, or diffuse pattern of neoplastic infiltration at bone marrow biopsy. Patients without any of these features were defined as having indolent disease. The additional parameter of a short doubling time of the tumor burden, usually considered in prospective therapeutic GISL trials, was not evaluated in the present retrospective analysis.

In all patients the histology was documented from the biopsy of involved tissue and clinical staging was performed by common investigations which included CT scan and bone marrow biopsy. Response to therapy was also defined according to currently used criteria.[15]

The main clinical features, the distribution of patients in both prognostic systems, and the therapeutic approaches are reported in Table 1. In detail, treatment consisted mainly of single agent therapy with chlorambucil with or without prednisone; a minority of patients received anthracycline-containing combination chemotherapy. In 15 cases a *watch-and-wait* policy was used; so far, only one of these patients has required chemotherapy.

Statistical analysis

Overall survival was calculated from diagnosis to death of any cause, and response duration was evaluated on complete and partial responders from the date of response to the date of relapse or progression. Pearson's chi-square and Fisher's exact test (2-tail) for 2×2 tables were used for overall comparisons of clinical complete response (CR) + partial response (PR) versus no response (NR) + progressive disease (PD). Survival was calculated by Kaplan and Meier's method. Differences in survival between prognostic groups was evaluated in univariate analysis by the log-rank test, and the respective influence on survival of the different variables, significant at $p < 0.05$, was calculated in a stepwise fashion according to the Cox regression method. All calculations were performed using the SPSS for windows, release 7.0, 1995.

Results

Survival

International Prognostic Index (IPI)

The distribution of patients between the four original IPI risk groups, reported in Table 1, appears rather unbalanced, because of the very few cases (6%) classified in the H risk subset, while intermediate risk presentation was largely prevalent (75%).

The median overall survival of 137 patients evaluable for the IPI was 117.1 months (Figure 1). After stratification according to the four IPI risk groups, the overall survival rate at 8 years was 83%, 53% and 36% for L, IL and IH risk subsets, respectively; H risk patients displayed 7.4 months of median survival. The difference between these groups was highly significant (p=0.0005) (Figure 2A).

Because of the similar behavior of IL and IH patients, especially in the first years of the disease, these two subsets were pooled and a simplified mod-

Table 1. Main data of the present series.

No. of cases reported to the GISL registry	256	
No. of evaluable cases	137	
Median age, years (range)	65.8 (26-84)	
Male/female	79/58	
Median follow-up (months)	44.9	
Median survival (months)	117.07	
IPI risk distribution	No.	%
Low	25	18.2
Intermediate-low	64	46.7
Intermediate-high	39	28.5
High	9	6.6
Distribution by GISL	No.	%
Prognostic categories		
indolent disease	65	53.3
aggressive disease	57	46.7
No. of evaluable cases treated	71	
with single agent	40	
with regimens without anthracycline	20	
with regimens with anthracycline	9	
other therapy	2	

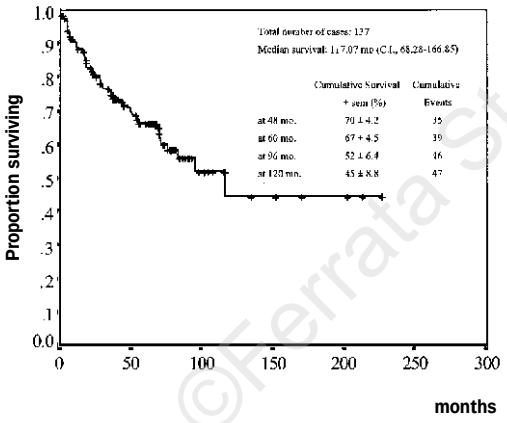

Figure 1. Overall survival of the present series of low-grade non-follicular lymphoma patients.

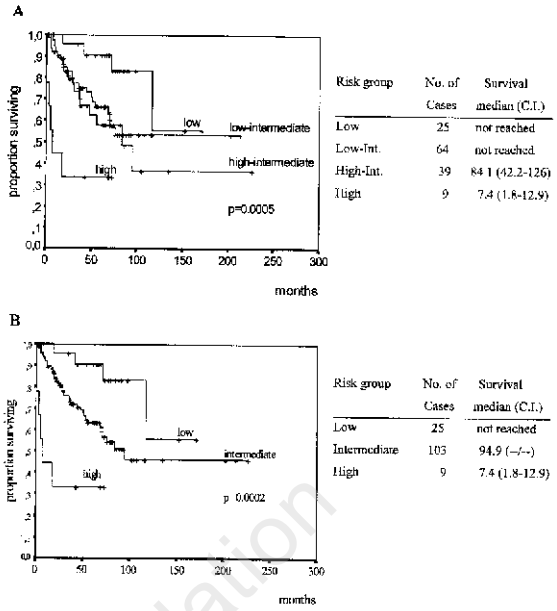

Figure 2. Overall survival of patients stratified according to IPI risk categories: 2A original IPI model; 2B simplified IPI model.

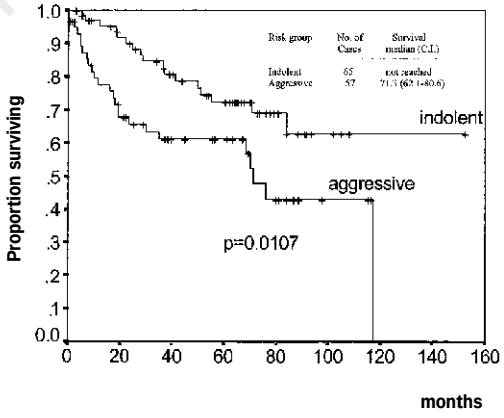

Figure 3. Overall survival of patients divided according to indolent and aggressive presentation as defined by GISL criteria.

el with H, intermediate (I) and L risk was designed. This simplified IPI model predicted survival at a highly significant level (p=0.0002), with a median survival of 7.4 and 94.9 months and not reached by 168 months for H, I and L subsets, respectively (Figure 2B).

Indolent and aggressive disease according to GISL criteria

By dividing patients according to indolent or aggressive disease presentation, as defined by GISL criteria, a significant difference in overall survival was demonstrated (p = 0.0107) (Figure 3). The median survival was 71.3 months (CI 62.08-80.59) for patients with aggressive disease versus a not reached median survival for the indolent subgroup. The survival rate at 4 and 8 years was 79% and 62% for the latter subset and 62% and 43% for cases with aggressive disease.

A multivariate analysis was performed taking into account the simplified IPI, the indolent and aggressive presentation and sex, which is a parameter not incor-

Table 2. Multivariate analysis of parameters influencing overall survival.

Variable	X^2	*p**	*RR (95% C.I.)*
GISL prognostic categories (indolent vs aggressive)	4.74	0.0293	2.0 (1.0-3.7)
Simplified IPI (low vs intermediate v high)	15.13	0.0001	4.3 (2.0-8.9)

**Cox regression analysis.*

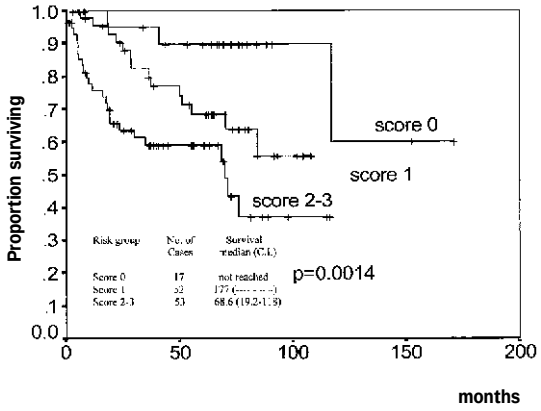

Figure 4. Overall survival of patients stratified by integrating simplified IPI and GISL systems.

porated in the above mentioned systems. It is noteworthy that both prognostic models independently and statistically significantly predicted survival (Table 2). Therefore, we designed a score system integrating the simplified IPI and GISL systems. By giving score 0 to indolent disease by GISL and IPI low risk, score 1 to aggressive disease by GISL and intermediate risk by simplified IPI and score 2 to IPI high risk, a system including three prognostic groups with Score 0, Score 1 and Score 2 or 3 patients is obtained. As reported in Figure 4, this score system allows a more balanced distribution of patients with highly significant difference in overall survival (p=0.0014).

Response to therapy and duration of response

Response to therapy, evaluable in 51.8% of patients, was analyzed by comparing responders (complete and partial) versus non-responders. The response rate ranged from 80 to 87.5% without a significant difference by type of therapy (data not shown). When the impact of sex, indolent or aggressive disease presentation and simplified IPI was assessed, only the last variable resulted to have significant prognostic power in univariate analysis (Table 3).

The median duration of response was 48 months (CI 29-67). None of the above-considered prognostic factors had a significant impact on this parameter (data not shown).

Table 3. Univariate analysis of prognostic variables for clinical response.

Variable	*CR+PR*	*NR+PD*	**Univariate p*
Age, years (≤ 60 v > 60)	20 v 37	3 v 7	NS
Sex (male vs female)	34 v 21	7 v 3	NS
GISL prognostic categories (indolent vs aggressive)	26 v 22	2 v 5	NS
Simplified IPI (low vs intermediate vs high)	13 v 42 v 2	0 v 6 v 4	0.001

**Pearson's chi-square; NS: not significant.*

Discussion

Accurate assessment of the prognostic features at presentation is mandatory in low-grade NHL because of the wide variability of therapeutic options: indeed the choice is even wider than in aggressive histology, since approaches such as *watch-and-wait*, biological response modifiers, and monoclonal antibodies, can appropriately be employed in low-grade subsets. Moreover, the use of high dose chemotherapy with stem cell rescue in younger patients requires correct prognostic evaluation of individual cases, taking into account the possibility of a long survival in spite of it being almost impossible to achieve disease eradication with conventional therapy.

In this respect, many prognostic factors in low-grade NHL have been identified and some prognostic systems have been proposed, mainly concerning follicular histology,[4-6] but none of them has gained general agreement and is currently used for therapeutic stratification. More recently, the IPI, originally designed for aggressive lymphoma, has been validated in indolent diseases.[8-11] These studies evaluated either all low-grade NHL as a whole, or specifically follicular lymphoma. As far as the subset of non-follicular low-grade NHL is concerned, previous studies identified nodal architecture, large cell presence, stage, systemic symptoms, performance status, LDH, and β_2-microglobulin as prognostic factors influencing survival,[12-14,16] but neither a specific prognostic system nor the validation of the IPI has been reported for this category.

The present study considered only WF group A patients and, in spite of the possible variety of different entities included in this NHL subgroup, validated the IPI system as a reliable predictor of survival and response rate. In fact, the analysis by IPI risk group showed that H risk cases had a median survival of 7.4 months, while 83%, 53%, 36% of patients with L, IL, IH patients, respectively, were alive at 8 years. Like a previously reported study,[10] our series includes patients from a lymphoma registry, thus not always eligible for clinical trials; the two series differ in the longer survival of H risk cases in the population studied by Hermans *et al.*[10] The difference of survival was highly significant and confirmed by both univariate and multivariate analyses.

A more detailed analysis of the survival curves showed that both intermediate groups had a similar

behavior, especially in the first two years of follow-up. This observation prompted us to merge the two groups and to verify the validity of a simplified IPI model consisting of 3 prognostic groups (high, intermediate and low risk). As reported for follicular NHL,[9] this model was of significantly prognostic value in terms of survival and response rate.

The similar behavior of the intermediate risk groups and the unbalanced distribution of patient between the IPI categories, with the vast majority of cases classified as being intermediate risk and very few cases as high risk, hamper the extended use of the IPI model alone in this histologic subgroup and suggest the need to consider additional prognostic stratifications.

For this purpose we validated in this series the prognostic accuracy of the definition of indolent and aggressive disease used in the GISL prospective trials, a definition which is based on criteria completely different from the IPI factors and more similar to the prognostic parameters commonly employed for CLL, this disease being very close to lymphocytic NHL. The present study confirmed the significant and independent prognostic power in terms of survival of the GISL definition of indolent and aggressive disease with 8-year survival rates of 62% and 43% of cases, respectively. Moreover, the integration of GISL system and IPI simplified model results in a prognostic score which could be useful to identify patients at different risks with a balanced distribution between these groups, although it should be verified on a larger series.

Unfortunately, the retrospective character of the present study, dealing with a relatively rare subset of NHL, and requiring an adequate period of observation, did not allow the analysis of the prognostic significance of newly identified biological features such as cytogenetics, p53, molecular markers and soluble factors.

In conclusion, in the absence of information on relevant biological parameters, the validation of IPI in indolent non-follicular NHL, improved by the addition of specific variables, i.e. the GISL criteria, could be of value to identify among WF group A NHL patients eligible for a *watch-and-wait* policy in IPI L risk group, patients potentially eligible for up-front very intensive approaches in an IPI H risk setting and in the IPI I group with aggressive presentation of the disease, while conventional treatment can be offered as the treatment of choice for the remaining IPI I cases.

Appendix

GISL co-operative Institutions participating in the present study:

Dipartimento di Ematologia e Oncologia (Dir. Prof. F. Nobile), Azienda Ospedaliera Bianchi-Melacrino-Morelli, Reggio Calabria; Servizio di Ematologia (Dir. Prof.ssa A.T. Maiolo), Ospedale Maggiore IRCCS, Milano; Medicina Interna e Oncologia Medica (Dir. Prof. E. Ascari), IRCCS, Policlinico S. Matteo, Pavia; Dipartimento di Ematologia e Oncologia, Presidio Ospedaliero, Pescara; Cattedra e Divisione di Oncologia (Dir. Prof. V. Silingardi), Dipartimento di Scienze Mediche, Oncologiche e Radiologiche, Policlinico, Modena; Divisione di Medicina (Dir. M. Grandi), Ospedale Civile, Sassuolo (Modena); Servizio di Ematologia (Dir. Prof. L. Gugliotta), Azienda Ospedaliera Arcispedale S. Maria Nuova, Reggio Emilia; Divisione di Medicina I, Sezione di Ematologia (Dir. Prof. L. Cavanna), Ospedale Civile, Piacenza; Sezione di Medicina I (Dir. Prof. U. Torelli), Dipartimento di Scienze Mediche, Oncologiche e Radiologiche, Policlinico, Modena; Sezione di Ematologia (Dir. Prof. G. Torelli), Dipartimento di Scienze Mediche, Oncologiche e Radiologiche, Policlinico, Modena; Clinica Medica (Dir. Prof. D. Quaglino), Università di L'Aquila-Teramo, Ospedale Civile, Teramo; Divisione di Ematologia (Dir. G. Peta), Ospedale A. Pugliese, Catanzaro; Cattedra e Divisione di Ematologia con Trapianto di Midollo (Dir. Prof. G. Mariani), Palermo.

Contributions and Acknowledgments

CS and MB conceived, designed and drafted the study; MF, as GISL Trial Office co-ordinator and FM analyzed and interpreted the data and critically reviewed the draft; LB, CP, VC, FA, VeC, FrM and LC were the main contributors of patient data; FM, MF, MB, VS finally reviewed the concepts and conclusions of the study.

CS conceived and drafted the study; LB, CP, VC, FA, VeC, GP, FrM, LC are listed in the order of the amount of data they contributed; FM, MF, MB, VS are the last names because of their peer review of the data and manuscript.

Disclosures:

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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Potential Implications for clinical practice

- The subset of indolent non-follicular non-Hodgkin's lymphoma includes patients with variable prognosis, thus suitable for a very large variety of therapeutic programs. Thus, an accurate prognostic stratification is of fundamental importance. A combination of the IPI and GIL prognostic systems could provide such a stratification.

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