Leukemia and Lymphoma, 2002 VOL. 43 (10), pp. 1933–1938

Taylor&Francis
healthsciences

Prospective Study of Indolent Non-follicular Non-Hodgkin's Lymphoma: Validation of *Gruppo Italiano Per Lo Studio Dei Linfomi* (*GISL*) Prognostic Criteria for Watch and Wait Policy

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(Received 24 April 2002)

Only recently both the *Revised European American Lymphoma* (REAL) and *World Health Organization* (WHO) classifications clearly identified indolent non-follicular non-Hodgkin's lymphoma (NHL) as a distinct group of precise histological entities. Therefore, prognostic models, specifically designed for this NHL subset, are still lacking. In this study, we prospectically evaluated the prognostic criteria proposed by the *Gruppo Italiano per lo studio dei linfomi* (GISL) to identify patients with an indolent non-progressive clinical course, eligible for a watch and wait policy within this histological subset defined according to stringent criteria of histomorphology and immunophenotype. Fifty-three patients affected with small lymphocytic, marginal zone, lymphoplasmacytic lymphoma and lacking at presentation the following: B symptoms, bulky disease, anemia, thrombocytopenia, diffuse pattern of bone marrow infiltration and short tumor doubling time, were registered in a prospective therapeutic GISL trial and addressed to a *watch and wait* program. After 41.3 months of median follow-up, the median progression free survival (PFS) was not reached and 73% of cases did not progress. When additional variables were considered, in order to improve the prognostic model, it was evident that LDH level and the number of extranodal sites were of statistical significance in the multivariate analysis. Based on this finding, a prognostic score was devised which was able to further identify a small group of patients more likely to undergo early progression, and thus suitable for immediate treatment. In conclusion, the GISL definition of indolent disease is a reliable tool to design the appropriate therapeutic strategy in this histological setting.

Keywords: Indolent non-Hodgkin's lymphoma; Prognosis; Watch and wait policy; Progression free survival; Prospective study

INTRODUCTION

Non-Hodgkin's B-cell lymphomas (NHL) are a very heterogeneous group of disorders that markedly vary with respect to presenting features and natural history [1]. The major contributions of the *Revised European American Lymphoma* (REAL) and *World Health Organization* (WHO) classification schemes were both the incorporation of several recently described new entities and the utilization of information beyond pure histopathology, such as immunophenotyping, cytogenetics and molecular characteristics [2,3]. Since clinical practice strongly requires information on outcome, patients with NHL are also classified on the basis of their life expectancy and response to therapy. Accordingly, the indolent forms of NHL include those patients with an expected survival measurable in years, with a tendency to relapse and with little convincing evidence that any therapy may be curative for advanced stages [4]. In contrast, patients with localized indolent NHL, experience a long lasting

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ISSN 1042-8194 print/ISSN 1029-2403 online © 2002 Taylor & Francis Ltd
DOI: 10.1080/1042819021000016050

disease-free survival and may be cured by radiotherapeutic approach, either alone [5] or in combination with chemotherapy [6]. Unfortunately, this group of patients represents less than 30% of the entire category of indolent NHL. On the other hand, current therapeutic recommendations for the advanced stage patients range from the single agent low-dose therapy through standard combination chemotherapy regimens [7,8] and high-dose regimens [9], to the most recent non-myeloablative approach with allogeneic stem cell support [10].

Despite so many treatment approaches and so many years of clinical trials, overall survival curves appear superimposable. This is disappointing for involved researchers considering the very long period of follow-up required to assess the impact of any therapy on natural history of indolent NHL. Another intriguing approach, as part of the overall treatment plan of the indolent NHL, is the *watch and wait* policy [11,12] where the goal is to spare or at least to defer unnecessary exposure to drug side-effects. *Watch and wait* is generally preferred when indolent NHL patients fail to show any disease-related symptoms or signs of rapid lymphoma growth. To our knowledge, the clinical profile of indolent NHL patients who can be selected for deferred therapy has until now been based on the results of retrospective studies [4]. This may be a major problem for practicing hemato-oncologists. In fact, the compliance of many patients to a no-treatment policy may be low, since this option is intentionally associated with no immediate expected action against cancer. Therefore, it is of great importance in a prospective setting to validate the selection criteria in order to address indolent NHL patients to a *watch and wait* program. In this regard, in 1993, the *Gruppo Italiano per lo Studio dei Linfomi* (GISL) designed a prospective trial on advanced indolent non-follicular NHL with both the aims to evaluate the efficacy of two randomized therapeutic programs and to validate the criteria for *what and wait* policy. The results of the latter part of the study are the subject of the present report.

PATIENTS AND METHODS

Patients

Since 1993, after two years of a pilot study, up to the time of the present evaluation 162 patients affected by histologically and immunophenotypically strictly defined indolent non-follicular NHL in advanced stage entered a still open prospective study (GISL LL01) aimed both to evaluate two different therapeutic options by randomization of cases presenting with more aggressive disease and to validate the GISL prognostic criteria by applying the *watch and wait* strategy up to progression in those cases with indolent disease presentation.

The diagnostic criteria were strict and only patients affected with small lymphocytic, lymphoplasmacytic and non-MALT marginal zone NHL according to both REAL [2] and WHO [3] classifications were included in the study. In case of leukemic phase at presentation flow cytometry analysis of peripheral blood lymphocytes was mandatory and patients were included when the immunophenotypic profile was compatible with the histologic subtypes listed above. According to the GISL prognostic system, patients were defined as presenting with aggressive disease deserving immediate treatment by the presence of at least one of the following features: B symptoms, bulky lesion (>5 cm), Hb < 10 g/dl, platelet count $< 100 \times 10^9$/l, diffuse pattern of neoplastic infiltration at bone marrow biopsy and short doubling time (<12 months) of the tumor burden. Patients without any of these features were defined as presenting with indolent disease and addressed to a *watch and wait* program. Out of 53 patients registered to GISL Trial Office for the study on indolent disease, at the time of the present evaluation 42 were evaluable for progression free survival (PFS), while the remaining 11 patients could not be included either because the histologic and phenotypic or clinical characteristics were different from the inclusion criteria or because they were lost to follow-up too early. Table I shows the main clinico-hematological data of evaluable patients. Table II shows the distribution in the present series of the variables utilized by the *International Prognostic Index* (IPI) system [13] and *Intergruppo Italiano Linfomi* (IIL) [14] for defining different risk categories in aggressive and follicular NHL, respectively. In particular, the original IPI score takes into account five unfavorable parameters (age over 60, high LDH, performance status (PS) WHO > 1, number of extranodal sites > 1) while six variables (age, sex, number of extranodal sites, B symptoms, LDH level and ESR) were considered by IIL prognostic system [14]. In the present series, all patients presented a PS WHO < 1, four patients exceeded the upper limit of LDH, one patient had > 1 extranodal site and, as required by the GISL definition of indolent disease, no patient presented B symptoms.

TABLE I Main clinico-hematological data of the present series

Number of cases with indolent disease according to GISL criteria addressed to *watch and wait* program	53
Number of evaluable cases	42
Median age, years (range)	62.6 (43–84)
Median follow-up (months)	41.3
Real classification	No. (%)
Small lymphocytic	10 (23.8)
Lymphoplasmocytic/immunocytoma	25 (59.5)
Non-MALT marginal zone	7 (16.7)
Leukemic phase	
Yes	28
No	14

Clinical staging was performed by usual investigations which included CT scan and bone marrow biopsy. Progression and response to therapy were also classified according to the currently used criteria. All patients had given their informed consent, according to the rules of each cooperative institution.

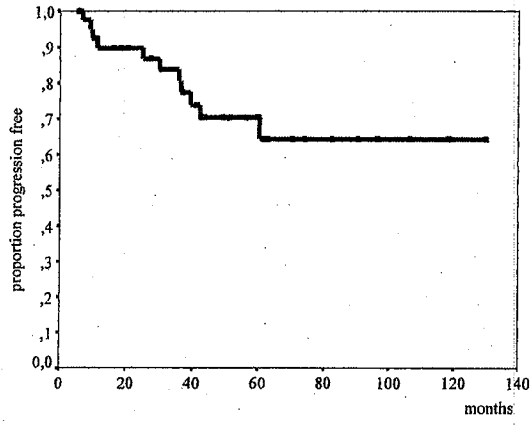

FIGURE 1 Progression free survival of the present series of non-follicular non-Hodgkin lymphoma patients with indolent disease presentation as defined by GISL criteria.

Flow Cytometry Analysis and Phenotypic Profiles

Peripheral blood mononuclear cells (PBMC) from leukemic cases, as defined by $>4 \times 10^9$/l peripheral lymphocyte count, were separated by Ficoll–Hypaque density gradient. Monoclonal antibodies (mAbs) specific for CD19 and CD23 (Becton Dickinson, Mountain View, CA), CD5, and sIg-FITC (Dako, Glostrup, Denmark) were exploited. A FITC-labeled $F(ab')_2$ preparation of a rabbit anti-mouse Ig (Becton Dickinson) was used as a secondary reagent. The events analyzed (10^4) were scored using an EPICS Profile II flow cytometer (Coulter Electronics, Hialeah, FL). Lymphocytes were gated on a two parameter forward angle vs. 90° light scatter histogram and the histograms elaborated using the XL software (Coulter).

TABLE II Prognostic variables of *International Prognostic Index* (IPI) for aggressive lymphomas and *Intergruppo Italiano Linfomi* (IIL) for follicular lymphomas: distribution in the present series

IPI variables	
Age	
≤ 60 years	16
> 60 years	26
LDH	
Normal	38
Abnormal	4
Extranodal sites	
0	5
1	36
2	1
IIL variables	
Disease stage	
II	2
IV	40
Sex	
Male	26
Female	16
ESR	
< 30	8
≥ 30	34

Statistical Analysis

All calculations were performed using the SPSS for windows, release 9.0, 1999. Age, hemoglobin level and leukocyte and platelet count were transformed into binary variables, as appropriate. PFS was defined as the time from diagnosis, which coincides with the date of the decision not to treat, to the date of first progression or last follow-up. PFS was analyzed by the method of Kaplan and Meier. Difference in PFS between prognostic groups was evaluated in univariate analysis by the log-rang test, and the respective influence on PFS of the different variable, significant at $p \leq 0.01$, was calculated in a stepwise fashion according to Cox regression method.

RESULTS

Analysis of Progression Free Survival by Clinico-hematological Variables

The median PFS of the 42 evaluable patients was not reached at 130 months, after a median follow-up period of 41.3 months (Fig. 1) and 73.4% of them did not receive therapy at 4 years. In fact, only 11 out of 42 cases actually progressed after a median period without treatment of 30.1 months (range 6.8–60.4). At progression, 5 cases were treated according to the trial, 6 with other regimens. Out of the 9 evaluable cases for response, 1 achieved a CR, 6 a PR, 1 remained stable and 1 progressed on therapy, resembling a pattern of response similar to that observed in patients treated at diagnosis. Finally, 2 out of the 11 progressed cases died because of lymphoma.

In order to possibly improve the prognostic system by the initial identification of cases more likely undergoing to progression, we evaluated whether additional variables, already utilized by the IPI and IIL models, did influence PFS of this series. Among these parameters (Table II), age, sex, disease stage and ESR failed to show any relevance, while LDH level and number of extranodal sites were associated with a shorter PFS (Fig. 2). In addition, we found that histologic subtype did not influence PFS, while hemoglobin levels, and leukemic phase and platelet counts did show some influence on PFS (Fig. 3). In spite of the limitation due to the low number of cases analyzed in this study, multivariate analysis, performed by taking into account these parameters, showed that number of extranodal sites ($p = 0.0399$) and LDH ($p = 0.0158$) remained significant. Therefore, we designed a clinical score system attributing a score 0 to patients with normal LDH and without extranodal sites, a score 1 to patients with abnormal LDH or with one extranodal site, and a score 2 to patients with two extranodal sites and to patients with both abnormal LDH and 1 extranodal site. Figure 4 shows the PFS of these three groups. The great majority of patients belonged to score 1 group while only five patients were accounted in score 0 and 2 groups with a significantly different PFS. Of the 11 progressed cases, 8 belonged to the group with score 1 and 3 cases had score 2.

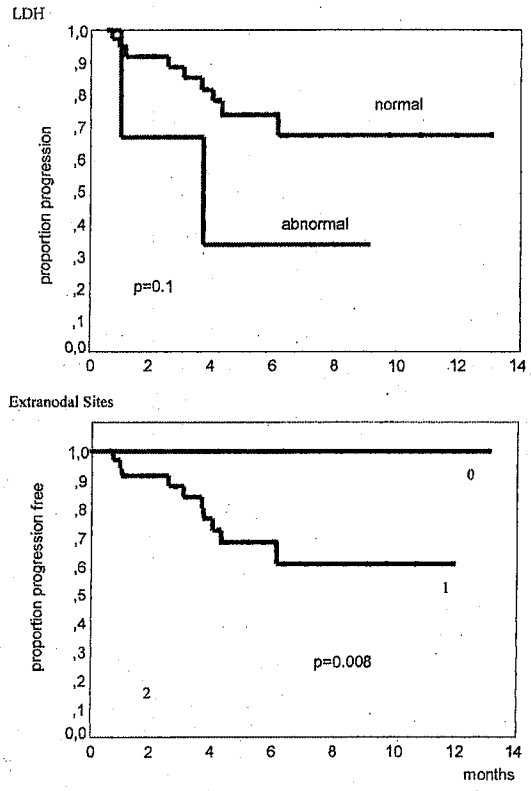

FIGURE 2 Progression free survival of patients divided according to LDH values and number of extranodal sites.

DISCUSSION

Indolent lymphomas are a markedly heterogeneous group of lymphoproliferative disorders with specific hallmarks consisting of a relatively long natural history, a continuous tendency to relapse and an inability to obtain disease eradication [4,6,8]. The heterogeneity also applies within each histologic category, thus an accurate assessment of prognostic features at presentation becomes mandatory in these NHL subtypes because of the wide variability of the therapeutic options. There are a number of factors that govern the outcome of patients presenting with NHL. Before the introduction of the REAL classification, the classifications used for NHL tended to obscure the clinical relevance of the pathological subtype. Nonetheless, additional prognostic information within the same histologic subtype are necessary to better design a correct therapeutic strategy. In fact, one of the major goal of a prognostic classification is to clearly distinguish those patients worth of aggressive or even experimental therapies from those who should avoid, or at least defer, useless drug-related toxicity.

Until now the identification of prognostic factors influencing the outcome of the specific histological subset of indolent non-follicular NHL has been explored by

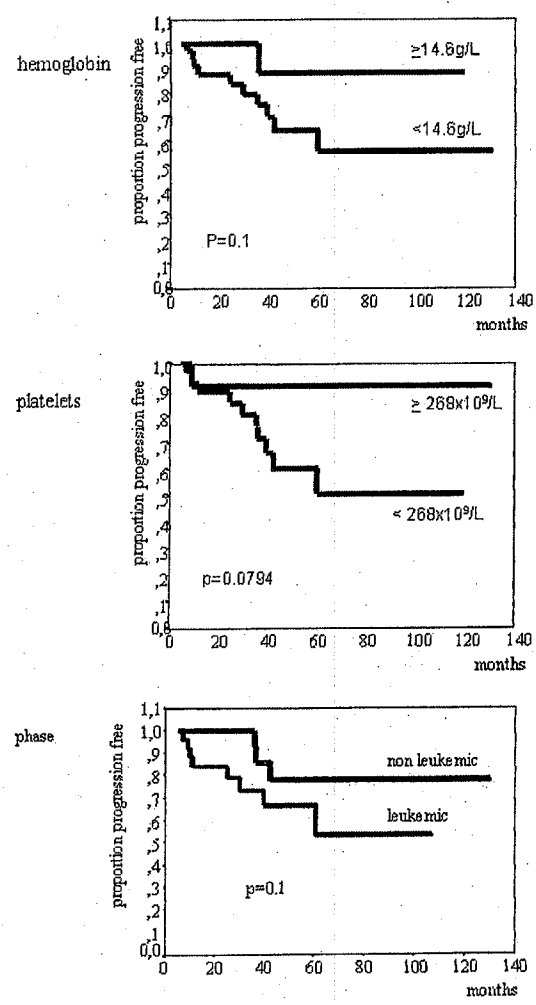

FIGURE 3 Progression free survival of patients divided according to the median cut-off values of hemoglobin and platelet counts, and of leukemic or non-leukemic presentation of the disease.

retrospective studies, often dealing with the whole category of so-called low-grade NHL; only recently was the attention focused on the subtypes of indolent non-follicular NHL [15–17]. Nonetheless, there are no prospective studies aimed to verify whether commonly used criteria to allocate the patient to a *watch and wait* policy are appropriate. At the time when the present prospective study on indolent non-follicular NHL was designed, it was planned to identify patients to be allocated to a *watch and wait* policy on the basis of recognized prognostic parameters appropriate for indolent lymphomas and also for chronic lymphocytic leukemia considering the similarity of the two disease entities, as more recently stressed by the last classifications of lymphoid neoplasms [2,3,18]. According to the GISL prognostic stratification, patients were defined as

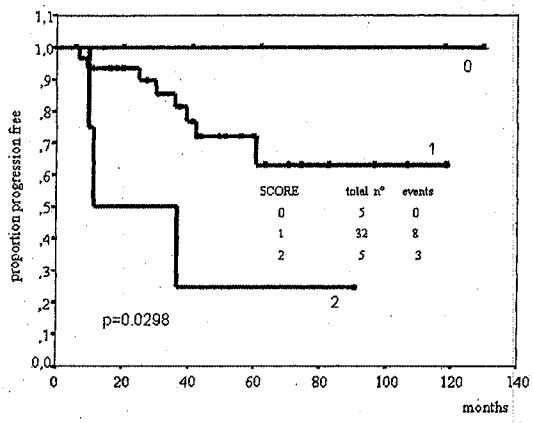

FIGURE 4 Progression free survival according to the clinical score system designed as follows: score 0 for those cases with normal LDH and absence of extranodal sites; score 1 for those with either abnormal LHD or one extranodal site; score 2 for patients with two extranodal sites or high LDH and one extranodal site.

presenting with indolent disease when the absence of all the following features were noted: B symptoms, bulky lesion, anemia, thrombocytopenia, diffuse pattern of neoplastic infiltration on the bone marrow biopsy and a short doubling time of the tumor burden. Patients fulfilling these criteria entered a *watch and wait* strategy. The aim of the study was to prospectively validate whether the GISL criteria actually recognized, among histologically classified indolent non-follicular NHL patients with a long-lasting stable disease as demonstrated by PFS duration. After a median follow-up period of 41.3 months, 26.2% of the entire population progressed, all of them in the first 5 years. Conversely, disease status remained unchanged in more than 73% of patients (31 cases) up to 96 months of observation without therapy. In particular 11 of them (36%) were censored on the plateau of the curve. Interestingly, the leukemic presentation *per se* did not represent an unfavorable prognostic factor in this histological setting, as suggested by previous reports [17,19].

We tried to establish whether variables utilized by IPI and IIL models could give additional prognostic information on this subset of NHL. The IPI, originally designed for aggressive lymphoma, has been applied and validated in indolent, follicular and non-follicular diseases [20–21]. More recently, an IIL prognostic model, able to identify patients with follicular lymphomas as low, intermediate and high risk has been described [14]. We found that an abnormal LDH level and the number of extranodal sites predicted a shorter PFS, as confirmed by multivariate analysis. In order to take into account these variables, a clinical score proposal was designed, where we attributed a score 0 to cases with normal LDH and absence of extranodal lesions, a score 1 to cases with either abnormal LHD or with one extranodal site, and, finally a score of 2 to patients with two extranodal sites or both abnormal LDH and 1 extranodal site. None of the cases with normal LDH and no extranodal lesions progressed, while only 5 out of the 42 analyzed patients, categorized as score 2, showed a significantly shorter PSF, clearly indicating that the GISL criteria for the definition of indolent disease are indeed informative and appropriate. To our knowledge, this is the first time that clinical criteria for indolent disease have been prospectively validated in a series of cases which are histologically and phenotypically accurately defined.

In conclusion, our study suggest that the adoption of the criteria specifically devised by GISL for indolent non-follicular lymphoma enables the treating physician to identify cases with a truly indolent course of the disease and potentially eligible for a *watch and wait* policy. These criteria should be considered especially for many elderly NHL patients, where a *watch and wait* policy is often the more convenient therapeutic choice.

Acknowledgements

GISL (*Gruppo Italiano per lo Studio dei Linfomi*): Coordinators Prof. E. Ascari, Prof. V. Silingardi, Cooperative Institutions participating to the present study: Dipartimento di Ematologia e Trasfusionale (Prof F. Nobile), Azienda Ospedaliera *Bianchi-Melacrino-Morelli*, Reggio Calabria; Servizio di Ematologia (Prof.ssa A.T. Maiolo), Ospedale Maggiore IRCCS, Milano; Cattedra e Divisione di Oncologia (Prof V. Silingardi), Dipartimento di Scienze Mediche, Oncologiche e Radiologiche, Policlinico, Modena; Servizio di Ematologia (Prof. L. Gugliotta), Azienda Ospedaliera *Arcispedale S. Maria Nuova*, Reggio Emilia. The present study was supported by AIL, *Associazione Italiana contro le Leucemie*, Sezione di Reggio Calabria, Italy, Associazione *Angela Serra* per la ricerca sul cancro, Modena, Italy and Fondazione *Ferrara-Storti*, Pavia, Italy.

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