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To what extent can indolent lymphoma be considered? Results of a long term follow-up study from a single center

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Abstract

Background and Objective. **In general, low-grade non-Hodgkin's lymphomas are characterized by a low to moderate proliferative activity and a long clinical course with median survival times ranging from approximately 3 years to 5-8 years. We reviewed data of 209 low-grade non-Hodgkin's lymphoma entered in our institute in 1975 to 1986 to assess their survival.**

Design and Methods. **Treatment was given according to disease stage and current protocols. Thirty patients were treated with radiation therapy, 21 patients with a single alkylating agent, 145 patients with polychemotherapy, and 13 patients were included in the *watchful waiting* conservative approach.**

Results. **With a median follow-up of 13 years, the actuarial overall survival rates at 5, 10, and 15 years were 60%, 38%, and 27%, respectively. The relapse-free survival was 66% at 5 years, 57% at 10 years, and 45% at 15 years. Concerning the 38 continuous complete responders, 21 were stage I-II and 17 were patients in advanced stage (III-IV).**

Interpretation and Conclusions. **Therapy of low-grade lymphomas depends mainly on the extent of the disease. Advanced stage disease is often considered incurable. The possibility to obtain a little percentage of complete response must provide considerations in the search for new therapeutic strategies.**

Key words: radiation therapy, chemotherapy, complete response, long-term follow-up

The different histological subtypes that constitute the group of disorders known as low-grade non-Hodgkin's lymphoma (LG-NHL) are characterized by several common features: disease is often widespread at the time of diagnosis; it usually responds to chemotherapy, and patients with the most advanced stage presentations manifest a continuous relapse pattern after they have achieved complete response (CR). In spite of the disseminated nature of the disease and its tendency to relapse, the median survival is usually approximately 8 years. The data of several studies indicate that patients with stages I and II experience long lasting disease-free survival and may even be cured by extended field or total nodal irradiation using doses of around 30 Gy.[1-5] It has been reported that the addition of chemotherapy to radiation therapy may increase the probability of cure for patients with stages I or II.[6] In contrast to the clear indication for radiation therapy in limited stages of the disease, controversy continues about the most appropriate treatment of patients in stages III and IV.[7-16] Current recommendations range from the *watch and wait* approach, through single agent low-dose therapy and combination regimens of intermediate intensity to high-dose protocols and even myeloablative chemo-radiotherapy followed by subsequent bone marrow or peripheral stem-cell transplantation. The survival curves for patients in advanced stages treated by a variety of approaches all resemble one another closely:[17-19] half the patients survive for nearly 10 years from diagnosis, but only a quarter remain disease free during this time, with the majority having several regressions and recurrences.

To reassess the state of the current clinical art, we reviewed the clinical course of 209 newly diagnosed patients with LG-NHL at our institute over a 12-year period. During this time, we developed a program of treatment resulting in a median overall survival of 8 years with careful allocation of treatment according to disease presentation.

Patients and Methods

Patient population

Between January 1975 and December 1986, 209 patients were presented to our institute with previously untreated LG-NHL. Diagnostic specimens of all patients were reviewed and classified according to the updated Kiel classification.[20] Staging evaluation included initial hematologic and chemical survey, in addition to chest x-rays, computerized tomography of the chest and abdomen, and bone marrow biopsy in all patients. Bulky disease was defined as a tumor mass ≥ 6 cm. Staging and definition of extranodal sites were based on the Ann Arbor classification.[21] The characteristics of the 209 patients are shown in Table 1.

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Table 1. Characteristics of 209 LG-NHL patients.

No. of patients	209
Sex (M/F)	118/91
Median Age (range)	54.5 (24-79)
No. of patients with age <60 years	118 (56%)
Histology	
follicular	134 (64%)
immunocytoma	65 (31%)
small lymphocytic	10 (5%)
Symptoms	
No	197 (94%)
Yes	12 (6%)
Stage	
I	31 (15%)
II	24 (12%)
III	32 (15%)
IV	122 (58%)
Bulky	
Yes	16 (8%)
No	193 (92%)
Bone marrow involvement	
Yes	104 (50%)
No	105 (50%)

Treatment subsets

Localized lymphoma patients were usually treated with involved field radiation therapy; disseminated lymphoma patients were usually treated with chemotherapy (courses of chlorambucil or cyclophosphamide 10 days a month) or multidrug regimens (CVP [cyclophosphamide, vincristine and prednisolone], MEV [methotrexate, vepesid and vincristine],[22] CHOP [cyclophosphamide, doxorubicin, vincristine and prednisolone], and m-BACOD [methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and prednisolone]). The time from the initial diagnosis of LG-NHL to the start of the treatment ranged from 3 to 153 months (median 6 months); for all patients it was possible to wait 6-9 months from the time of diagnosis before starting with the treatment. Table 2 summarizes the therapeutic approach related to the stage disease.

Watchful waiting

Only 13 patients were included in this conservative approach.

Radiation therapy

Twenty-seven patients with stage I and II disease were treated with radiation therapy. The treatment volume for involved-field radiation therapy encompassed the known tumor volume with a margin and often included one or more uninvolved lymph node groups. Total radiation doses of 35 Gy to 50 Gy were given in 1.5 to 2.5 Gy fractions five times per week in 20 fractions over 28 days; most patients received ≤ 45 Gy.

Chemotherapy

A single alkylating agent was given in 21 cases (15 chlorambucil plus prednisolone and 6 cyclophosphamide and prednisolone, respectively). One hundred and forty-five patients were treated with combination chemotherapy: of these 107 received conventional chemotherapy without anthracycline (88 CVP regimen and 19 MEV) and 38 had anthracycline-containing regimens (31 CHOP and 7 m-BACOD).

Table 2. Treatment at presentation related to the stage disease.

	I	*II*	*III*	*IV*	*Total*
Watchful waiting	4	/	4	5	13
Radiotherapy	18	9	/	3	30
Monochemotherapy	/	/	1	20	21
Polichemotherapy					
without anthracycline	11	14	18	64	107
with anthracycline	/	1	9	28	38
Total	31	24	32	122	

Response

Complete response (CR) was defined as the complete disappearance of signs and symptoms due to disease, as well as the normalization of all previous abnormal investigations. Partial response (PR) was defined as at least 50% reduction of known disease with disappearance of the systemic manifestations. No response was anything less than PR. We checked the response one month after the cessation of treatment by repeating radiologic or other examinations to ensure an accurate re-evaluation of all manifestations due to lymphoma. The survival curve was measured from entry into the protocol until death; the relapse-free survival interval was calculated from the date of response until relapse or death. Survival and relapse-free survival curves were calculated according to the method of Kaplan and Meier.[23]

Statistical methods

Outcome was analyzed according to Cox's linear logistic model,[24] adjusting for six prognostic factors: age, sex, stage according to Ann Arbor staging system,[21] histologic subtype according to the updated Kiel classification,[20] presence or absence of bone marrow involvement, and different therapeutic approach. Unfortunately, we could not apply the *International Prognostic Index*,[25] as performance status and LDH level data were not available in all patients. To assess the effect of covariates on the relapse-free survival time, Cox's proportional hazards model was fitted.[26] These two tests were performed with the SOLO statistical system (version 4.0) distributed by BMDP Statistical Software, Inc (Los Angeles, CA, USA). Chi-square test was used whenever appropriate for comparison of groups or group variables, with two-sided P values being used throughout.

Table 3. Complete response rates to first treatment.

Sex		
Male	57/118 (48%)	p=ns
Female	51/91 (56%)	
Age		
< 60	71/118 (60%)	p=0.005
> 60	37/91 (41%)	
Histology		
follicular	77/134 (57%)	p=0.003
immunocytoma	23/65 (35%)	
small lymphocytic	8/10 (80%)	
Bone marrow		
Yes	29/104 (28%)	p=0.000
No	79/105 (75%)	
Stage		
I	27/31 (87%)	p=0.000
II	23/24 (96%)	
III	17/32 (53%)	
IV	41/122 (33%)	
First treatment		
Radiotherapy	27/30 (90%)	
Monochemotherapy	2/21 (9%)	
Polichemotherapy		
without anthracycline	55/107 (51%)	p=ns
with anthracycline	24/38 (63%)	

Results

With a median follow-up time of 13 years, the overall median survival duration was 9 years. At the time of analysis, 59 patients were alive (51 with no evidence of disease and 8 with relapse) and 150 were dead (127 from lymphoma, 14 from intercurrent disease, 6 from second cancer and 3 for undetermined reasons). All 23 patients who died from causes unrelated to lymphoma were in CR.

Response rate

With regard to disease stage, we observed CR in 27/31 (87%) stage I patients, 23/24 (96%) stage II patients, 17/32 (53%) stage III patients, and 41/122 (33%) stage IV patients (stages I-II vs. stages III-IV: 91% vs. 38%, P= 0.000). Global CR rate was 52% (108 patients); 70 patients relapsed. The median duration of first response was 39 months. Among 55 stage I-II patients, 27 were treated with radiation therapy alone and 28 with combination chemotherapy; the CR rate was 92% and 83%, respectively (Table 3).

No statistically significant difference in terms of CR rate was reported between anthracycline containing regimens and conventional chemotherapy without anthracycline (63% versus 51%, and 49% versus 44% including only advanced stage patients). With respect to histology, the CR rate for the follicular subtype was 57% (77/134), whereas the immunocytoma lymphoplasmacytoid subtype presented a CR rate of 35% (23/65) (P= 0.003). Among the few cases of the small lymphocytic variety the CR rate was 80% (8/10). No relationship was observed between sex and CR rate (48% in males and 56% in females). With regard to bone marrow involvement, we observed CR in 29/104 (28%) patients with bone marrow involvement, and in 79/105 (75%) patients without bone marrow involvement (p=0.000). As regards age, patients greater than 60 years of age had a CR rate of 41%, as compared with patients less than 60 years of age who obtained a CR rate of 60% (p= 0.005).

Concerning the 13 patients of the initial no-treatment policy (*watchful waiting*) subset, at a mean follow-up time of 53 months, 12 patients experienced disease progression; only one patient died from intercurrent disease (after 252 months, without lymphoma progression).

Evaluation of the percentages of histologic progression was impossible because in this period the lymph node biopsy was not yet a routine investigation at the time of progression or relapse time.

Overall survival analysis

Figure 1 shows the actuarial overall survival rate for the entire group: 5, 10 and 15-year overall survival were, respectively 60%, 38%, and 27%. At the time of writing, 59 patients are still alive: of these 38 (18%) are in first CR, 13 (6%) in second CR, and 8 (4%) have disease. Concerning stage I-II patients, in the radiotherapy subset 63% of patients are still alive versus 54% of patients treated with combination chemotherapy.

A number of potential prognostic factors at the time of presentation were analyzed for their impact on survival: CR occurrence, age (<60 years vs. >60 years), stage (I-II vs. III-IV), bone marrow involvement, histologic subtype (follicular vs. immunocytoma lymphoplasmacytoid), and chemotherapy regimen (anthracycline containing regimens vs. anthracycline noncontaining regimens). In univariate analysis, we observed four significant parameters: age (Figure 2), stage (Figure 3), CR occurrence (Figure 4), and bone marrow involvement (Figure 5). Anthracycline and histologic subtype did not influence overall survival. At multivariate analysis (CR occurrence was excluded from multivariate analysis since it is a post-treatment factor), age (p = 0.001), stage (p = 0.02), and bone marrow involvement (p = 0.03) remained significant.

Relapse-free analysis

Relapse-free survival was 66% at 5 years, 57% at 10 years, and 45% at 15 years (Figure 1) with a median of 156 months; these data included 38 patients in first CR and 13 in second CR, giving a total of 51 (24%) patients (Table 4).

Univariate analysis of the 38 patients in continuous first CR indicate that longer relapse-free survival was significantly correlated with age (> 60 years), stage I-II, and the radiation therapy approach (only for stage I-II). At multivariate analysis, age (p = 0.002) and stage (p = 0.03) remained significant prognostic factors for relapse-free survival.

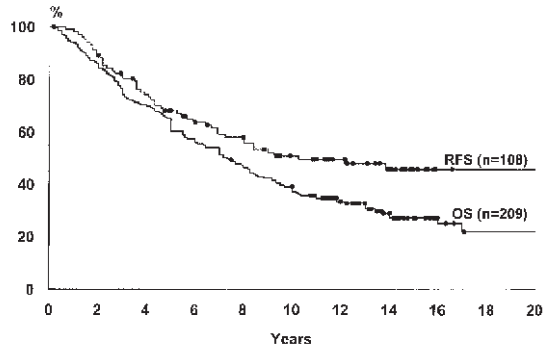

Figure 1. Overall survival (OS) and relapse-free survival (RFS) curves of 209 and 108 LG-NHL patients, respectively.

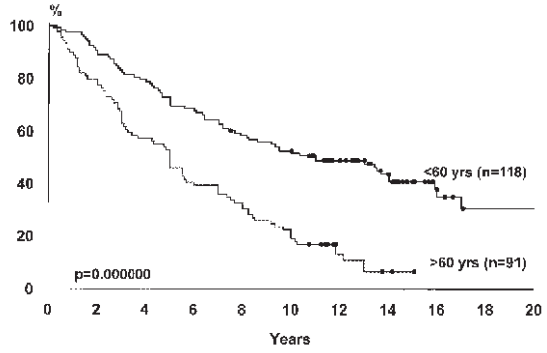

Figure 2. Overall survival curves according to age: <60 years vs. >60 years.

Discussion

LG-NHL, sometimes also referred to as indolent lymphoma, represents a heterogeneous group of B-cell lymphoproliferative disorders that reflect the functional and morphologic heterogeneity of the normal B-cell system. Their clinical hallmarks include a relatively long natural history, and treatment regimens interspersed with multiple relapses. In contrast to the rapidly expanding insights into the biology of the lymphatic system and the pathogenesis of lymphoproliferative disorders, comparatively little progress has been achieved in the treatment of LG-NHL. In fact, after decades of empirical trials, including attempts to deliver high-dose chemotherapy with autologous bone marrow transplantation, overall survival has remained essentially unchanged at 7-12 years from initial diagnosis. Most importantly, even after aggressive forms of therapy, there is no consistently observed *plateau* in the survival curves, suggesting that these patients are incurable with current approaches. The present series, comprising a large number of patients, treated and followed up in the same institution over a long period (median follow-up: 9 years) provides an opportunity to reassess and

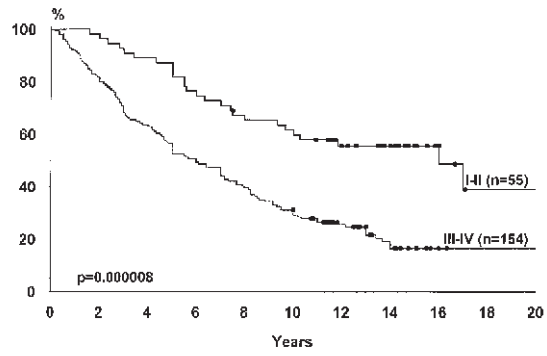

Figure 3. Overall survival curves according to stage: I-II vs. II-IV.

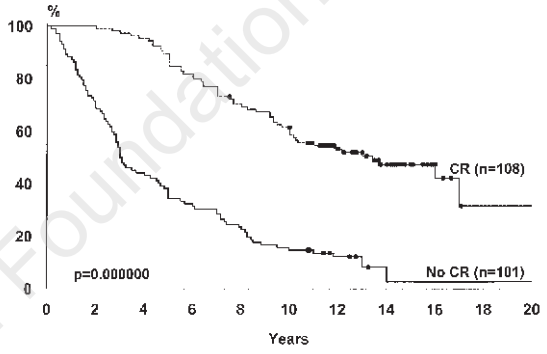

Figure 4. Overall survival curves according to CR occurrence: no CR vs CR.

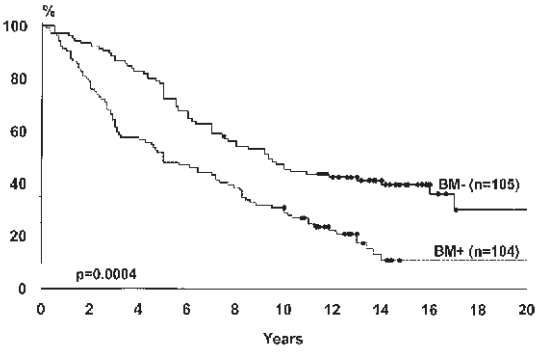

Figure 5. Overall survival curves according to bone marrow involvement: no vs. yes.

comment the current clinical situation.

Our results strongly underlined the importance relevance of staging for prognosis. The statistical data regarding poor prognostic factors (correlated with lower overall survival and higher incidence of relapse) confirmed the relevance for overall survival of age, stage,

Table 4. Continuous CR rates of 108 patients.

Sex		
Male	23/57 (40%)	p=ns
Female	15/51 (29%)	
Age		
< 60	33/71 (46%)	p=0.00006
> 60	5/37 (13%)	
Histology		
follicular	29/77 (38%)	p=ns
immunocytoma	6/23 (26%)	
Bone marrow		
Yes	7/29 (24%)	p=ns
No	31/79 (39%)	
Stage		
I	15/27 (56%)	p=ns
II	6/23 (26%)	
III	3/17 (18%)	
IV	14/41 (34%)	
First treatment		
Radiotherapy	14/27 (52%)	
Monochemotherapy	0	
Polichemotherapy		
without anthracycline	14/55 (25%)	p=ns
with anthracycline	10/24 (42%)	

CR occurrence and bone marrow involvement at univariate analysis, and of age (>60 years), advanced stages (III-IV), and bone marrow involvement at multivariate analysis. As regards relapse-free survival, age (>60 years) and advanced stages (III-IV) proved significant at both univariate and multivariate analysis.

Stage I-II patients, 50/55 (91%) obtained a CR, 21/50 (42%) of whom are still alive without disease, having undergone radiation therapy alone. Radiation therapy has been considered standard treatment for limited-stage LG-NHL, leading to cure in a large fraction of treated patients.[1-5] In the literature, stage has been recognized as an important prognostic factor both for relapse-free survival and overall survival: whereas patients with stage I disease have a relapse-free survival rate of 50-80% after irradiation alone, those with stage II disease have a relapse-free survival rate of only 30-40%.[27-30] Among our patients, we obtained a continuous CR (CCR) rate of 56% for stage I and 26% for stage II, respectively. This leads us to conclude that for early stage patients radiation therapy alone can permit a high CR rate with a long relapse-free survival rate, giving a cure rate of about 50%, comparable to that of advanced stage high-grade NHL patients. However, because of the indolent nature of the disease, most cases of LG-NHL are diagnosed at a later stage. Among our patients with stage III-IV disease, the CR rate was 38% (53% for stage III and 33% for stage IV, respectively) and the CCR rate was 26% (18% for stage III and 34% for stage IV, respectively). All these patients underwent chemotherapy regimens; the introduction of doxorubicin did not show any benefit either for CR rate, relapse-free survival or overall survival.

Advanced stage LG-NHL is often considered an *incurable disease*. However, we think that this expression may not be altogether appropriate, since our data and the reports of others document a small but relevant percentage (11% of the initial patients in our series) of patients who achieve a long CCR. This observation could provide food for thought in the search for new therapeutic strategies. It is to be hoped that future investigations will lead to the identification of unfavorable biological factors (such as p53, bcl-2, bcl-x_L, CDK family, sCD23, tumor necrosis factor-α, and vascular endothelial growth factor).[31-33] This could provide a key to separate those patients who require immediate treatment (distinguishing conventional and high-dose therapies) from those with relatively indolent disease, for whom deferral of initial treatment, single-agent therapy, or conservative chemotherapy (such as chlorambucil- or cyclophosphamide-prednisone) may be appropriate. As regards novel new therapeutic perspectives, the new purine analogs[34-36] and probably some of the anthracycline analogs (e.g., idarubicin)[37,38] appear more effective than the alkylating agents in providing favorable response rates for LG-NHL. Furthermore, immunologic approaches could allow elimination of residual malignant cells responsible for relapses following chemotherapy-induced remissions.[39,40] So it is not unreasonable to hope that a long-awaited improvement in the outlook for advanced stage patients may be on the horizon.

Contributions and Acknowledgments

PLZ was the principal investigator responsible for the conception of the study, its design, and the writing of the paper. FG helped the principal investigator (PLZ) for data analysis and interpretation. MM, MB, PA, EM collected the study data. ST revised critically the paper and gave the final approval for publication.

The order of authorship has been made according to the substantial contribution given to the study.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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