Leukemia & Lymphoma, VOL. 44, No. 11 (November 2003), pp. 1911–1917

Taylor&Francis healthsciences

The Role of Anthracyclines in Combination Chemotherapy for the Treatment of Follicular Lymphoma: Retrospective Study of the *Intergruppo Italiano Linfomi* on 761 Cases

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(Received 14 April 2003)

In order to elucidate the role of anthracycline based combination chemotherapy regimens for the treatment of follicular lymphoma we conducted a retrospective study on a large series of patients with a histologically confirmed diagnosis of follicular lymphoma. The Italian lymphoma intergroup (ILI) promoted a retrospective study of patients with follicular lymphoma treated in cooperative trials between 1985 and 1996. Six hundred and thirty three cases were treated with an anthracycline-containing regimen and 128 patients were treated without anthracyclines. The two groups were prognostically comparable; in particular, no difference was observed according to both IPI and ILI prognostic index. Results showed a complete remission (CR) rate for patients treated with anthracyclines was 69.2% and overall response rate was 92.5%. After a median follow-up of 51 months (54 months for patients still alive), the 5- and 10-year overall survival (OS) rates were 80 and 66%, respectively. Disease-free survival (DFS) and failure-free survival (FFS) rates at 5 years were 61 and 49%, respectively.

In the group of patients treated with combination chemotherapy not including anthracyclines, the CR rate was 67.5% and the overall response rate was 85.4%. A longer OS (80% at 5 years) was observed in patients treated with anthracyclines compared to 67% OS rate in patients treated without anthracyclines ($p = 0.0004$). FFS was significantly longer in patients treated with anthracyclines (49 vs. 34% $p = 0.006$). Patients treated with anthracyclines with low or intermediate risk according to ILI prognostic index showed a significantly longer OS ($p = 0.0001$ and $p = 0.0009$, respectively); those in the high-risk group showed a trend for a longer survival. In conclusion, this retrospective study shows that patients with follicular lymphoma treated with an anthracycline containing regimen had a better outcome compared to patients treated with other combination regimens non including anthracyclines in terms of CRs, OS and FFS. On the basis of these results anthracycline-containing regimens (ACR) should be considered as the standard treatment of patients with advanced follicular lymphoma.

Keywords: Follicular lymphoma; Anthracycline containing regimen; Conventional chemotherapy; Disease-free survival

INTRODUCTION

Follicular lymphomas represent one of the most frequent subtypes of malignant lymphoma in Western countries [1,2] and are considered as indolent diseases on the basis of their long survival in spite of frequent relapses. The inability of combination chemotherapy and radiation therapy to eradicate the disease has led to radically divergent treatment approaches ranging from a "watch and wait" policy to high dose chemotherapy with stem

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ISSN 1042-8194 print/ISSN 1029-2403 online © 2003 Taylor & Francis Ltd
DOI: 10.1080/1042819031000123564

cell transplantation [3–6]. Since the majority of these patients initially respond to low dose oral alkylating agents for a long period, more aggressive treatment was not considered for a long period of time. However, the high sensitivity of this disease to single agent chemotherapy is not associated with the achievement of a durable complete remission (CR). The large experience and long follow-up of patients from St Bartholomew's hospital with 299 consecutive cases treated with single agent therapy showed a median survival of about 10 years with a natural history of the illness characterized by a continuous pattern of relapse [7]. Better results in terms of CR rate and disease-free survival (DFS) were reported with combination chemotherapy especially when anthracyclines were employed [8,9]. However, no randomized study demonstrated the superiority of combination chemotherapy. Recently, particularly in younger patients, high dose therapy has been proposed for the purpose of obtaining a high percentage of durable complete clinical and molecular remissions and, if possible, cure of the disease [10–13]. In the last years the Italian lymphoma intergroup (Intergruppo Italiano Linfomi) (ILI) has collected information on a large series of follicular lymphoma patients treated at cooperating centers from 1985 to 1996 and developed a prognostic index specifically devised for this disease [14].

Furthermore, the impact of anthracyclines in combination chemotherapy regimens on disease outcome was investigated. We report here the results of this analysis, performed by comparing 633 patients treated with anthracycline-containing regimens (ACR) to 128 cases treated with cyclophosphamide, vincristine, prednisone (CVP) or CVP-like therapy.

METHODS

Eligibility Criteria

We considered eligible for this study the same 987 cases from whom the prognostic index was developed [14]. These patients had a histologically confirmed diagnosis of centroblastic-centrocytic follicular lymphoma, including follicular large-cell lymphoma, according to the updated Kiel classification [15] and were enrolled in prospective clinical trials or treated at participating centers according to specific guidelines between 1985 and 1996. Initial diagnosis was not revised, and thus the grading of follicular lymphoma was not assessed. Out of these 987 cases, 761 patients with active disease were treated with combination chemotherapy.

Information on parameters already known as prognostically relevant were collected. In particular, bone marrow and spleen as sites of extranodal involvement were added to other extralymphatic tissues, while peripheral blood involvement was not recorded for the purpose of this study. Bulky disease was defined as a mass with the largest dimension greater than or equal to 10 cm or, for mediastinum expansion, larger than one-third of the chest diameter. All patients were clinically staged according to the Ann Arbor staging classification [16] and recurrent fever (more than 38°C), night sweats or the loss of more than 10% of body weight were defined as systemic symptoms. Due to the retrospective character of the study, all variables were not always available for each patient.

Response to therapy was assessed uniformly 1 month after the end of induction therapy by performing laboratory and instrumental examinations needed to assess abnormal findings present at diagnosis. CR was defined as the disappearance of all clinical, laboratory and instrumental evidence of the disease, including normalization of bone marrow, if initially involved. Partial remission (PR) was defined as a greater than 50% reduction in the largest dimension of each anatomic site of measurable disease for at least 1 month. No response (NR) was defined as less than 50% regression or stable or progressive disease. All early deaths due to disease progression or treatment-related toxicity were considered to be treatment failures, and included in the NR group.

The evaluations of clinical stage and response to therapy were based on the original data recorded by local physicians.

All 761 patients considered for this study were treated with combination chemotherapy, with or without anthracyclines. Out of 633 patients treated with ACR, 426 (70%) received CHOP (cyclophosphamide, hydroxyldaunomycin, vincristine [Oncovin], and prednisone) [17] or CHOP-like regimens (other doxorubicin-containing regimens) [18,19]; 106 (14%) were treated with second generation regimens [20] and 101 (16%) received third generation regimens [21,22]. One hundred and twenty-eight (17%) patients were treated without anthracyclines, receiving CVP [23] or CVP-like regimens. Patients' characteristics are summarized in Table I.

The two groups of patients appeared prognostically comparable; in fact, although some differences were found between the two groups with some favorable prognostic variables more common in the ACR group (better performance status and younger age lower percentage of extra nodal involvement) and other ones in the CVP subset (female sex, normal LDH), overall, there was no significant difference in the distribution of patients among the different risk groups as defined by both IPI and ILI prognostic scores. The ILI prognostic model was developed using six variables identified with a multivariate analysis. They were: age (over 60 years), sex (male), B symptoms, number of extra nodal sites (more than one), LDH level (elevated level) and ESR (more than 30) [14].The ILI score defined three risk groups with different prognosis.

All data were analyzed with the statistical package for the social sciences (SPSS) [24]. Differences in response rates and treatment failures were analyzed by the Fisher's exact test for contingency tables. Overall survival (OS), relapse free survival (RFS) and failure

TABLE I Characteristics at diagnosis of 761 patients: 128 treated with combination chemotherapy without anthracyclines (CVP or CVP-like), and 633 treated with anthracyclines containing regimens

Characteristics (number evaluable)	Regimens without anthracylines number (%)	Regimens with anthracyclines number (%)	p
Sex (761)			0.03
Male	51 (39.8%)	318 (50.2%)	
Female	77 (60.2%)	315 (49.8%)	
Symptoms (755)			n.s.
Absent	112 (87.5%)	521 (83.1%)	
Present	16 (12.5%)	106 (16.9%)	
LDH value (697)			0.01
Normal	98 (90.7%)	476 (80.8%)	
Abnormal	10 (9.3%)	113 (19.2%)	
Hemoglobin value (654)			n.s.
Normal	108 (90%)	496 (92.9%	
Abnormal	12 (10%)	38 (7.1%)	
ESR value (622)			n.s.
Normal	88 (79.3%)	421 (82.4%)	
Abnormal	23 (20.7%)	90 (17.6%)	
Albumin value (546)			n.s.
Normal	87 (94.6%)	436 (96%)	
Abnormal	5 (5.4%)	18 (4%)	
Performance Status (578)			0.04
0–1	99 (86.1%)	426 (92%)	
2–4	16 (13.9%)	37 (8%)	
No. of extranodal sites (761)			0.01
0–1	116 (90.6%)	606 (95.7%)	
> 1	12 (9.4%)	27 (4.3%)	
Stage (761)			n.s.
I-II	26 (20.3%)	156 (24.6%)	
III-IV	102 (79.7%)	477 (75.4%)	
Age (761)			0.000
< 61	62 (48.4%)	424 (67%)	
> 60	66 (51.6%)	209 (33%)	
Bone marrow (757)			n.s.
Negative	56 (43.8%)	296 (47.1%)	
Positive	72 (56.3%)	333 (52.9%)	
Bulky disease (761)			n.s.
No	111 (86.7%)	549 (86.7%)	
Yes	17 (13.3%)	84 (13.3%)	
ILI risk score (574)			n.s.
Low risk	55 (58.5%)	288 (60%)	
Intermediate risk	27 (28.7%)	121 (25.2%)	
High risk	12 (12.8%)	71 (14.8%)	
IPI risk score (576)			n.s.
Low risk	87 (75.7%)	371 (80.5%)	
Low-intermediate risk	24 (20.9%)	67 (14.5%)	
Intermediate-high risk	3 (2.6%)	18 (3.9%)	
High risk	1 (0.9%)	5 (1.1%)	

free survival (FFS) curves were estimated by the method of Kaplan–Meier.

The date of start of therapy was not available in some cases, thus the survival was calculated from the date of diagnosis until death from any cause. However, the mean interval between the date of diagnosis and start of therapy in patients with complete data was less than 1 month. RFS was applied only to patients in CR and was calculated from the end of induction therapy to the first evidence of relapse. FFS was calculated for all patients and was measured from the beginning of therapy to the time of disease progression (date of assessment of response for patients with less than PR; date of start of second line therapy for patients with PR), relapse (for patients in CR) or death. The log-rank test was used to assess the difference in survival for each prognostic factor. The Cox proportional hazards regression model was used in multivariate analysis to determine whether the identified risk factors independently influenced SR. In addition, the possible impact of age was analyzed using a test for equality of survival distribution [24] for therapy adjusted for age. The limit of significance for all analyses was defined as $p = 0.05$. Two sided tests were used in all calculations.

RESULTS

Response to therapy was assessable in 710/761 patients (93.3%). Overall response rate was 91.3, 92.5% for ACR and 85.4% for non-ACR treated cases ($p = 001$). In the group of ACR treated patients, 406 cases achieved CR (69.2%), 137 obtained PR (23.3%) and 44 patients (7.5%) did not respond to therapy or showed progressive disease.

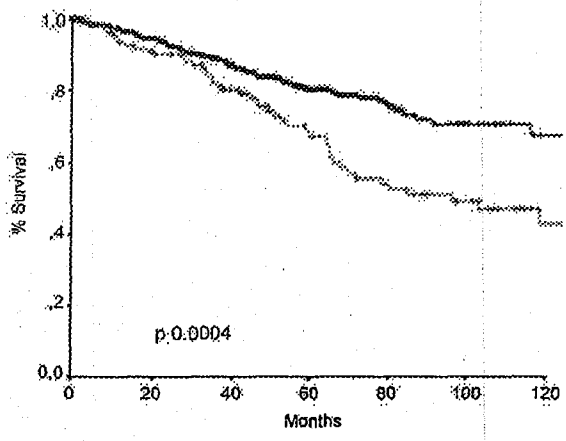

FIGURE 1 Overall survival. Anthracycline containing regimens: mean 112 months (106–118), median not reached (upper line). Non anthracycline containing regimens: mean 94 (83–105), median 97 (55–137) (lower line). $p = 0.0005$.

Among patients treated without anthracyclines 83 cases (67.5%) obtained CR, 22 obtained PR (17.9%) and 18 patients (14.6%) did not respond to therapy or showed a progressive disease.

After a median follow-up of 51 months (54 months for patients still alive), 150 patients had died: 104 (16.4%) in the group of ACR treated cases and 46 (35.9%) in the group of patients treated without anthracyclines. Out of 611 living patients 49 cases (6.4%) lost to follow-up were considered censored at the date of their last contact (29 in CR and 20 alive with disease). The 5- and 10-year OS rates were 80 and 66% for ACR treated patients and 67 and 42% for patients treated without anthracyclines, respectively ($p = 0.0004$) (Fig. 1). In the whole series FFS at 5 and 10 years was 46 and 25%, respectively, with a significant difference between the two groups of therapy; in fact 5- and 10-year FFS was 49 and 30% for patients treated with anthracyclines and 34 and 12% for patients treated without anthracyclines ($p = 0.006$) (Fig. 2).

To assess the value of the type of treatment we performed a multivariate analysis including ILI prognostic score and therapy. This analysis (Table II) showed that both ILI and therapy had an independent prognostic impact on survival. Moreover, in a survival analysis adjusted for age, which could be the main influencing feature at diagnosis, the type of therapy retained its statistically significant relevance ($p = 0.01$). Finally, when patients were divided according to their ILI risk score, we observed a significant difference in OS for low or intermediate risk patients treated with ACR compared to patients treated without anthracyclines with 5- and 10-year survival rates of 93 and 72% vs. 78 and 43%, respectively, in the low risk group ($p = 0.0001$) and 80 and 78% vs. 46 and 35%, respectively, in the intermediate risk group ($p = 0.0009$) (Fig. 3a and b).

In the small group of patients with a high ILI risk score no statistical difference was observed between the two groups of treatment although a trend toward a better outcome was observed in patients treated with anthracyclines (Fig. 3c). In patients achieving CR no difference in RFS was observed regardless of type of initial therapy.

DISCUSSION

This large retrospective study considered 761 patients treated because of active disease and clearly demonstrates that treatment of follicular lymphoma with ACR affects positively the outcome of the disease. A group of patients

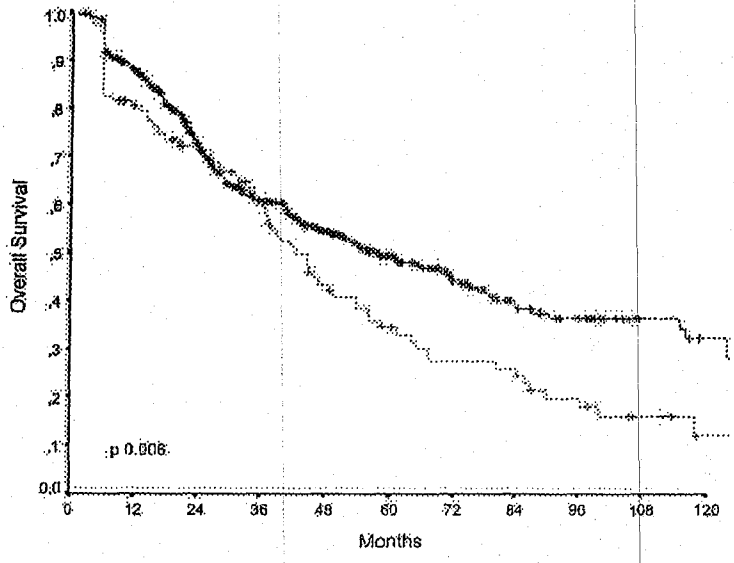

FIGURE 2 Failure-free survival. ACR upper line and non ACR lower line.

TABLE II Factors with independent prognostic impact on survival at multivariate analysis

Factor	Relative risk	95% CI	p value
ILI prognostic index (low vs. intermediate vs. high risk)	2.5	1.9–3.2	0.000
Type of therapy (no anthracyclines vs. anthracyclines containing regimens)	0.3	0.2–0.5	0.000

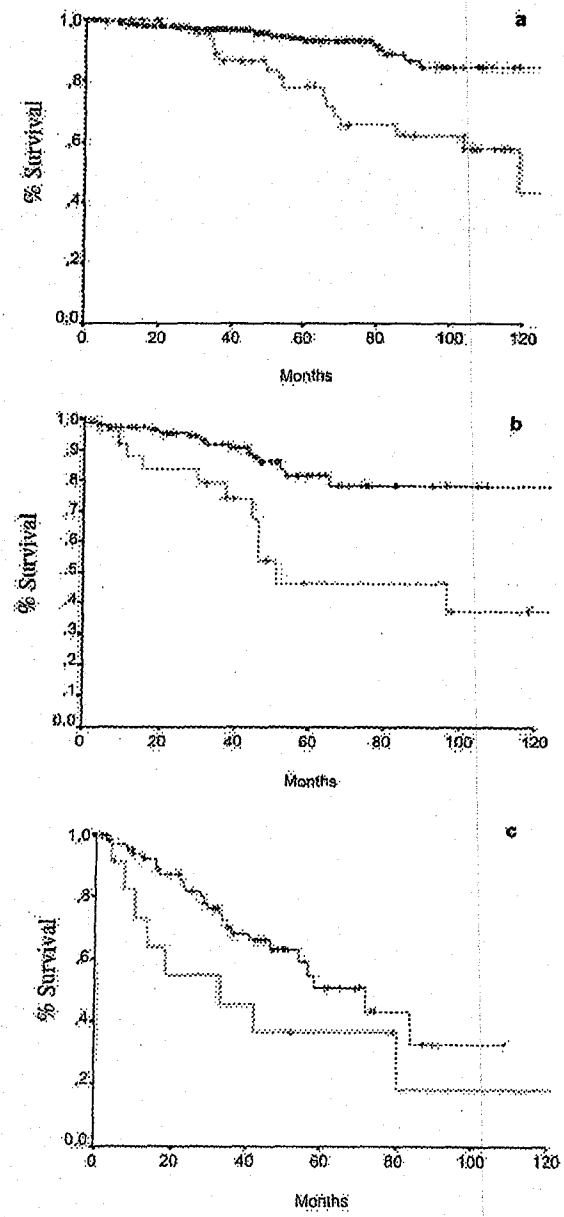

FIGURE 3 Overall survival of patients divided according to ILI prognostic index. Low (a), intermediate (b) and high (c) risk. Upper line regimens with anthracyclines and lower line regimens without anthracyclines.

treated with ACR (633 cases) was retrospectively compared to a group of patients (128 cases) treated with combination chemotherapy without anthracyclines. In spite of some differences of the clinical and laboratory features at presentation, the two groups were comparable according to both IPI [25] and ILI [14] prognostic scores. The present retrospective study shows that the use of anthracycline in the treatment of follicular lymphoma improves the overall outcome by reducing the failure rate. In fact, the overall response rate was 92.5% for patients treated with anthracyclines and 85.4% for the group of patients treated with CVP or other CVP-like regimens ($p = 0.01$). The same high CR and OR rate have been recently reported with the use of FND regimen [26] or R-CHOP protocol [27] in patients with follicular lymphoma. These results significantly affect OS with 5-year OS rate of 80 vs. 67% in the two groups, respectively ($p = 0.0004$). It was possible to rule out that the better outcome of ACR treated patients was not related to their younger age compared to patients treated without anthracyclines by the results of survival analysis adjusted for age; in this analysis also survival was significantly longer in the ACR treated group. The analysis of OS has shown a median improvement of 38 months in the group of patients treated with anthracyclines compared to the group treated with CVP. FFS was statistically superior for the group of patients treated with anthracyclines (49 vs. 34%, respectively; $p = 0.006$).

Interestingly, OS of patients who did not obtain CR was significantly longer in the group of patients treated with anthracyclines, suggesting that the use of anthracyclines in induction therapy does not reduce the possibility of achieving a satisfactory response to second line therapy. On the contrary, patients who relapsed after obtaining CR in both treatment groups did not show a significant difference in survival, but just a trend for a longer survival in ACR treated patients with 5-year OS of 75 vs. 68% (data not shown). After dividing cases according to the ILI prognostic score, the group of ACR treated patients showed a better survival in low and intermediate risk compared to the CVP treated group. In high risk patients we have observed a trend toward a better outcome in ACR treated patients, although the difference was not statistically significant, possibly because of the small number of patients treated with CVP.

To our knowledge very few studies were performed in order to evaluate the usefulness of anthracyclines in the treatment of follicular lymphoma. Moreover, almost all these study examine low-grade lymphoma as a whole, including in the analysis both follicular and non-follicular

entities. Previously, Ezdinli *et al.* [28] reported the results of a randomized study demonstrating that more aggressive chemotherapy without anthracyclines was followed by the achievement of a significantly higher disease free survival rate (57 vs. 22% at 5 years) without difference in OS compared to moderate treatment. A retrospective study by Dana BW *et al.* [29] reviewed survival data of patients with low-grade lymphoma and their conclusions were that doxorubicin containing regimen did not prolong OS of low-grade lymphoma patients. Two randomized studies comparing CHOP to chlorambucil [30] or CVP + procarbazine [31] were performed in low grade lymphoma.

The study by Young and coworkers [32], which included 104 patients with advanced follicular and non-follicular indolent lymphomas, was aimed at comparing two radically different treatment approaches, "watchful-waiting" and aggressive combination chemotherapy containing anthracyclines. The results of this study demonstrated different DFS but comparable OS in the two treatment arms. Peterson *et al.* reported as an abstract [33] the comparison of cyclophosphamide as single agent therapy with CHOP-Bleo regimen concluding that there was a similar response rate for either treatment. Again in the whole setting of low-grade malignancy, Dana *et al.* demonstrated that the use of an anthracycline-based regimen gave an advantage in terms of response rate [34]. In spite of the lack of demonstration in prospective randomized studies of the superiority of ACR for the treatment of advanced follicular lymphoma, this therapeutic choice is now commonly adopted particularly in young patients. Today it would be considered rather out-of-date to propose a prospective randomized trial on therapy of follicular lymphoma with a control arm without anthracyclines, thus hampering the possibility to prospectively demonstrate the usefulness of anthracyclines in this setting.

Several clinical trials published recently aimed at finding drugs which could improve the results obtained with chemotherapy. Solal–Céligny *et al.* [8] reported that CHVP combination chemotherapy associated with interferon as maintenance treatment improved DFS compared to no therapy after induction. Similar results were reported by McLaughlin *et al.* with the use of alfa-interferon after CHOP-Bleo in patients with stage IV low-grade lymphoma [9]. Moreover, immunotherapy with anti-CD20 monoclonal antibody used in association with adriamycin-containing chemotherapy (CHOP) in relapsed follicular lymphoma by Czuczman and coworkers [35] was highly effective with an overall response rate of 95% and a high rate (88%) of molecular response. Since the detection of bcl-2 positivity after treatment is significantly associated with increased risk of relapse [36], it can be expected that the use of anthracyclines in association with anti-CD20 antibody could reduce the risk of relapse by increasing the molecular remission rate. In conclusion, our study, although retrospective, formally confirms that patients with follicular lymphoma and active disease should be treated whenever possible with anthracycline containing regimens as already commonly accepted. Less intensive treatments should be offered only to cases at high risk of anthracycline toxicity.

Acknowledgements

Associazione Angela Serra per la Ricerca sul Cancro, Modena.

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APPENDIX

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