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Combined therapy in advanced stages (III and IV) of follicular lymphoma increases the possibility of cure: results of a large controlled clinical trial

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Abstract: *Objectives*: We evaluate the long-term results of a randomized clinical trial in patients with advanced stages (III and IV) of follicular lymphoma using chemotherapy or combined therapy (chemotherapy following by adjuvant radiotherapy in patients with nodal bulky disease). *Material and methods*: Between 1981 and 1995, patients with follicular lymphoma were treated with combined chemotherapy, mostly anthracycline-based regimens; patients who achieved complete response were randomly assigned either to receive adjuvant radiotherapy to sites or to nodal bulky disease or not (control group). *Results*: Four hundred and sixty-nine patients were randomized; in an intent-to-treat analysis all were evaluable for efficacy and toxicity. Actuarial curves at 20 yr showed that event-free survival (EFS) and overall survival (OS) in the control group were 41% [95% confidence interval (CI) 36–56%) and 71% (95% CI 65–78%), respectively; these were statistically different from results for the patients who received adjuvant radiotherapy: 68% (95% CI 62–72%) and 89% (95% CI 79–96%), respectively ($P < 0.01$). Acute and late toxicity were minimal; only four patients (<1%) developed myelodysplastic syndrome/acute leukemia. Cardiac toxicity was 2%, but one case was lethal. Thirty-six patients (8%) died secondary to unrelated causes, in complete remission. *Conclusions*: The use of adjuvant radiotherapy in patients with poor-prognosis follicular lymphoma increases EFS and OS with minimal toxicity. We feel that follicular lymphoma should be treated curatively because <80% of patients will be in first complete response at <20 yr. The use of adjuvant radiotherapy will be considered in the first line of treatment in this set of patients.

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Patients with follicular lymphoma typically have an indolent course with a median survival of 7 yr, but event-free survival is significantly minor. Early stages (I and II) treated with radiotherapy can achieve a high rate of complete response (CR), and at 10 yr overall survival (OS) could be >80% (1–3). However, the treatment of advanced stages (III and IV) remains unresolved. Chemotherapy, including new drugs such as fludarabine, can achieve CR between 35 and 77%, but at 10 yr OS remains unchanged, and more patients have frequent relapses. Thus, at 10 yr EFS has been found to be between 22 and 53% (4–6). The use of maintenance therapy with chemotherapy (4) or interferon (7, 8) can increase EFS and in some cases OS, but some studies did not confirm this finding (9).

The use of myeloablative chemotherapy and stem cell transplantation has been reported as a good therapeutic approach, but the patients were highly selected, and most studies included a low number of patients in non-controlled clinical trials (10). Thus, it appears that treatment options in follicular lymphoma remain open.

Ten years ago we demonstrated in a small controlled clinical trial that the use of combined therapy (chemotherapy followed by adjuvant radiotherapy) increases EFS and OS when compared with chemotherapy alone in patients with advanced stages of nodular lymphoma and in the presence of bulky disease (tumor mass >10 cm) (11). Other studies confirm that bulky disease is a poor prognosis factor and that combined therapy improves EFS and OS (12–14). However, in these studies chemotherapy comprised CVP (cyclophosphamide, vincristine, prednisone), a regimen that can be considered as a palliative. In an effort to improve the outcome in these patients, we introduced different chemotherapy regimens, mostly anthracycline-based, to determine if the use of more aggressive chemotherapy and adjuvant radiotherapy can improve EFS and OS. Because in previous studies we showed that extended field at a low dose of radiation is sufficient (11, 15), in subsequent studies we employed this radiation technique. The results of these large and long-term follow-up studies are present herein.

Material and methods

From January 1981 to March 1995, patients with follicular lymphoma that fulfilled the following entry criteria were considered candidates for this study: (a) a diagnosis of follicular lymphoma, based on the histopathology concepts of the World Health Organization; (b) previously untreated; (c) age >18 yr with no upper limit; (d) ECOG <2; (e) stage III or IV according to the Ann Harbor system; (f) normal hepatic, renal, cardiac, and hematological functions, unless these were secondary to lymphoma infiltration.

Patients were carefully staged: physical examination, together with a complete blood count with platelet, renal, hepatic, and pulmonary function were performed in all cases. From 1988, human immunodeficiency virus test was mandatory. Serum determinations of lactic dehydrogenase (LDH) and β2-microglobulin (from 1986) were made. Cardiac function was measured with the left ejection ventricular fraction (LEVF) (normal values >50%), before and after chemotherapy, 1, 3, 5, and 10 yr after completion of treatment, and after 10 yr if clinically necessary. Chest x-ray and computed tomography of the thorax, abdomen, and pelvis were obtained. Aspirate and bone marrow biopsy were performed in all cases. Other laboratory or radiological studies were performed according to each clinical condition. All patients provided their informed consent, and the study was approved by the Ethical Committee of our institution.

Response criteria

Complete response (CR) was defined as disappearance of all detectable clinical and radiological evidence of disease, disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities definitely assignable to lymphoma. Patients with partial response or unconfirmed complete response were considered as failures. Progression was defined as new or >50% increased lymph nodes; appearance of new lesions at the end of therapy, or organ failure secondary to lymphoma infiltration (16).

During this time different chemotherapy regimens were employed (Table 1). If after chemotherapy the patients achieved CR, they were randomly assigned to received either: (a) no further therapy (control group), or (b) adjuvant radiotherapy to sites of nodal bulky disease (tumor mass) as follows.

Radiotherapy for supradiaphragmatic disease using a 6-MeV linear accelerator or Co^{60} was limited to the affected lymphatic-bearing region. Treatment of supradiaphragmatic fields was administered at a rate of 2 Gy per fraction up to

Table 1. Chemotherapy regimens

CVP
Cyclophosphamide 800 mg m^2, i.v., day 1
Vincristine 1.4 mg m^2, i.v., day 1
Prednisone 40 mg m^2, p.o., days 1–5
Given every 14 d
CHOP-Bleo
Cyclophosphamide 750 mg m^2, i.v., day 1
Doxorubicin 50 mg m^2, i.v., day 1
Vincristine 1.4 mg m^2, i.v., day 1
Prednisone 60 mg m^2, p.o., days 1–5
Bleomycin 10 mg m^2, i.v., day 14
Given every 21 d
CEOP-Bleo
Epirubicin, instead of doxorubicin 70 mg m^2, i.v., day 1
COPP
Cyclophosphamide 600 mg m^2, i.v., day 1
Vincristine 1.4 mg m^2, i.v., day 1
Prednisone 40 mg m^2, p.o., days 1–14
Procarbazine 100 mg m^2, p.o., days 1–14
COPP + interferon
COPP, alternating monthly with interferon-α_{2b}
5.0 MU, three times a week for 3 wk

a total of 40 Gy in 4 wk. The mantle technique was not used unless the mediastinum was involved by bulky disease. When it was necessary to treat the mediastinum the tumor dose for the mediastinum was generally calculated in the mild-plane of the upper mediastinum, so that the dose in the lower mediastinum was approximately 25% lower. Treatment of the abdomen was given at a rate of 1.5 Gy per fraction up to a total of 30 Gy. The treatment fields for the upper two thirds of the abdomen extended from the dome of the diaphragm to the iliac crest. The right lobe of the liver was shielded anteriorly and posteriorly with five half-value layers of lead (HVL). The kidneys were shielded posteriorly with two HVL to reduce the received dose to approximately 18 Gy. Para-aortic and pelvic regions received an additional 'boost' of 10 Gy through reduced fields.

Analysis of data

The principal end-points of our study were to evaluate the usefulness of adjuvant radiotherapy in terms of EFS and OS, acute and late toxicity and the presence of unrelated deaths in patients with longer follow-up. The calculations of our study were recorded when we began the second step, i.e. when the patients were randomized to receive adjuvant radiotherapy or not. Event-free survival was defined as the time that elapsed between completing radiotherapy until the first clinical or radiological evidence of disease. If possible, a biopsy was taken to evaluate histology transformation. Overall survival was calculated from when the patient entered the study until death from disease progression or cause-related treatment. Unrelated deaths were censored.

Results

Seven hundred and sixty-nine patients were considered candidates for the study and received the corresponding chemotherapy. CR was achieved in 469 cases (65%) and the patients were randomized to receive adjuvant radiotherapy. In an intent-to-treat analysis all patients were considered evaluable.

Table 2 shows the salient pretreatment characteristics and treatment factors. No statistical differences were observed between the two arms. Patients were classified according to the International Prognostic Index and again no differences were observed between low and low–intermediate vs. high–intermediate and high clinical risk. Median follow-up was 13.6 yr (range 7.3–21.6 yr) at last follow-up.

Table 2. Clinical and laboratory characteristics

	Numbers. receiving adjuvant radiotherapy (%)	
	No	Yes
Number	218 (100)	251 (100)
Age (yr)		
Median	56.7	53.4
Range	21–80	26–83
Sex		
Male	108 (49)	126 (50)
Female	110 (51)	121 (49)
Stage		
III	89 (45)	100 (39)
IV	129 (55)	151 (60)
B symptoms	160 (77)	160 (61)
Clinical risk		
Low	41 (18)	38 (15)
Low–intermediate	58 (25)	59 (23)
High–intermediate	73 (33)	83 (33)
High	46 (21)	70 (27)
Chemotherapy program		
CHOP-Bleo × 6	32 (14)	42 (17)
CEOP-Bleo × 6	41 (18)	49 (19)
CEOP-Bleo × 3 + CVP × 6	73 (34)	74 (29)
COPP × 6	38 (17)	30 (18)
COPP, alternating with interferon × 6	34 (15)	39 (16)

Table 3. Radiotherapy fields

Number	251
Involved field	215
Supradiaphragmatic	46
Infradiaphragmatic	169
Mantle	36

Table 4. Current status

	No (%)	
	Chemotherapy	Combined therapy
First complete response	91 (41)	176 (68)
Relapse	101 (46)	63 (25)
Nodal	48	26
Disseminated disease	53	37
Irradiated site	–	6
Died, in complete response	26 (11)	10 (5)

Table 3 shows the anatomic sites which were irradiated.

Table 4 shows the actual clinical condition of these patients. At this time, 91 out of 218 [41%, 95% confidence interval (CI) 36–56%] patients who were treated with chemotherapy alone remain in first CR, while the median of EFS was 11.4 yr, which is statistical different from patients who were treated with combined therapy: 176 out of 251 (68%, 95% CI 61–74%) remain alive in first CR,

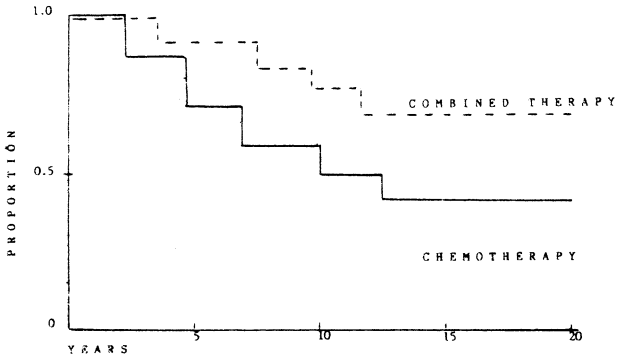

Fig. 1. Actuarial curve for event-free survival.

and median EFS has not been reached yet ($P<0.01$). Figure 1 shows the actuarial EFS at 20 yr.

Relapse

One hundred and one (46%, 95% CI 41–58%) of the patients in the chemotherapy arm have relapsed. Nodal and disseminated relapse were similar. Sixty-three (25%, 95% CI 20–30%) relapsed in the combined therapy group ($P<0.01$). Six patients relapse in the radiated site group (2%).

Cause of death

In the chemotherapy arm, 81 patients died, 65 (29%) secondary to tumor progression or cause-related treatment, which is statistically different to patients in the combined therapy arm: 40 (15%, 95% CI 11–18%) patients died, and only 30 (11%, 95% CI 7–15%) secondary to lymphoma or treatment (Table 5). Four patients (<1%) developed malignancy, myelodysplastic syndrome, or acute leukemia, two in both arms. Thirty-six patients (26 in the chemotherapy group and 10 in the combined therapy arm) died from causes unrelated to lymphoma or treatment: more of these deaths were common at this age. Figure 2 shows the actuarial curve at 20 yr of OS: 71% (95% CI 65–78%) of the patients in the chemotherapy arm vs. 89% (95% CI 79–96%) in the combined therapy arm ($P<0.01$). No relapse or death was observed after 15 yr.

Cardiac toxicity

A female patient aged 34 yr died secondary to myocardial infarction in the chemotherapy group. She had received six cycles of CHOP-Bleo, relapsed at 3 yr, and was treated with high doses of cyclophosphamide (3 g m^2) and etoposide, and achieved a second response. However, 6 months later she died suddenly: autopsy showed massive myocardial infarction. We felt that secondary to anthracycline therapy no evidence of lymphoma was observed.

Table 5. Cause of death

	Chemotherapy	Combined therapy
Related lymphoma	65	30
Tumor progression	57	26
Related treatment	8	4
Infection	5	2
Myocardial infarctation	1	0
Second malignancy	2	2
Myelodysplatic syndrome	1	1
Acute leukemia	1	1
Unrelated lymphoma	26	10
Diabetes mellitus	5	2
Renal failure	3	2
Cerebral vascular accident	5	3
Car accident	4	1
Suicide	2	1
Homicide	2	0
Hepatic failure	4	1
Not determined	1	0

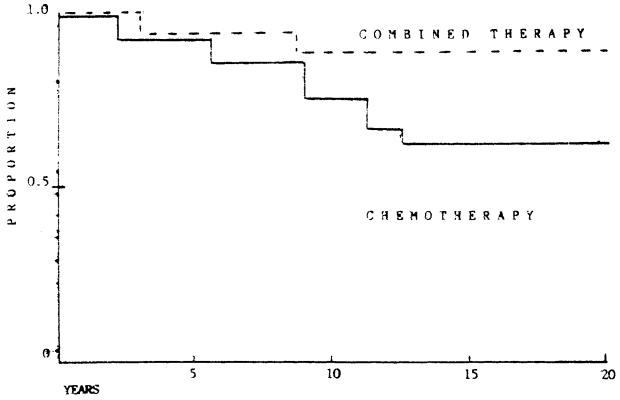

Fig. 2. Overall survival.

Ten patients (six in the combined group, four receiving mantle radiation therapy, and four in the chemotherapy arm) developed abnormalities in LEVF drop >15%, but all patients showed no clinical evidence of congestive heart failure and have a normal life. Thus, 2% of patients developed cardiac toxicity secondary to treatment.

In the multivariate analysis only bulky disease can influence both EFS and OS (data not shown). Clinical risk, as previously reported, did not influence EFS and OS (17).

Discussion

Currently, the optimal treatment of advanced-stage follicular lymphoma remain undefined. Therapeutic approaches range from initial deferred therapy to aggressive myeloablative chemotherapy with

transplant procedures. However, some of these treatments can be offered only to a select number of patients: <20% of patients with advanced-stage follicular lymphoma could be considered candidates for transplant procedures. On the other hand, late complications can impact OS and quality of life, and acute leukemia and myelodysplastic syndromes are often lethal, as has been reported in about 12% of cases (18). The use of anthracycline-based chemotherapy has been demonstrate to prolong EFS and, in some studies, OS (13, 14, 19), but this has not been confirmed in other reports (5). Moreover, acute and late cardiotoxicity can increase death secondary to treatment or affect quality of life through the appearance of congestive heart failure in older patients (19, 20).

Thus, it is evident that different treatments should be developed for these patients. More studies agree that the presence of bulky disease in follicular (8, 12, 13, 21) or diffuse malignant lymphoma (2, 15) as an adverse prognostic factor, which is not considered in the International Prognostic Index. Twenty years ago we began controlled clinical trials to assess the efficacy and toxicity of adjuvant radiotherapy in patients with advanced-stage follicular lymphoma. Our initial results with improved in EFS and OS were the base from which to evaluate more aggressive chemotherapy in an effort to improve the outcome in these, considered incurable, patients.

Our long-term follow-up confirms that the use of adjuvant radiotherapy at low doses in limited fields improves EFS and OS, independently of the chemotherapy employed to achieve CR, when compared to patients treated with chemotherapy alone. Moreover, we confirm that more aggressive chemotherapy improves EFS and OS, 41 and 66%, respectively, at 20 yr in comparison with other reports that used anthracycline-based chemotherapy, and that it is superior to more conventional therapies without excessive acute or late complications. The International Prognostic Index confirms that it is not useful in our population of patients with advanced follicular lymphomas treated with uniform therapy.

The presence of a low number of late complications is of paramount importance, because quality of life in these, generally older patients, was not affected. Although a cure is not considered possible in this set of patients, in recent years an increase in EFS and OS has been observed, as in the results of new therapeutic approaches, that include combined therapy, biological modifiers, and recently monoclonal antibodies (7, 8, 12, 13, 20). Thus, it is possible that >50% of patients with advanced-stage follicular lymphoma could be considered cured, because patients are alive in first complete remission at >15 yr. However, death unrelated to lymphoma and relationship to ageing will increase in this group of patients: in our study 8% of patients died secondary to independent diseases.

In conclusion, we feel that the use of aggressive, non-myeloablative chemotherapy, with adjuvant radiotherapy at low dose and limited fields should be considered as part of the initial treatment in this group of patients if an attemped cure is to be considered the end-point in this set of patients.

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