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The long term follow-up of early stage follicular lymphoma treated with radiotherapy, chemotherapy or combined modality treatment

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ABSTRACT

Local (involved-field or recently involved-site) radiotherapy is the standard therapy in limited-stage follicular lymphoma (FL). We retrospectively analyzed the value of chemotherapy in 130 patients with limited-stage FL (46 treated with radiotherapy alone [RT group], 30 with radiotherapy plus chemotherapy [COMBINED group] and 43 with chemotherapy alone [CHEMO group], 11 were managed with observation). Ninety-six percent of patients responded (RT 98%, COMBINED 100%, CHEMO 91%, $p = 0.179$), and 37% (40/107) of patients in complete response relapsed (RT 42%, COMBINED 27%, CHEMO 41%, $p = 0.371$). Progression-free survival (PFS) and overall survival (OS) probabilities at 10 years were similar in RT, COMBINED and CHEMO patients (PFS 41%, 61% and 39% [$p = 0.167$], and OS 77%, 81% and 72% [$p = 0.821$], respectively), while the COMBINED group showed a trend to better time-to-progression (TTP 43%, 72% and 47% [$p = 0.055$]). On multivariate analysis, only a FLIPI score ≥ 2 showed a trend to influence PFS (HR 2.1 [95% confidence interval 0.9–4.6], $p = 0.067$), and OS (HR 2.4 [0.9–6.5], $p = 0.084$), while patients treated with radiotherapy plus chemotherapy (COMBINED group) showed a significantly better TTP compared with those receiving only RT (HR 0.3 [0.1–0.8], $p = 0.024$). In our study no benefit was observed in survival with the use of systemic therapy compared with local radiotherapy.

1. Introduction

Follicular lymphoma (FL) is the most frequent low-grade lymphoma, defined in most cases by an indolent behavior and with a continuous pattern of relapses. Although most of the patients show advanced disease at the time of diagnosis, almost 25–30% are in limited stage [1], encouraging the use of a curative approach. In these cases, radiotherapy constitutes the standard of treatment recommended by most of the published guidelines and reviews [2–7], based on the results of retrospective studies, with overall survival (OS) rates at 10 years ranging between 55% and 70% [8–13] and progression-free survival (PFS) or relapse-free survival rates at 10 years of 44–54% [8,11,13]. However, the dose and field of irradiation are not well established due to the scarcity of randomized trials [11,14]. In addition, in most of these studies, the main cause of treatment failure is relapse outside the radiation field, although relapses beyond 10 years seem to be infrequent. In retrospective studies systemic therapy has been used in addition to local radiotherapy or after lymphadenectomy with the aim of decreasing the incidence of non-local relapses. Nonetheless, the benefit of this approach remains controversial [15–19].

The objective of this study was to analyze the value of the use of systemic chemotherapy compared with local/locoregional

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Table 1
Demographic and clinicobiological characteristics of the overall series and comparison among the patients treated with radiotherapy alone (RT group), radiotherapy plus chemotherapy (COMBINED group) and chemotherapy alone (CHEMO group).[a]

	Overall series ($n=130$)	RT group ($n=46$)	COMBINED group ($n=30$)	CHEMO group ($n=43$)	P value
Male, *n* (%)	48/130 (37)	19/46 (41)	10/30 (33)	14/43 (33)	0.694
Median age (range), years	58 (17–93)	56.5 (17–78)	55 (19–79)	59 (29–76)	0.316
ECOG PS ≥2, *n* (%)	12/127 (9)	1/45 (2)	2/29 (7)	6/42 (14)	0.104
B symptoms, *n* (%)	9/128 (7)	1/45 (2)	0	8/42 (19)	0.002
Bulky disease (≥6 cm), *n* (%)	19/117 (16)	3/44 (7)	7/30 (23)	9/43 (21)	0.095
Histologic grade, *n* (%)					
I/II	94/125 (75)	41/43 (95)	14/30 (47)	29/42 (69)	<0.001
IIIa	31/125 (25)	2/43 (5)	16/30 (53)	13/42 (31)	
Ann Arbor stage, *n* (%)					
I	67/130 (52)	36/46 (78)	16/30 (53)	9/43 (21)	<0.001
II	63/130 (48)	10/46 (22)	14/30 (47)	34/43 (79)	
FLIPI score					
0–1	91/116 (78)	36/39 (92)	24/27 (89)	25/40 (63)	<0.002
2–3	25/116 (22)	3/39 (8)	3/27 (11)	15/40 (38)	
Hemoglobin, mean (SD), g/dL	13.3 (1.6)	14.1 (1.5)	13.1 (1.3)	12.7 (1.7)	0.001
WBC, mean (SD), $\times 10^9$/L	6.7 (1.9)	6.8 (1.6)	6.6 (1.7)	6.9 (2.4)	0.751
Platelets, mean (SD), $\times 10^9$/L	233.8 (75)	222 (82.5)	242.4 (68.4)	249.3 (123.4)	0.122
Increased serum LDH, *n* (%)	25/116 (22)	5/39 (13)	4/28 (14)	15/39 (39)	0.014
Increased serum β_2 microglobulin, *n* (%)	22/104 (21)	5/35 (14)	4/24 (17)	12/37 (32)	0.144

ECOG PS: Eastern Cooperative Oncology Group Performance Status; FLIPI: Follicular Lymphoma International Prognostic Index; LDH: lactate dehydrogenase; WBC: white blood cells; SD: standard deviation.

[a] Eleven patients (8%) did not receive any therapy after lymphadenectomy and were excluded from the comparative analysis.

radiotherapy in a series of 130 patients diagnosed with limited stage (I and II) FL.

2. Material and methods

This was a retrospective study of patients diagnosed with stage I or II FL in three Spanish hospitals from 1989 to 2012. The main demographic and clinical variables of each patient were collected, as well the treatment strategy, response and follow-up. Diagnosis of FL was reviewed in each participant hospital for this study (using the WHO classification), but no central pathology review was performed. The lymphoma staging system, the decision to treat and the type of treatment as well as the response evaluation were established and recorded by the treating physician. Initial staging and response to therapy was evaluated by whole body computed tomography (CT) scan and bone marrow biopsy. This study was approved by the institutional review boards of the three participant hospitals.

For the comparative analysis of this study, three groups were considered according to the treatment strategy: radiotherapy alone (RT group), combined radiotherapy plus chemotherapy (COMBINED group) and chemotherapy alone (CHEMO group). Patients in whom no additional therapy was administered after diagnostic lymphadenectomy (observation or 'watch-and-wait strategy' [WS]) were considered for the descriptive analysis but were not included in the comparative study.

PFS was defined as time from diagnosis to lymphoma progression or death by any cause. OS was defined as the time from diagnosis to death or last follow-up. Time to progression (TTP) was defined as the time from diagnosis to lymphoma progression or death by lymphoma [20].

2.1. Statistical analysis

Baseline demographic and clinicobiological characteristics were presented as mean and standard deviation for continuous variables and frequency and percentage for categorical variables. Comparisons of these variables among the three treatment strategies were performed by χ^2, Fisher's exact, Student-*t* or Mann–Whitney *U* test, as appropriate.

PFS, OS and TTP curves were plotted by the Kaplan–Meier method and were compared by the log-rank test [21,22]. Univariate and multivariate analyses for PFS, OS and TTP were performed using the Cox proportional hazards regression model [23]. Ninety-five percent confidence intervals (95% CI) for probabilities and median survival times were calculated. On multivariate analysis, the factors included were those that remained significant on univariate analysis, as well as variables that showed a different distribution among the three groups. Two-sided P values <.05 were considered as statistically significant. The statistical package SPSS, version 15.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

3. Results

From 1989 to 2012, 130 patients with de novo limited stage FL were included, 67 (52%) of whom were in stage I and 63 (48%) in stage II. The median age was 58 years (range 17–93), and 82 (63%) were females. The demographic and the main clinical and biological characteristics are summarized in Table 1. Most of the patients showed a good performance status, without B symptoms. Twenty-five percent of patients had a grade 3a FL and the Follicular Lymphoma International Prognostic Index (FLIPI) score was 0–1 in 78% of the cases. The median follow-up of the series was 6.8 years (range 0.2–22.9).

Regarding the treatment strategy, 46 patients (36%) belong to the RT group (involved field radiotherapy with doses ranging from 30 to 45 Gy), 30 (23%) to the COMBINED group (including chemotherapy plus involved field radiotherapy with doses between 30 and 50 Gy) and 43 (33%) to the CHEMO group; 42 received rituximab as part of the systemic therapy (15 in the COMBINED group and 27 in the CHEMO group). Table 2 shows the chemotherapy schedules administered to the patients in the COMBINED and the CHEMO groups. Overall, 31 patients received chemotherapy regimens without rituximab, whereas 42 received chemotherapy containing rituximab, being CHOP the most frequent schedule

Table 2
Detailed treatment schedules administered to patients in the COMBINED and CHEMO groups.

Treatment schedule	COMBINED Group[a] ($n=30$)	CHEMO Group[a] ($n=43$)
Chlorambucil	2 (6)	6 (6)
CVP	1 (4)	0
CHOP	11 (4)	7 (6)
FCM	1 (6)	3 (6)
R-CVP	6 (4)	7 (4)
R-CHOP	9 (4)	20 (6)

Chlorambucil 8 mg/m^2, days 1–7, administered every 28 days; CVP: cyclophosphamide (750 mg/m^2, day 1), vincristine (1.44 mg/m^2, day 1) and prednisone (60 mg/m^2/d, days 1–5), administered every 21 days; CHOP: cyclophosphamide (750 mg/m^2, day 1), doxorubicin (50 mg/m^2, day 1), vincristine (1.4 mg/m^2, day 1) and prednisone (60 mg/m^2/d, days 1–5), administered every 21 days; FCM: fludarabine (25 mg/m^2/d, days 1–3), cyclophosphamide (200 mg/m^2/d, days 1–3) and mitoxantrone (6 mg/m^2, day 1), administered every 28 days; R-CVP: rituximab (375 mg/m^2, day 1), cyclophosphamide (750 mg/m^2, day 1), vincristine (1.44 mg/m^2, day 1) and prednisone (60 mg/m^2/d, days 1–5), administered every 21 days; R-CHOP: rituximab (375 mg/m^2, day 1), cyclophosphamide (750 mg/m^2, day 1), doxorubicin (50 mg/m^2, day 1), vincristine (1.4 mg/m^2, day 1) and prednisone (60 mg/m^2/d, days 1–5), administered every 21 days.

[a] Expressed as number of patients (median of the number of cycles administered).
CHEMO: patients treated with chemotherapy alone; COMBINED: patients treated with radiotherapy plus chemotherapy.