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LOW-DOSE RADIOTHERAPY (2x2 Gy) IN INDOLENT LYMPHOMA

THESE

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et présentée à la Faculté de biologie et de médecine de
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Low-Dose Radiotherapy In Indolent Lymphoma

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Dans la prise en charge des maladies oncologiques, la priorité est évidemment d'assurer le contrôle de la maladie (soit le taux de récidive local et la survie globale), surtout lorsque celle-ci est diagnostiquée tôt, à un stade précoce. Cependant, lorsque la maladie est plus avancée et que ce contrôle ne peut être assuré de façon raisonnable, l'accent de la prise en charge est surtout axé sur le confort du patient. Le principe est de fournir à celui-ci, dans la mesure du possible, une qualité de vie acceptable, avec notamment des douleurs bien contrôlées.

Dans le cadre de ce travail de thèse, nous nous sommes intéressés à la prise en charge palliative des lymphomes non hodgkiniens (LNH) de bas grade. La survie de ces patients peut être relativement longue (de 5 à 10 ans selon les séries), cependant, le traitement est rarement à visée curative, contrairement aux lymphomes de haut grade, dont la survie est bien moindre, mais avec une chance de guérison après un traitement intensif.

Plusieurs études cliniques, à la fois prospectives et rétrospectives, ont démontré l'intérêt d'une irradiation à faible dose (2x2 Gy) lors d'atteintes lymphomateuses à l'origine de symptômes gênants (douleurs, compression par une masse, dyspnée, entre autres). Etant donné la facilité d'administration de ce traitement (seulement 2 séances de radiothérapie sont nécessaires), et sa quasi absence de survenue d'effets secondaires avec cette faible dose totale (4 Gy), nous avons voulu y apporter une contribution suisse.

Notre étude rétrospective a permis d'inclure 43 patients entre le CHUV et les HUG. Les résultats que nous avons obtenus sont également dans la ligne des autres études parues, avec un excellent contrôle local, soit un soulagement rapide et durable des symptômes dans la majorité des cas.

Nous espérons que ce travail de thèse, publié sous forme d'un article dans « International Journal of Radiation Oncology, Biology, Physics », permettra une prise en charge plus optimale des ces patients en leur apportant un traitement facile à administrer, efficace, sans effets secondaires dans la majorité des cas, et pouvant être répété un grand nombre de fois si nécessaire.

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CLINICAL INVESTIGATION

LOW-DOSE RADIOTHERAPY IN INDOLENT LYMPHOMA

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Purpose: To assess the response rate, duration of response, and overall survival after low-dose involved-field radiotherapy in patients with recurrent low-grade lymphoma or chronic lymphocytic leukemia (CLL).
Methods and Materials: Forty-three (24 women, 19 men) consecutive patients with indolent lymphoma or CLL were treated with a total dose of 4 Gy (2 × 2 Gy) using 6- 18-MV photons. The median age was 73 years (range, 39–88). Radiotherapy was given either after ($n = 32$; 75%) or before ($n = 11$; 25%) chemotherapy. The median time from diagnosis was 48 months (range, 1–249). The median follow-up period was 20 months (range, 1–56).
Results: The overall response rate was 90%. Twelve patients (28%) had a complete response, 15 (35%) had a partial response, 11 (26%) had stable disease, and 5 (11%) had progressive disease. The median overall survival for patients with a positive response (complete response/partial response/stable disease) was 41 months; for patients with progressive disease it was 6 months ($p = 0.001$). The median time to in-field progression was 21 months (range, 0–24), and the median time to out-field progression was 8 months (range, 0–40). The 3-year in-field control was 92% in patients with complete response (median was not reached). The median time to in-field progression was 9 months (range, 0.5–24) in patients with partial response and 6 months (range, 0.6–6) in those with stable disease ($p < 0.05$). Younger age, positive response to radiotherapy, and no previous chemotherapy were the best factors influencing the outcome.
Conclusions: Low-dose involved-field radiotherapy is an effective treatment in the management of patients with recurrent low-grade lymphoma or CLL. © 2011 Elsevier Inc.

Indolent lymphoma, Palliation, Radiotherapy.

INTRODUCTION

Low-grade non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) occur with dramatically increasing frequency, with about 23,400 new cases annually in the United States (1, 2). Whereas Stage I and II disease can be treated with radical intent using radiation doses of 25–40 Gy or/and chemotherapy with a 10-year disease-free survival rate of 50%; 80% of all patients with indolent NHL present with advanced Ann-Arbor Stage III or IV (3, 4). Although such disseminated indolent NHL is considered to be incurable, patients have a relatively long life expectancy, with a median survival ranging from 6 to 10 years (4, 5). Treatment is therefore directed toward palliation in case of symptomatic disease due to progression, compression of a vital organ by a bulky mass, or cytopenia.

Many systemic therapy options such as chemotherapy (6, 7) and/or immunotherapy (8–10) are available for these patients, but, given the high radiation sensitivity through apoptosis (11–13) and the indolent course of this disease, involved-field radiotherapy (IFRT) has proved to be highly attractive as a palliative treatment (14). Moreover, many trials have shown that high response rates and durable remission can be achieved with very low-dose (4 Gy) limited-field RT (15–21).

Another option in Stage I follicular lymphoma can be a wait-and-see policy, which does not seem to modify the prognosis in these patients (22).

The objective of this retrospective study was to assess the response rate, duration of response, and overall survival (OS) after IFRT in patients with recurrent low-grade NHL or CLL treated in two Swiss centers.

METHODS AND MATERIALS

Patients' characteristics

A total of 43 consecutive patients with low-grade NHL or CLL were treated between June 2001 and May 2008 with low-dose (2 × 2 Gy) IFRT. All patients had histologically confirmed disease, which had been staged with computed tomography, bone-marrow

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biopsy, and/or positron emission tomography as appropriate. Of these patients, 25 were treated in Geneva and 18 in Lausanne. The patients' characteristics are summarized in Table 1.

The median age was 73 years (range, 39–88 years). There were 24 women and 19 men. Twenty-six patients (60%) had Stage IV disease (including CLL), 10 patients (23%) Stage III, 5 patients (12%) Stage II, and 2 patients (5%) Stage I. Thirty percent presented with CLL, 39% with follicular lymphoma, and 31% with mantle, marginal zone, or mucosa-associated lymphoma tissue lymphoma.

Eighteen patients (42%) had head-and-neck (HN), thoracic (T) or abdominal (A) disease. Ten patients (23%) had T and A disease, 2 patients (5%) had HN and A disease, 8 patients (18%) had HN disease, 3 patients (7%) had A disease, and 2 patients (5%) had T disease only.

Twelve patients (28%) had high lactate dehydrogenase (LDH) levels. In 72% of patients, the LDH levels were normal or unknown.

Preirradiation treatments

In 32 of the 43 patients (75%), a median of four cycles of chemotherapy (range, 0–16 cycles) preceded low-dose IFRT. For 11 of these patients (25%), low-dose IFRT was the first therapy they received.

Table 1. Patient characteristics

Characteristic	$n = 43$	%
Age (y)		
<73	16	37
≥73	27	63
Sex		
M	19	44
F	24	56
Anatomic site		
THA	18	42
TA	10	23
H	8	18
A	3	7
T	2	5
HA	2	5
Stage		
I	2	5
II	5	12
III	10	23
IV (including CLL)	26	60
Pathology		
CLL	13	30
Follicular Grade I/II/III	17	39
Mantle, marginal, or MALT	13	31
LDH		
High	12	28
Normal/unknown	31	72
Bcl-2		
High	16	37
Normal/unknown	27	63
B2m		
High	13	30
Normal/unknown	30	70
Prior chemotherapy		
0 cycles	11	26
Median 4 cycles	32	74
Rituximab		
Y	29	68
N	14	32

Abbreviations: T = thorax; H = head and neck; A = abdomen; CLL = chronic lymphocytic leukemia; MALT = mucosa-associated lymphoma tissue; LDH = lactate dehydrogenase; B2m= beta-2 microglobulin.

Table 2. Univariate analyses for prognostic factors.

Variable	$n = 43$	3-year in-field control (%)	95% CI	p value
Age (y)				
≥73	28	36	10–62	0.08
<73	15	50	28–72	
Sex				
M	19	45	20–70	0.69
F	24	42	18–66	
Site				
THA	18	24	22–70	0.64
TA	10	34	0–55	
H	8	36	33–100	
A	3	53	0–86	
T	2	100	—	
HA	2	68	0–100	
Stage				
I	2	100	—	0.41
II	5	53	4–100	
III	10	60	30–90	
IV	26	30	8–52	
Pathology				0.63
Mantle + follicular G3	9	36	0–72	
Other	34	47	28–66	
LDH				
High	12	28	1–55	0.15
Normal/unknown	31	52	30–74	
Bcl2				
High	16	49	10–78	0.74
Normal/unknown	27	42	20–64	
B2m				
High	13	35	9–79	0.68
Normal/unknown	30	45	20–70	
Prior chemotherapy				
0	11	69	40–98	0.13
4	32	34	13–55	
Rituximab				
Y	29	39	17–60	0.49
N	14	55	25–85	

Abbreviations: T = thorax; H = head and neck; A = abdomen; LDH = lactate dehydrogenase, B2m = beta-2 microglobulin; Bc12 = B-cell lymphoma 2 gene.

Twenty-nine patients (68%) received rituximab before irradiation. The median time between chemotherapy or rituximab and radiation therapy was 7 months (mean, 15 months; range, 1–120 months).

Radiation techniques

The RT was delivered using either a telecobalt unit or a linear accelerator. Treatment planning consisted of either two-dimensional or three-dimensional conformal RT. The patients received a total dose of 4 Gy in two fractions, given once daily over 2 to 4 days. The RT was applied only to the involved site or to the affected lymph nodes with a 2-cm margin. Megavoltage photon beams of 6 to 18 MV or gamma beams were used.

Endpoints and statistical methods

The primary endpoint of the study was time to in-field progression. The OS and time to local (in-field) or distant (out-field) progression were calculated according to the Kaplan-Meier method (23). The duration of response for each irradiated site was calculated from the start of RT to the first documented disease progression. Confidence intervals (CI) were computed from standard errors.

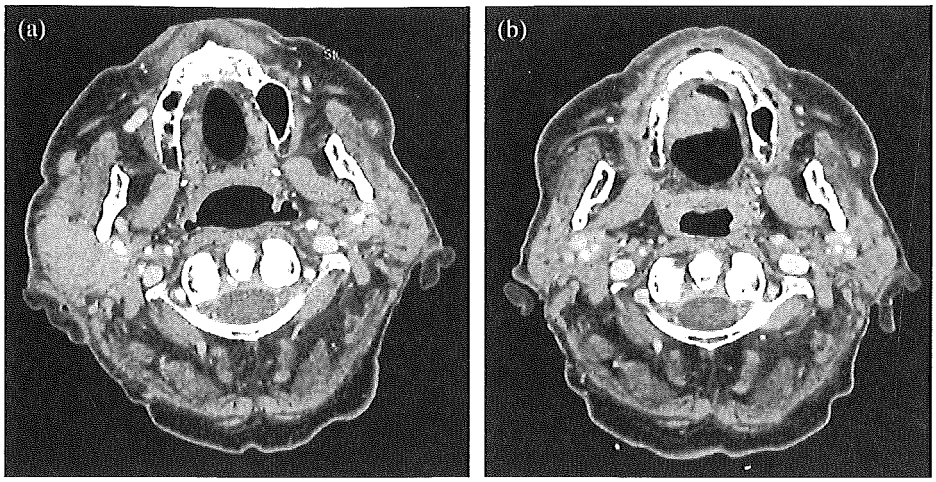

Fig. 1. (a) Mucosa-associated lymphoma tissue lymphoma of the right parotid gland, before radiation therapy. (b) After radiation therapy, 2 Gy in two fractions, complete response.

Objective responses were assessed clinically or radiologically according to the Response Evaluation Criteria in Solid Tumors criteria (24). The first evaluation was performed 6 weeks after the end of treatment and subsequent evaluations every 3 to 6 months. A complete response (CR) was defined as a complete disappearance of clinically or radiologically detectable disease within the treatment field; a partial response (PR), as a decrease of at least 30% in the sum of diameters of target lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Only patients with PD with at least 20% increase in the sum of diameters of the target lesions (PD) were considered as nonresponders. Toxicity was scored according to the toxicity scale of the National Cancer Institute Common Terminology Criteria for Adverse Events 3.0 (25). Multivariate analysis was done using the Cox stepwise regression method to determine the independent contribution of each prognostic factor (26).

RESULTS

The median follow-up period was 20 months (range, 1–56), and the median time since diagnosis was 48 months (range, 1–249 months). All patients completed their treatment. Among the 43 patients, 13 (30%) had a CR, 17 (40%) had a PR, and 7 (16%) presented with SD after irradiation. Only 6 patients (14%) had PD. Figure 1 shows selected clinical images of 1 patient who had a CR after receiving 4 Gy IFRT. The median overall survival was 30 months. The median time to in-field progression was 21 months (range, 0–24 months), and the median time to out-field progression was 8 months (range, 0–40 months) (Fig. 2). The actuarial 3-year freedom from in-field local progression was 92% (95% CI, 76–100) for patients with a CR. The response to low-dose IFRT in cases of indolent lymphoma was also highly predictive for the OS, with a p value of 0.0013 (Fig. 3).

Univariate analyses were performed to determine which factors were predictive of in- field control (Table 2). Age (<73 vs. ≥73 years) seemed to predict response without reaching statistical significance (p = 0.083) (Fig. 4). Other prognostic factors for in-field control (*i.e.*, sex, number

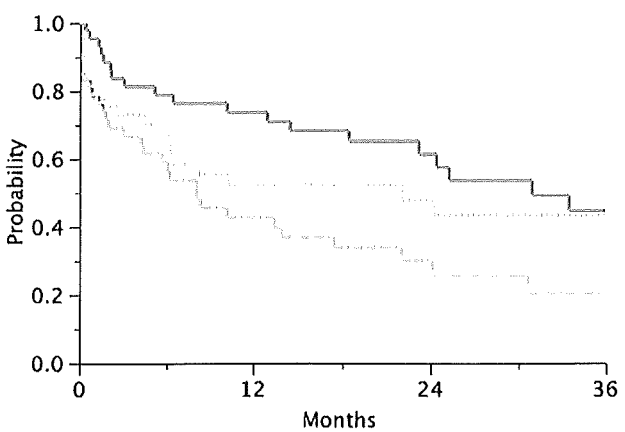

Fig. 2. Overall survival (solid line), in-field control (dotted line), and disease control out of irradiated volume (dashed dotted line) in 43 patients with indolent lymphoma or chronic lymphocytic leukemia (median overall survival, 30 months; median in-field control, 21 months; median out-field control: 8 months).

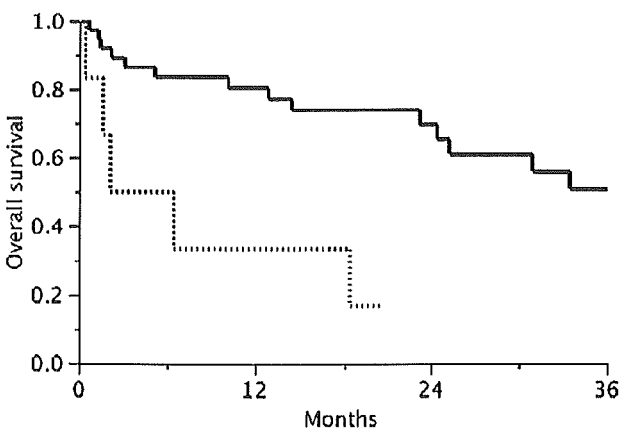

Fig. 3. Overall survival according to symptomatic response in 43 patients with indolent lymphoma or chronic lymphocytic leukemia. Solid line = complete response (CR) + partial response (PR) + stable disease (SD); dotted line = progressive disease (PD). Median survival for positive response (CR, PR, and SD) = 41 months; median survival for negative response (PD) = 6 months; p = 0.0013.

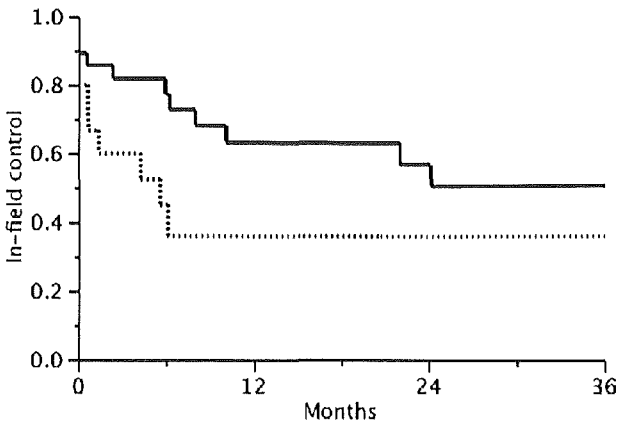

Fig. 4. In-field control according to age in 43 patients with indolent lymphoma or chronic lymphocytic leukemia. Median in-field control = 5 months for age ≥73 years (dotted line) vs. 24 months for age <73 years (solid line), $p = 0.0833$.

and history of systemic therapies, stage and grade of the disease, number of sites, presence of bulky disease, bcl2 overexpression, and LDH rates) could not be distinguished in these patients.

In multivariate analysis, younger age (<73 years was better) and previous chemotherapy (no chemotherapy was better) independently influenced in-field control with IFRT (relative risk = 1.79, $p = 0.02$ for age; and relative risk = 1.96, $p = 0.02$ for prior chemotherapy).

Toxicity was minimal or absent except for Grade 1–2 nausea in 2 patients irradiated on the upper abdomen.

DISCUSSION

The results of the present study using a total dose of 4 Gy in two fractions showing an overall response rate of 90% are in agreement with previous reported data. Girinsky *et al.* (18) and Johannsson *et al.* (19) showed an overall response rate of 81% and 82%, respectively (Table 3). The slight difference may be because we considered patients with stable disease (26%) to be responders, unlike either of the other authors. Our complete response rate, however, was only 28%, compared to 55–61% reported in the other series. It is important to point out that our patients may have been in worse general condition: the median age in our series was 73 years, significantly higher than in the Dutch (62 years) (27) or French (59 years) (18) studies. Moreover, in the French series (18), the patients had a short disease history and more favorable outcomes; only 31% of them presented with Stage IV disease compared with 60% in ours. In our series, patients were often referred to our department after a long course of disease and multiple chemotherapies.

Regarding the prognostic factors, very few of them could be already reported in the literature. In our series, older age (≥73 years) and previous chemotherapy were the worst prognostic factors regarding the benefit of such irradiation. The median in-field disease control was 5 months vs. 24 months for patients older vs. younger than 73 years, respectively. Patient age was also reported as an adverse factor by Girinsky *et al.*, with a cutoff value of 65 years (18). These authors proposed to increase the dose per fraction from 2 to 3 Gy in the older age groups to extend the efficacy of the local treatment. The same team confirmed the significant influence of the number of chemotherapy regimens on 2-year freedom from local progression (96% vs. 48% for 0–1 cycles vs. 2 or more cycles). In our series, the 4-year in-field control rate was 70% (median was not reached) for patients not receiving chemotherapy before irradiation, and the median 9 months for those who received chemotherapy (with a median of four cycles). However, in the prospective trial by Haas *et al.* (27), which included 109 patients and 304 irradiated sites with this protocol, neither CR nor overall relative risk was associated with age or the number of previously administered chemotherapy regimens.

Girinsky *et al.* (18) reported that a bulky tumor >5 cm in diameter was an important adverse factor regarding the efficacy of low-dose IFRT (CR in 29% of patients vs. 58%). In the prospective trial by Haas *et al.* (27), a p value of borderline clinical significance was found for the

Table 3. Selected studies reporting the use of low-dose involved-field radiotherapy in non-Hodgkin lymphoma

Study	No. of patients and sites	Median age (y)	Follicular histology (%)	Bulky (%)	CT given (%)	Median time from diagnosis to RT	CR (%)	PR (%)	Overall RR (%)	Median FU (mo)	2-y FFLP (%)	Median time to LP (mo)
Ng *et al.* (21)	10 (14 sites)	70	10	NR	90	32.5	70	20	90	6.5	NR	6
Girinsky *et al.* (18)	48 (135 sites)	59	67	21	94	32.4	57	24	81	54	56	47
Johannsson *et al.* (19)	22 (31 sites)	62	59	39	NR	NR	55	22	82	8	NR	22
Sawyer and Timothy (17)	11 (16 sites)	75	55	69	73	Mean 44	38	56	94	NR	NR	5
Haas *et al.* (27)	109 (304 sites)	62	90	44	94	44	61	31	92	NR	33	25
Luthy *et al.* (20)	33 (43 sites)	52	85	29	52	43	84	12	95	NR	NR	4
Current study	43	73	39	37	75	48	30	40	86	20	45	21

Abbreviations: CT = computed tomography; RT = radiation therapy; CR = complete response; PR = partial response; RR = response rate; FU = follow-up; FFLP = freedom from local progression; LP = local progression; NR = not reported.

difference in CR rates between patients with nodal size ≤7 cm and patients with larger nodes. A recent North American series by Luthy *et al.* (20) of 33 patients found similarly that the likelihood of achieving a CR was influenced by sites with a higher response in the head-and-neck areas and for disease size <4 cm. In our series, the median tumor size was 46.5 mm and the mean value was 67 mm. Inasmuch as we have not found a uniform definition for bulky disease in the literature, we have tried two different cutoff values. Using a cutoff value of 50 mm, the time to in-field progression was 24 months for nonbulky disease and 6 months for bulky disease, with a p value of 0.37. Therefore, a cutoff value of 50 mm did not seem to be significant. By contrast, with a cutoff value of 100 mm, the time to in-field progression was 24 months for nonbulky disease and 3 months for bulky disease, with a p value of 0.032. Therefore, we can assert, in our series, that a bulky disease of more than 100 mm predicts local failure.

Histologic characteristics have also been shown to influence the benefit of such a treatment. Patients with CLL/small lymphocytic lymphoma were less likely to achieve CR in the prospective Danish trial (19) than were patients with follicular lymphomas (74 vs. 29%). In our series, 39% of the patients had a follicular histology, and among them, 7% presented a Grade 3 lymphoma, which could be a borderline indication for a low-dose IFRT. We also included mantle zone lymphomas. This point could also explain in part our moderate CR rate. We also observed that the overall OS was higher for patients with follicular lymphoma Grade 1 or 2 than for mantle and follicular Grade 3 disease ($p = 0.013$). This seems to reflect the biologic aggressiveness of the disease, but it did not affect the local control after 2 × 2 Gy, which was the aim of our study.

In view of these results, we also wonder if this simple treatment could not be an indication in selected higher-grade lymphomas (for example, diffuse large B cell lymphoma), especially for older patients with multiple comorbidities who are not able to tolerate chemotherapy or more aggressive treatments. One study (15) has already confirmed that good palliation can be obtained in these difficult situations. If the treatment does not work or if its effect does not last, it can be repeated many times or can be replaced by a longer course of irradiation.

Our results confirm that low-dose IFRT remains a very effective, simple, long-lasting, and cost-effective palliative treatment for patients with advanced-stage or recurrent indolent NHL. However, achieving CR could be more difficult in elderly patients with refractory lymphomas after multiple chemotherapy regimens. Therefore, we encourage hematologists, oncologists, and other physicians to refer their patients earlier in the course of the disease.

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