Results of radiotherapy in primary cutaneous lymphoma

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Introduction. **Multiple therapeutic strategies have been proposed for the management of primary cutaneous lymphomas. We report the outcome data and therapeutic response of a group of patients treated with local radiotherapy.**

Material and methods. **Twenty seven patients with diagnostic of cutaneous lymphoma and treated with local radiation were evaluated for clinical response. Thirteen cases corresponded to cutaneous T-cell lymphomas (CTCL) and 14 to cutaneous B-cell lymphomas (CBCL). Orthovoltage radiotherapy of 100 Kv was used and total dose of radiation ranged from 15 to 30 Gy (mean 24 Gy; median 20 Gy).**

Results. **The immediate response to the treatment was satisfactory in all cases. In 24 patients (89%) complete response was obtained in the irradiated lesion and in 3 cases (11%) the response was partial. With a mean follow-up of 25.4 months (range 1-100 months) the overall response rate was 96.3%. Fourteen patients (52%) were alive without evidence of disease (6 CTCL and 8 CBCL), 5 patients (18%) retained cutaneous disease or had systemic progression (3 CTCL and 2 CBCL) and 8 patients died (30%). In 7 patients lymphoma progression was the factor leading to death (26%) and in one patient the cause was not related with the disease.**

Conclusions. **Radiotherapy was demonstrated to be able to induce clinical remission of primary cutaneous lymphomas.**

Key words: radiotherapy, cutaneous T-cell lymphomas, cutaneous B-cell lymphomas.

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INTRODUCTION

Primary cutaneous lymphomas (PCL) represents 10% of extranodal non-Hodgkin's lymphomas and are second in frequency after lymphomas arising in the gastrointestinal tract. PCL are defined as lesions confined to the skin without evidence of extra-cutaneous disease[1].

PCL, cutaneous T-cell lymphomas (CTCL) and cutaneous B-cell lymphomas (CBCL) are a heterogeneous group with a highly variable clinical presentation, histology, inmunophenotype and prognosis[2] that require a different therapeutic approach.

The existent data of the relative frequency of various forms of PCL in European Institutions are approximately 20% for CBCL, while in USA it is 4.5%[3]. Mycosis fungoides is the most common type of CTCL and the neoplastic tumour-infiltrating T lymphocytes shows marked epidermotropism, mainly in early stages. MF and its leukaemic counterpart, Sézary syndrome, have a reported relative frequency ranging from 50% to 80% in the different study groups[4].

Multiple strategies have been proposed for the management of PCL. Therapies can be classified in three main groups: *1.* Local superficial therapies as are corticosteroids, mecloretamine, carmustine, phototherapy and radiotherapy, such as total skin electron beam irradiation or local radiation (LR); *2.* Biologic response modifiers: retinoids, cytokines, interferon and *3.* Systemic chemotherapy. For patients with limited skin disease, topical therapies may be administered[4,5]. Localized forms of primary CBCL and nonepidermotropic T-cell lymphoma usually respond to radiotherapy.

We evaluated the results of 27 patients treated with LR for PCL.

PATIENTS AND METHODS

Between year 1992 and 2000, 27 patients with histologically confirmed cutaneous lymphoma were treated with local radiation in the Department of Radiation Oncology of Hospital Clínic i Universitari of Barcelona. All patients were initially seen in the Department of Dermatology. A total of 139 patients with PCL were diagnosed in our institution during this period.

For each patient we considered the following clinical parameters: sex, age at the time of diagnosis, histological diagnosis, extent and localization of cutaneous

involvement, the initial staging (lactatedehydrogenase blood level expressed as abnormal when above the normal range, thoracoabdominal computerized X ray scan and bone marrow biopsy). All treatments given were noted.

Diagnosis was based on clinical appearance, patient history, histopathological and inmunophenotype studies of the cutaneous biopsies. Biopsy specimens were classified according to the EORTC (1997) classification of PCL. The only exception was the term reticulohistiocytoma of the dorsum used by Crosti to define a clinicopathologic entity characterized by figurate eythematous patches and firm nodules that developed on the back and the lateral portion of the thorax in the adult life. Indeed, the lesions are markedly sensitive to radiation therapy and the course of the disease was very slow.

A detailed description of the clinico-pathologic features of the different types of PCL included is beyond the scope of this report.

Orthovoltage radiotherapy of 100 Kv (8 mA, filter 1,7 mm Al, source skin distance 10 cm) was used, with a safety margin of 1 cm of clinical normal skin. Treatment was delivered in 200 cGy daily fractions, 5 days a week. The prescribed dose was calculated to the 100% isodose. The response was evaluated by clinical examination after completion of radiation therapy. A complete response (CR) was defined as complete resolution of plaques or tumors. If this was not achieved patients were recorded in partial response (PR) or with progressive disease (PD). The relapse was assessed by biopsy to confirm recurrence.

The number of patients was too small to determine if statistically significant differences existed between different primary cutaneous lymphomas or between patients with different clinical outcome.

RESULTS

Population characteristics: Twenty-seven patients, mean age 53.6 years old (range 25-90) were included. There were 17 males and 10 females. Thirteen cases corresponded to CTCL and 14 to CBCL. The mean follow-up was 25.4 months (median 17 months, range 1-100). Details of the patient characteristics are shown in table 1.

TABLE 1. **Results of radiation therapy in 27 patients with cutaneous lymphoma**

N.º	Age	Sex	Diagnosis	Site	CT/BMB	Treatments	Total radiation dose (Gy)	Relapse	Follow-up	Time
1	58	M	CTCL pleomorphic	Buttock	N/N	PCT	15	No	CR	100
2	35	F	CTCL/MF	Cheek	A/A	PCT, TSEBT,INF, AHPT	30	No	Cutaneous disease	71
3	40	F	CTCL/MF	Paranasal	A/A	PUVA, PCT, TSEBT, INF	30	No	Exitus (PD)	9
4	50	M	CBCL-FCL	Back (dorsal)	N/N	No	30	No	CR	1
5	67	M	CTCL/MF	Multiple (S)	N/N	PUVA, PCT, TSEBT, INF	20	No	Exitus (PD)	2
6	75	F	CBCL-MZ	Back (dorsal)	N/N	No	20	No	CR	53
7	88	M	CBCL large-cell	Nose (S)	No/N	PCT	18	No	Exitus (PD)	1
8	28	M	CBCL-MZ	Nose	N/N	No	20	No	CR	48
9	41	M	CBCL-FCL	Forehead	N/N	No	20	No	CR	46
10	90	M	CBCL large-cell	Leg	N/N	No	30	No	Exitus (not related)	3
11	40	M	CTCL CD30+	Leg	N/N	PCT	30	No	Cutaneous disease	39
12	49	F	CTCL CD30+	Thorax	N/N	No	26	No	CR	38
13	86	M	CBCL large-cell	Temporal	A/A	PCT	20	PR	Exitus (PD)	4
14	46	M	CBCL-MZ	Abdomen (S)	N/N	No	26	No	CR	38
15	71	M	CTCL pleomorphic	Leg	N/N	No	30	No	CR	36
16	58	M	CBCL large-cell	Face and back	A/N	PCT	30	No	Exitus (PD)	60
17	37	F	CTCL pleomorphic	Leg	N/N	No	30	No	CR	31
18	25	M	CTCL pleomorphic	Clavicle	N/N	No	20	No	CR	20
19	56	F	CTCL subcutan.	Leg	N/N	INF	30	No	Cutaneous disease	17
20	42	F	CBCL-FCL	Scalp	N/N	No	20	No	CR	17
21	76	M	CTCL/MF	Shoulder	No/No	No	30	PR	Exitus (PD)	9
22	60	F	CBCL large-cell	Leg	A/N	PCT	20	Yes	PD (cutaneous, nodal)	12
23	90	F	CBCL-FCL	Scalp	No/No	No	15	No	CR	7
24	35	M	CBCL Crosti	Back	N/N	No	30	No	Cutaneous disease	10
25	54	F	CTCL-PMP	Back (lumbar)	N/N	PCT	20	PR	Exitus (PD)	3
26	26	M	CBCL Crosti	Back	N/N	No	20	No	CR	9
27	43	M	CTCL pleomorphic	Hand (dorsa)	N/N	No	20	No	CR	3

Age (years). Sex: M = male, F= female. Diagnosis: MF = mycosis fungoides, FCL = follicular center cell lymphoma, MZ = marginal zone, PSM = pleomorphic small/medium size. Site: S = several lesions. CT (computed tomography)/ BMB (bone marrow biopsy): N = negative, A = affectation, No = not performed. Treatments = other treatments: PCT = polichemotherapy, TSEBT = total skin electron beam therapy, INF = interferon, AHPT = autologous haematopoietic progenitor transplantation. Relapse: PR = partial response. Follow-up: CR = complete remission, PD = progressive disease. Time period: after the radiation therapy (months).

Clinical presentation of the lesions differs widely, ranging from limited tumors to more extensive disease. The most common localization was the cephalic area followed by the lower extremities. In two cases the localization was multiple.

Staging work-up was performed in all patients, including computed tomographic scan and bone marrow biopsy. Serum lactate dehydrogenase (LDH) levels were raised in all of these patients.

Most often, radiotherapy was the single treatment (16 patients, 71.4% CBCL); 7 received a combination of radiotherapy and chemotherapy and 3 patients were treated with several therapeutic options, all three were mycosis fungoides. The only patient with subcutaneous CTCL was also treated with interferon.

The mean total dose of irradiation was 24 Gy (median 20 Gy; range 15-30 Gy) delivered in 200 cGy daily fractions, 5 days a week. For patients with CTCL the median radiation dose was 30 Gy (mean 25.5 Gy), while patients with CBCL the median radiation dose was 20 Gy (mean 22.8 Gy).

Disease status and response

The immediate response to the treatment was satisfactory. As acute side effects, only light erythema (*grade I RTOG toxicity criteria*) in the treated area was observed, with complete spontaneous healing in all patients in a maximum period of two weeks after the radiotherapy was concluded. The patients' assessment of the aesthetic results was good or excellent in all cases. In 24 patients (89%) CR was obtained in the irradiated lesion and in 3 cases (11%) was PR. Eleven of these 24 patients with CR were CTCL (CR in CTCL 85%) and thirteen were CBCL (CR in CBCL 93%). Of the three patients with PR, two were CTCL (15% of the 13 CTCL) and one was CBCL (7% of patients with CBCL).

The overall response rate was 96.3%. In one patient local recurrence was observed in the treated area during the follow-up period (case 22) and relapsed after 7 months of follow-up. New lesions outside the irradiated area appeared at the same time. Fourteen cases (52%) were alive without evidence of disease (6 CTCL patients and 8 CBCL patients); 5 patients (18%) retained cutaneous disease and one of them experienced skin progression and extension to lymph nodes (3 CTCL and 2 CBCL), and 8 cases (29.6%) died. Lymphoma was the factor leading to death in 7 patients (overall rate 25.9 %; 30.8% CTCL, 21.4% CBCL). In one CBCL patient the cause of death was not related with the disease.

DISCUSSION

Primary cutaneous lymphomas are markedly sensitive to local radiotherapy[6]. Radiotherapy with a curative or palliative purpose is considered a first line treatment in the lymphoproliferative lesions. Local radiation presents minimum acute or chronic toxicity. The treatment is complete in two or three weeks and it allows the application of other treatments (PUVA, mecloretamine) and management with local radiotherapy is feasible if local or distant relapses occur[4,7].

The use of radiation therapy as complementary treatment in PCL is efficient and well-tolerated procedure. Local treatment is highly effective and the complete response rate is in excess of 90% in CTCL, for both plaques and tumors[7].

Approximately 5% of patients with mycosis fungoides (MF) in stage IA, present with a solitary cutaneous lesion or several in close proximity. These patients may be managed effectively with LR alone, without adjuvant therapy[5-7]. Several authors have reported the effectiveness of LR[4,5,8-10] (table 2). Cotter et al[8] determined that doses of at least 30 Gy, 2 Gy/fraction, were necessary for local control with palliative intention in cutaneous mycosis fungoides, these results were obtained in 14 patients treated. Micaily et al[10] evaluated the treatment outcome of 18 patients with the diagnosis of unilesional mycosis fungoides. They used local electron beam therapy and a total dose range of 20 to 40 Gy. They obtained complete regression of all treated lesions. Actuarial disease-free survival (DFS) and overall survival at 10 years was 86.2% and 100%, respectively. The median follow-up was 43 months (mean 71 months, range 12-240). Wilson et al[4] reported the results of 21 patients with stage IA mycosis fungoides treated with LR with radical intention. The median dose was 20 Gy (17 patients received 20 Gy or more) and the median follow-up was 36 months (15-246 months). A CR was achieved in 97% of the patients, and DFS was 75 and 64% respectively at 5 and 10 years. For patients with unilesional disease, the

TABLE 2. **Cutaneous T-cell lymphoma treated with local radiotherapy**

Author	Patients	Diagnosis	Median dose (range)	CR
Cotter et al[8]	14	CTCL	(6-40) Gy	94%
Wilson et al[4]	21	CTCL	20 (6-40) Gy	97%
Mycaily et al[10]	18	CTCL	30.6 (22-40) Gy	100%
Present study	13	CTCL	30 (15-30) Gy	85%

CTCL: cutaneous; T-cell lymphoma; CR = complete response.

TABLE 3. **Cutaneous B-cell lymphoma treated with local radiotherapy**

Author	Patients	Diagnosis	Median dose (range)	CR
Santucci et al[15]	44	CBCL	40 Gy	44 (100%)
Piccino et al[13]	31	CBCL	30 (10-40) Gy	31 (100%)
Rijlaarsdam et al[14]	40	CBCL	(30-40) Gy	40 (100%)
Kirova et al[11]	25*	CBCL	(30-40) Gy	23 (92%)
Present study	14	CBCL	20 (15-30) Gy	13 (93%)

CBCL: cutaneous B-cell lymphoma; CR = complete response.
*Nineteen patients treated with local radiotherapy and six patients with extended field irradiation.

DFS was 85% at 10 years and for those treated with at least 20 Gy, the DFS was 91%. The recommended total dose prescription was 20 Gy in 10 fractions.

In our series, palliative radiotherapy was considered in the patients with CTCL with lesions resistant to other treatments or lesions whose characteristics o localization or ulceration were the main cause of symptoms (cases: 2, 3, 5, 21 and 25). Most often, patients with MF received a dose of 30 Gy. Radiotherapy with radical intention was used in pleomorphic T-cell lymphoma (cases: 1, 15, 17, 18 and 27), large-cell CD30+ T-cell lymphoma (cases: 11 and 12) or subcutaneous panniculitis-like T-cell lymphoma (case 19).

In cutaneous B-cell lymphomas without systemic disease, LR could be considered the treatment of choice, with a very high local control (85-100%). Relapses may occur and the new skin lesions can be treated with local re-irradiation. The number of patients included in studies of CBCL treated with LR is more elevated that in those of CTCL. The response to radiotherapy is favorable, this treatment was found to be successful, CR was achieved in all cases (100%). The results of these studies are listed in table 3. There were a significant number of relapses (20-75%), the majority of these resulted in complete remission after re-treatment[12-15]. Metastasis are unusual, 3 to 18% of CBCL can extent to internal organs, more frequently to lymph nodes, bone and bone marrow.

Rijlaarsdam et al[14] did not find any relationship among relapse of CBCL treated and radiation dose, tumor size or age, but the anatomical localization of lesions had prognostic implications. In 6 cases the lesion was located in the lower extremities, 4 relapsed (67%) and three patients who died as a consequence of the disease had involvement in this anatomical area. When this subgroup of 6 patients were excluded, 5 year survival was 96%, while it decreased to 89% for the entire group.

In our series, in two patients with CBCL, the lesion was located on the lower extremities, one of these patients is the only one that the disease relapsed in the irradiated area, and progressed to lymph nodes. The other patient died for cause not related to the disease. Our study confirms the good response of cutaneous lesions in CBCL although three patients progressed to extracutaneous disease.

In summary, we confirm the results reported by several authors concerning LR feasibility, efficacy, stabilization or palliation of symptoms. All patients had clinical response to irradiation. After follow-up period overall response rate was 96.3%. At the end of the study 46.2% of CTCL and 57.1% of CBCL were alive and free of disease. Partial response was obtained in 23.1% of CTCL and 7.1% of CBCL patients, respectively. Relapse ocurred in one patient with CBCL after seven months (3.7%) and eight patients experienced a fatal progression.

CONCLUSION

Radiotherapy in cutaneous lymphomas can be considered a highly effective treatment with good cosmetic results. LR is a single effective modalilty able to cure patients with skin-confined disease. It may be considered a first line treatment in cases of CBCL, pleomorphic, large-cell CD30+ T-cell lymphoma or subcutaneous panniculitis-like T-cell lymphoma and as a palliative treatment in MF patients with lesions resistant to other treatments focused on symptomatic relief.

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