Results of Radiotherapy in 153 Primary Cutaneous B-Cell Lymphomas Classified According to the WHO-EORTC Classification

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**Objective:** To evaluate the results of radiotherapy in patients with primary cutaneous B-cell lymphoma (CBCL) classified according to the criteria of the World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) classification.

**Design:** Multicenter, 20-year, retrospective, cohort analysis.

**Setting:** Eight dermatology departments collaborating in the Dutch Cutaneous Lymphoma Group.

**Patients:** From 1985 until 2005, a total of 153 patients with CBCL were initially treated with radiotherapy with curative intent. These cases were classified according to the WHO-EORTC classification and consisted of 25 primary cutaneous marginal zone lymphomas (PCMZLs), 101 primary cutaneous follicle center lymphomas (PCFCLs), and 27 primary cutaneous large B-cell lymphomas, leg type (PCLBCLs, LT).

**Interventions:** Local radiotherapy with a median dose of 40 Gy (range, 20-46 Gy) applied to all visible skin lesions.

**Main Outcome Measures:** Complete remission rate, relapse rate, 5-year relapse-free survival, 5-year overall survival, and 5-year disease-specific survival.

**Results:** Complete remission was reached in 151 of 153 patients (99%). Relapse rates for PCMZL, PCFCL, and PCLBCL, LT were 60%, 29%, and 64%, and the 5-year disease-specific survival was 93%, 97%, and 59%, respectively. The PCFCLs presenting on the legs had a higher relapse rate (63%) and a much lower 5-year disease-specific survival (44%) than PCFCLs at other sites (relapse rate, 25%; 5-year disease-specific survival, 99%).

**Conclusions:** Radiotherapy is a suitable treatment for a large group of patients with CBCL. However, patients with PCFCL presenting with lesions on the leg and patients with PCLBCL, LT display a more unfavorable clinical course and should therefore be treated with more aggressive treatment modalities.
tively, were assigned to another prognostic category when the WHO-EORTC classification was used. These observations prompted us to evaluate the results of RT as initial treatment in CBCL reclassified according to the criteria of the new WHO-EORTC classification.

The purpose of this retrospective study was to define complete remission (CR) rates, relapse rates, relapse-free survival (RFS), 5-year overall survival (OS), and 5-year DSS after RT for these newly defined groups of CBCL, and to establish for which patients RT is a safe and effective mode of treatment.

METHODS

SELECTION OF PATIENTS

Between October 1, 1985, and July 31, 2005, a total of 320 patients with CBCL were included in the registry of the Dutch Cutaneous Lymphoma Working Group. Follow-up data had been collected each year from patients’ medical charts or referring physicians. In a recent study, clinical data and histologic sections of 300 CBCLs were reviewed and reclassified according to the criteria of the new WHO-EORTC classification. This group included 174 patients who had received RT as initial treatment. Patients in whom RT was administered in palliative dosages with no intention to be curative were excluded (n = 7), as were patients with a follow-up of less than 12 months (n = 14). However, patients who died of their lymphoma within 12 months after diagnosis were not excluded from the study. The final study group consisted of 153 patients with CBCL. According to the WHO-EORTC classification, this group included 25 PCMZLs, 101 PCFCLs, and 27 cases of PCLBCL, LT (Figure 1).

The following data were recorded for all patients: age at diagnosis, sex, involved skin site, extent of involved skin, result of initial therapy, occurrence and site of relapse, relapse treatment, result of relapse treatment, duration of follow-up, and status at last follow-up. Extent of involved skin was defined as solitary when it concerned a single tumor, localized when the lesion consisted of multiple plaques and/or tumors that could be irradiated within 1 radiation field, and multifocal if multiple nonadherent body sites were involved or when the lesions could not be irradiated within 1 radiation field.

TREATMENT

Most patients had been treated with electron beam irradiation (4-10 MeV), while 9 patients had received 6 to 10 MV of photon beams. The radiation dose varied between 20 and 46 Gy, with a median dose of 40 Gy (to convert the radiation dose to rad, multiply by 100). In all patients, a margin of at least 2 cm of healthy skin was included in the radiation field. In PCFCL, localized on the trunk, which often presents with tumors surrounded by annular erythemas, the erythematous areas were included in the radiation field because they represent early manifestations of the neoplastic process. Treatment response was evaluated 4 to 6 weeks after the end of RT by clinical examination and classified as CR, partial remission, no response, and progressive disease. Complete remission was defined as the disappearance of all visible skin lesions; partial remission, 50% or more remission of clinical lesions; no response, less than 50% remission; and progressive disease, development of new skin lesions during treatment. Outcome measures for results of RT were CR rate, relapse rate, 5-year RFS, 5-year OS, and 5-year DSS.

STATISTICAL ANALYSIS

Overall survival was calculated from the date of diagnosis until the patient’s death or last follow-up without event. Disease-specific survival was calculated from the date of diagnosis until death from lymphoma or last follow-up without event. Relapse-free survival was calculated from the date CR was reached until first relapse or last follow-up without event. Survival curves were estimated by the method of Kaplan and Meier, and curves were statistically compared by log-rank testing. The χ2 test was used to analyze differences between subgroups. All statistical analyses were done with SPSS software, version 12.0.1 (SPSS Inc, Chicago, Illinois).

RESULTS

The total group consisted of 87 men and 66 women, with a median age of 62 years (range, 23-92 years). Median follow-up for the whole group was 62 months (range, 3-336 months). The clinical characteristics, results of RT, and follow-up data for the total group of patients with CBCL are presented in the Table. Clinical characteristics, treatment results, and follow-up data for the 3 subgroups of CBCL are also summarized in the Table and will be described in more detail in the subsequent paragraphs.

PRIMARY CUTANEOUS MARGINAL ZONE B-CELL LYMPHOMA

The group of patients with PCMZL consisted of 18 men and 7 women, with a median age of 49 years (range, 23-79 years). Nine patients had a solitary lesion, 5 patients had localized skin lesions, and 11 patients presented with multifocal disease. Most patients presented with lesions on the trunk or arms (Table).

Treatment with RT resulted in CR in all 25 patients. Fifteen patients (60%) experienced a relapse after a median relapse-free interval of 16 months (range, 3-144 months). Twelve of these patients showed relapses confined to the skin, 1 had a cutaneous and an extracutaneous relapse, and 2 experienced an extracutaneous relapse without concurrent skin lesions. Cutaneous relapses always occurred at nonirradiated sites. Patients with a PCMZL had an excellent prognosis, with a 5-year OS and DSS of 90% and 95%, respectively (Figure 2).

PRIMARY CUTANEOUS FOLLICLE CENTER LYMPHOMA

The PCFCL group consisted of 61 men and 40 women, with a median age of 58 years (range, 27-85 years). Most patients (92% [93 of 101]) presented with solitary lesions (48 patients) or localized skin lesions (45). Only 8 of 101 patients had multifocal disease at the time of presentation. Most presented with the typical lesions on the head (41 patients) or trunk (55). Eight patients had lesions on 1 (7 patients) or both (1) legs. Six of these 8 patients were previously classified as having primary cutaneous large B-cell lymphoma of the leg (PCLBCL, leg), following the EORTC classification. Treatment with RT resulted in CR in all 101 patients. A relapse was noted.
in 29 patients 2 to 62 months (median, 12 months) after initial treatment. In 21 patients the relapse was confined to the skin, 3 had a relapse in the skin and an extracutaneous localization, and 5 had a relapse at an extracutaneous site without concurrent skin lesions. All cutaneous relapses occurred outside the irradiated area. Skin relapses were generally treated with an additional course of RT, which resulted in another CR in all cases. Ultimately, 10 of 101 patients developed extracutaneous disease and 4 of 101 patients died of lymphoma. The 5-year OS and DSS were 90% and 97%, respectively (Figure 2).

Comparison between PCFCL with solitary or localized lesions confined to the head (n=38) or trunk (n=48) showed no difference in relapse rate (26% [10 of 38] vs 21% [10 of 48]) or 5-year DSS (95% vs 98%). However, 8 patients with PCFCL presenting with lesions on the legs had a higher relapse rate (63% [5 of 8] vs 26% [24 of 93]; P = .03), more often developed extracutaneous disease (38% [3 of 8] vs 8% [7 of 93]; P = .006), and had a considerably lower 5-year DSS (44% vs 99%; P < .001) than did the patients without lesions on the legs.

Our study group contained only 5 patients with PCFCL presenting with multifocal skin lesions without involvement of the leg. Three of these 5 patients had a relapse in the skin; 1 of the 3 patients eventually developed intracerebral lesions and died of the lymphoma 26 months after the initial diagnosis.

Comparison between PCFCL with a follicular or follicular and diffuse growth pattern (32 cases; classified as cutaneous follicle center lymphoma in the WHO classification) and PCFCL with a diffuse growth pattern (69 cases;
classified as diffuse large B-cell lymphoma (DLBCL) in the WHO classification) showed no significant difference in relapse rate (41% [13 of 32] vs 23% [16 of 69], respectively; \( P = .07 \)) and no difference in DSS (100% vs 95%, respectively; \( P = .71 \)) between the 2 groups. This illustrates that the growth pattern of the malignant infiltrate has no prognostic significance and does not justify more aggressive treatment.

**PRIMARY CUTANEOUS LARGE B-CELL LYMPHOMA, LEG TYPE**

The PCLBCL, LT group contained 8 men and 19 women. The age at diagnosis in this group (median, 78 years; range, 50-92 years) was considerably higher than that of the other 2 groups. Twenty-five of 27 patients presented with skin lesions on the legs, while 1 patient presented with a solitary tumor on the scalp and another patient had lesions localized to the left forearm. These 2 cases were formerly classified as primary cutaneous follicle center cell lymphoma (PCFCCL) in the EORTC classification. According to the WHO classification, all 27 patients would have been classified as having DLBCL. Twelve patients had a solitary lesion at initial diagnosis and 15 patients presented with localized disease. This group did not contain patients presenting with multifocal skin lesions.

Treatment with RT resulted in CR in 25 of 27 patients (93%). In 2 patients, including the patient presenting with a solitary tumor on the scalp, new skin lesions developed outside the irradiated areas during initial RT, and both patients died of lymphoma 3 and 9 months after diagnosis. The patient previously classified as having PCFCCL (EORTC classification) and presenting with skin lesions on the left forearm reached CR that had been sustained for more than 5 years at last follow-up.

Of the 25 patients who did reach CR, 7 patients had relapses only in the skin, 4 in the skin as well as in an extracutaneous site, and 5 only extracutaneously.
of the 11 skin relapses were located within the irradiated area, although the cumulative dose in these patients (36 and 40 Gy) was comparable to that of the other patients.

Ultimately, 10 patients showed extracutaneous dissemination and 11 patients died of lymphoma. For the total group of patients with PCLBCL, LT, the 5-year OS was 40% and the 5-year DSS was 59% (Figure 2). Comparison between patients presenting with a solitary lesion and patients presenting with multiple localized skin lesions did not show significant differences in 5-year RFS (40% vs 32%; \( P = .51 \)) or 5-year DSS (61% vs 58%; \( P = .73 \)).

**COMMENT**

In this study we evaluated the results of RT in 153 patients with CBCL, reclassified according to the criteria of the WHO-EORTC classification. The PCFCL category formed the largest group (101 of 153 patients [66%]). In the WHO-EORTC classification, PCFCL is defined as a tumor of neoplastic follicle center cells, with a predominance of large centrocytes and variable numbers of centroblasts, which may have a follicular, follicular and diffuse, or diffuse growth pattern, and which generally present on the head or trunk, or, uncommonly, on the legs.\(^1\) In the EORTC classification, these rare cases presenting on the legs were included in the category PCLBCL, leg.\(^{11}\) The results of our study showed CR following initial RT in all 101 cases. The 5-year RFS was 70% (Figure 3). Twenty-one patients showed 1 or multiple relapses confined to the skin, while 8 patients had relapses at extracutaneous sites with or without concurrent skin lesions. No in-field recurrences were observed. In most patients, skin relapses were successfully treated again with RT. The 5-year DSS and OS of the total group were 97% and 90%, respectively. These observations are consistent with the results of most previous studies in patients with PCFCL as defined by the criteria of the EORTC classification\(^2,4,7,10\) but differ considerably from the results reported by Piccinno and coworkers.\(^8,9\) These authors performed a retrospective study of 102 PCFCLs and found a relapse rate of 75% and a 5-year RFS of only 23%. Moreover, in-field relapses were noted in 18 of 102 cases. These differences might be explained by the use of orthovoltage techniques and the narrow margins (0.5-1.0 cm) of clinically uninvolved skin included in the irradiation field, as previously postulated.\(^7\) The reported survival data and the low proportion of patients developing extracutaneous disease, however, are comparable in all of these studies, which illustrates the favorable biological behavior of this lymphoma.

Subgroup analysis showed that patients presenting with skin lesions on the leg more often had relapses, more often developed extracutaneous disease, and had a much more unfavorable prognosis than did patients presenting with skin lesions on the head or trunk. These observations confirm the results of recent studies and suggest that presentation on the leg is an unfavorable risk factor in PCFCL.\(^{13,17}\) It also suggests that such cases should not be treated routinely with RT.

Patients presenting with multifocal skin lesions represent another subgroup subjected to much debate.\(^2,6,9,18\) A previous study by our group\(^6\) found that PCFCLs presenting with multifocal skin lesions have the same clinical behavior and prognosis as PCFCLs presenting with solitary or localized skin lesions. Radiotherapy of all visible skin lesions proved as effective as multiagent chemotherapy. In fact, skin relapses were observed in 3 of 9 patients treated with multiagent chemotherapy and in none of the 5 patients treated with RT.
The present study group contained only 5 cases of PCFCL presenting with multifocal skin lesions, but not located on the leg. Three of these 5 patients had relapses in the skin, and 1 of them died of central nervous system involvement. Recent analysis of 13 PCFCLs with multifocal skin lesions (excluding localization on the leg) treated with multiagent chemotherapy showed relapses (in the skin) in 4 of 13 patients, while 1 of them developed extracutaneous disease during follow-up (N.J.S. and R.W., unpublished data, November 2006). Taken together, these small series do not allow firm conclusions to be drawn. Prospective collaborative studies on larger numbers of patients are required to evaluate whether PCFCL presenting with multiple skin lesions can indeed be treated safely and effectively with RT.

The lesions in the PCLBCL, LT category are defined as tumors with a predominance or confluent sheets of centroblasts and immunoblasts, characteristically presenting with skin lesions on the lower legs. Cases with similar morphologic features and phenotype (strong Bcl-2 [B-cell CLL/lymphoma 2] and MUM-1 [multiple myeloma oncogene 1] expression) arising at sites other than the leg are included in this group. In the EORTC classification, such cases were included in the group of PCFCLs. Recent studies found that cases presenting on the leg and cases presenting at other sites have a similar clinical behavior and prognosis, indicating that reclassification of such cases as PCLBCL, LT is an improvement. In the present study, 25 of 27 patients presented with skin lesion on the legs, while 2 patients presented with skin lesions at other sites. In general, PCLBCL, LT should be treated in the same way as other systemic DLBCLs, for instance, with a regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone in combination with rituximab (anti-CD20 antibody). However, in a previous European multicenter study including 48 patients with PCLBCL, leg, patients presenting with a solitary tumor on 1 leg had a significantly better prognosis than did patients presenting with multiple tumors on 1 or both legs. It was therefore suggested that patients with a solitary tumor could be treated with RT, while all other patients in this group should be treated with systemic chemotherapy. The results of the present study do not support this suggestion. No difference in relapse rate, OS, and DSS was observed between patients with a solitary lesion and patients presenting with multiple localized lesions.

Moreover, 2 patients developed new skin lesions outside the irradiated areas during initial treatment, and 16 of the other 25 patients showed relapses after initial therapy. In addition, this was the only group in which skin relapses developed within a previously irradiated area (2 patients). Only 9 of 27 patients showed a sustained CR after initial RT. Taken together, these results indicate that RT should not be used as first-line treatment in PCLBCL, LT, irrespective of the number of skin lesions. These patients should be routinely treated in the same way as those with other DLBCLs following current protocols. Only in patients who do not tolerate systemic chemotherapy because of a poor clinical condition or patients who refuse this type of treatment may RT be considered as an alternative option.

As described recently, RT is also a highly effective treatment in PCMZL presenting with a solitary or few scattered lesions. However, the relapse rate in PCMZL proved much higher than in PCFCL (5-year RFS, 45% vs 70%, respectively; Figure 3). In patients presenting with many scattered skin lesions, RT is no longer the first choice of treatment. In such patients, beneficial effects have been reported with chlorambucil or intraläsional treatment with interferon alfa 2A or rituximab. In patients developing chronically relapsing disease, treatment is aimed at palliation and no longer at cure, and therefore the benefits of treatment should be weighed carefully against their potential side effects. In such patients, an expectant policy should be considered. The results of a recent pilot study suggest that low-dose RT with $2 \times 2 \text{ Gy}$ is a useful alternative for such patients experiencing multiple skin relapses (K.J.N., E.C. Schimmel, MD, M.H.V., N.J.S., R.W., and E.M.N., unpublished data, 2006).

In conclusion, the results of our study indicate that RT is a safe and effective treatment in many patients with CBCL. In PCLFCL and PCMZL, RT is the first line of treatment, not only in patients presenting with solitary or localized skin lesions, but probably also in patients presenting with a few scattered skin lesions. However, prospective, collaborative studies are required to confirm this latter conclusion. Patients with PCLBCL, LT and the rare patients with a PCFCL presenting with skin lesions on the leg appear to have a more aggressive clinical course, and RT should not be considered as the first choice of treatment in these patients.

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