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Radiation Therapy for Primary Cutaneous Anaplastic Large Cell Lymphoma: An International Lymphoma Radiation Oncology Group Multi-institutional Experience

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Abstract

Purpose—To collect response rates of primary cutaneous anaplastic large cell lymphoma, a rare cutaneous T-cell lymphoma, to radiation therapy (RT), and to determine potential prognostic factors predictive of outcome.

Methods and Materials—The study was a retrospective analysis of patients with primary cutaneous anaplastic large cell lymphoma who received RT as primary therapy or after surgical excision. Data collected include initial stage of disease, RT modality (electron/photon), total dose, fractionation, response to treatment, and local recurrence. Radiation therapy was delivered at 8 participating International Lymphoma Radiation Oncology Group institutions worldwide.

Results—Fifty-six patients met the eligibility criteria, and 63 tumors were treated: head and neck (27%), trunk (14%), upper extremities (27%), and lower extremities (32%). Median tumor size was 2.25 cm (range, 0.6–12 cm). T classification included T1, 40 patients (71%); T2, 12 patients (21%); and T3, 4 patients (7%). The median radiation dose was 35 Gy (range, 6–45 Gy). Complete clinical response (CCR) was achieved in 60 of 63 tumors (95%) and partial response in 3 tumors

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(5%). After CCR, 1 tumor recurred locally (1.7%) after 36 Gy and 7 months after RT. This was the only patient to die of disease.

Conclusions—Primary cutaneous anaplastic large cell lymphoma is a rare, indolent cutaneous lymphoma with a low death rate. This analysis, which was restricted to patients selected for treatment with radiation, indicates that achieving CCR was independent of radiation dose. Because there were too few failures (<2%) for statistical analysis on dose response, 30 Gy seems to be adequate for local control, and even lower doses may suffice.

Introduction

Primary cutaneous anaplastic lymphoma (pcALCL) is part of the spectrum of primary cutaneous $CD30^+$ lymphoproliferative disorders (pc$CD30^+$ LPDs) that also includes lymphomatoid papulosis (LyP). It is the second most common subtype of cutaneous T-cell lymphoma (CTCL). Clinically, pcALCL presents as a rapidly growing solitary nodule or cluster of nodules, usually <5 cm. It may involve any region of the body, including head/neck, trunk, and upper and lower extremities. Histopathology demonstrates large anaplastic, pleomorphic, or immunoblastic T cells that express CD30, a cell membrane protein of the tumor necrosis factor receptor family. Primary cutaneous anaplastic lymphoma is usually positive for cutaneous lymphocyte antigen (HECA-452) but lacks epithelial membrane antigen and ALK-1 protein staining (ALK negative) (1, 2). Although the nomenclature suggests an aggressive tumor phenotype, pcALCL patients have a favorable prognosis, with 5-year survival rates from 85% to 100%, albeit with frequent cutaneous relapses (3–6).

Establishing a diagnosis of pcALCL requires a clinical-pathologic correlation to distinguish this entity from other primary cutaneous $CD30^+$ lymphoproliferative disorders, particularly LyP. Lymphomatoid papulosis is characterized by erythematous, dome-shaped papules or nodules that are frequently multifocal at presentation but regress spontaneously over weeks to months without treatment. Lymphomatoid papulosis may be associated with the development of other malignant lymphomas, including pcALCL, mycosis fungoides (MF), and Hodgkin lymphoma. Primary cutaneous anaplastic lymphoma must also be differentiated from systemic ALCL with cutaneous involvement, which may be either ALK negative/ positive or $CD30^+$ large cell transformed MF. By definition, extracutaneous disease cannot be present at the time of diagnosis. However, subsequent progression to involve extracutaneous sites may occur in as many as 16% of patients (7).

In 2011, international consensus guidelines were established for the management of pcALCL. These guidelines were based on the results of small retrospective series and case reports. Radiation therapy (RT) and surgical excision were recommended for solitary or closely grouped nodules, with an expected 95% complete clinic response (CCR) after RT and 100% after surgical excision (4). However, this study did not recommend a specific radiation dose.

Two small series independently reported 100% local control rates for patients receiving moderate-dose irradiation of 34 to 44 Gy and 40 to 50 Gy. Nevertheless, the study population consisted of only 8 and 14 patients, respectively, and excision followed by RT was used in the latter (8, 9). Because these tumors are rare, collecting an adequate number of

cases to study is challenging. Therefore, a proposal was submitted to International Lymphoma Radiation Oncology Group (ILROG) members to contribute cases of pcALCL treated with radiation over a 20-year period, to study the radiation dose response and potential prognostic factors predictive of outcome.

Methods and Materials

Patient population and treatment

This study was approved by the institutional review board at the Stanford Cancer Institute in July 2014. Once approved, Stanford distributed the institutional review board template to 7 other participating ILROG institutions, including Peter MacCallum Cancer Centre, MD Anderson Cancer Center, Princess Margaret Cancer Centre, Dana-Farber Cancer Institute, Yale School of Medicine–Yale Cancer Center, University of Turin, and Institut Curie. Over the course of 1 year, each institution contributed at least 3 cases of pcALCL that met the following criteria: (1) patient was at least 18 years of age at time of diagnosis; (2) diagnosis and treatment occurred between 1990 and 2014; (3) RT was given during initial treatment OR for local failure after surgical excision; and (4) patient received RT at the institution submitting the data.

The diagnosis of pcALCL was established using both clinical and pathologic criteria. Clinical criteria included the presence of persistent, solitary, grouped, or multifocal nodules, no clinical evidence of other $CD30^+$ CTCL, no prior history of MF, and no extracutaneous disease at time of diagnosis. Pathologic diagnosis was according to the World Health Organization classification for pcALCL. Histology typically showed dense, nodular, dermal infiltrates composed of large pleomorphic, anaplastic, or immunoblastic cells with large, irregularly shaped nuclei and abundant pale or eosinophilic cytoplasm. CD30 was expressed in all cases.

The International Society for Cutaneous Lymphomas–European Organization of Research and Treatment of Cancer TNM classification was used to classify patients and was applied retrospectively if patients had been diagnosed before the inception of the TNM classification (10). Tumor staging was divided into 3 classifications: T1 (solitary), T2 (regional, or multiple lesions limited to 1 or 2 contiguous body regions), and T3 (generalized, or multiple lesions in noncontiguous body regions). These classifications are further subdivided into T1a (≤5 cm) or T1b (>5 cm), T2a (≤15 cm) or T2b (>15 cm), and T3a or T3b for disease involving 2 or more noncontiguous body regions (Table 1).

Data were collected from all 8 institutions through a secure database called Research Electronic Data Capture. Data abstracted included patient demographics, tumor size, location, stage (TNM), history of Hodgkin disease, MF, LyP, or other lymphomas, CD30 confirmation, modality of RT (electron/photon), dose and fractionation, response to radiation treatment (CCR, partial response [PR], progressive disease [PD]), local recurrence after radiation, and status at patients' last follow-up appointment. Only 3 time points were collected: treatment start date, treatment end date, and date at last follow-up. Complete clinical response was defined as complete absence of clinical disease after therapy; PR was defined as regressing but persistent or unchanged disease on clinical examination; and PD

was defined as progressive disease unresponsive to treatment. Death was categorized as death from pcALCL or death due to a disease other than pcALCL.

Statistical methods

The data were analyzed using Fisher exact test. Time to event outcomes was analyzed using Kaplan-Meier methodology. All tests were 2-sided with an α level of 0.05. All analyses were performed in SAS v9.4 (SAS Institute, Cary, NC).

Results

Patient characteristics

Data from 67 patients were collected from the 8 collaborating institutions. Eleven patients were excluded from the analysis owing to presence of extracutaneous disease (4 patients), prior or concurrent history of MF (5 patients), or concurrent LyP (2 patients). Of the 56 patients included in the study, there were 37 men and 19 women (ratio of 1.9:1), with median age of 66 years (range, 28–97 years).

Forty patients (71%) were classified as T1a/b, 12 patients (21%) as T2a/b, and 4 patients (7%) as T3a/b. Sixteen patients had more than 1 tumor irradiated, for a total of 63 distinct tumors that were analyzed. The median size of the tumor was 2.25 cm (range, 0.6–12 cm). Tumor sites included 17 head and neck (27%), 9 trunk (14%), 17 upper extremity (27%), and 20 lower extremity (32%). Table 2 summarizes the characteristics of patients included in the analysis.

Treatment: Dose and response

The majority of the patients were treated with RT at the time of initial diagnosis; only 5 patients received RT after local failure following surgical excision. The most common RT modality was electron beam. Only 8 patients were irradiated with brachytherapy (5 patients) or photons (3 patients).

The RT dose ranged from 6 to 45 Gy, with a median dose of 35 Gy and mode of 30 Gy. The median dose per fraction was 2 Gy, ranging from 1.5 to 6 Gy per fraction. Only 1 patient received a single fraction. All patients responded to RT: 60 tumors had CCR (95%), and 3 tumors had PR (5%). Response rate by T classification included CCR of 95%, 93%, and 100% for T1, T2, and T3 tumors, respectively. Table 3 shows the tumor response by radiation dose. Of note, 11 tumors received doses <30 Gy (range, 6–26.6 Gy), and 10 of these 11 patients had a CCR to treatment. The 3 patients with PR to RT were staged T1a (1.8 cm), T2a (5 cm), and T1b (8.5 cm) and received doses of 34 Gy, 43.6 Gy, and 20 Gy, respectively.

Outcome: Local failure, survival, and predictive factors

The median follow-up was 3.5 years (range, <1 month-15 years). The local control rate at a median of 3.5 years was 98%. Only 1 patient, who had a 12-cm head and neck tumor treated with 36 Gy, developed a local recurrence 7 months after RT. Despite systemic therapy for relapse, the patient ultimately died from pcALCL. No other patient died of pcALCL.

Therefore, the disease-specific survival for the 56 patients was 98% at 15 years after RT, of which 45 patients (80%) were alive without pcALCL, 7 patients (13%) were alive with pcALCL due to relapses outside the original treatment field, and 3 patients (5%) died from unrelated causes (Table 4).

Analysis of potential predictive factors using Fisher exact test suggests that radiation dose, T stage, or RT modality does not correlate with treatment response (P=.39, 1.00, and 1.00, respectively).

Discussion

These pooled data from 8 ILROG institutions, which used the specific criteria of RT as primary treatment or after local failure following excision, demonstrate a 100% overall response rate and 95% CCR. A median dose of 35 Gy was used, but complete responses were seen with doses as low as 6 Gy, thereby highlighting the radiosensitivity of pcALCL. Of note, spontaneous regression is also part of the natural biology of this disease and may have contributed to the high CCR rates (11).

There were 3 partial responses, after doses of 20 Gy, 34 Gy, and 43.6 Gy. We have too few patients with PR to draw conclusions about an association between radiation dose, tumor size, and/or extent of disease (T classification) that could be used to predict a poor response to RT. Notably, 2 of the 3 patients with PR are alive without disease. Although we did not collect data on subsequent therapy or response assessments at multiple time points, possible explanations for why patients are alive without disease after PR include additional surgery, topical or systemic treatment that resulted in CCR, or spontaneous regression of the tumor.

The overall disease-specific survival for pcALCL was 98% at 15 years, attesting to the indolent nature of this disease. It is of interest that the sole local failure in our cohort also resulted in the only death attributed to pcALCL. This was an 83-year-old woman, who had a CCR after 36 Gy to a 12-cm tumor on the head and neck but experienced a local recurrence less than 6 months after RT. The patient was subsequently treated with 2 courses of palliative RT but continued to have local progression of disease. Because of deteriorating health from comorbid medical problems, the patient eventually withdrew from all active management and rapidly died. The cause of her death was related to uncontrolled local disease, hospital-acquired pneumonia, cachexia, and an extensive medical history including lupus. This suggests that biological factors, such as underlying immunosuppression, may have played a role in this patients' outcome.

There is currently no international standard for radiation dose for pcALCL, although the National Cancer Center Network recommends 30 to 36 Gy. Table 5 compares our data with results from 2 small series reporting on the response rates of pcALCL treated with radiation alone (demonstrating 100% CCR rate for doses ranging from 34–50 Gy) (8, 9). According to our data, doses lower than 30 Gy were associated with complete responses, suggesting that the minimal recommended dose may be <30 Gy. The efficacy of lower doses is further supported by Gentile et al (12), who reported a 100% CCR for pcCD30$^+$ LPD treated with a single fraction of 7.5 to 8 Gy. This study included mostly patients with LyP, in which

spontaneous regression without treatment is well documented. Thomas et al (13) also reported on single-fraction (7–8 Gy) palliative RT for CTCL (primarily patients with MF), demonstrating excellent CCR of >94%. Only 1 patient in our study received a single fraction of 6 Gy. The majority of patients received <2 Gy per fraction, with cosmesis presumably influencing the fractionation choice, particularly on head and neck sites.

Limitations of this study are that it is retrospective and spans 2 decades during which management practices have evolved, including superior diagnostic imaging with fluorodeoxyglucose positron emission tomography–computed tomography, which allows more precise identification of patients with extracutaneous disease, and diagnostic techniques including the use of immunohistochemical stains. Moreover, although data on 67 patients were submitted, 11 patients were excluded because they did not meet the strict diagnostic criteria for pcALCL as defined in the consensus recommendation paper for primary cutaneous CD30-positive lymphoproliferative disorders (4). Nonetheless, we believed that it was important to strictly select patients who fulfilled the international guidelines for diagnosis and treatment. Additionally, we did not collect the time point at which response to treatment assessment was completed, which may have been helpful in analyzing how quickly the disease responds to treatment and/or progresses thereafter.

The major advantage of this study is the ability to collaborate with ILROG members worldwide, pooling data on rare tumors through a secure, web-based platform. The data analysis allowed us to recommend lower doses of radiation than what have been used in the past. This data collection model can be used to study other rare lymphomas to inform RT recommendations.

In conclusion, pcALCL is a rare, indolent cutaneous lymphoma with a low death rate. This analysis, which was restricted to patients selected for treatment with radiation, indicates that a dose of 30 Gy is adequate for local control, and even lower doses may suffice. There are no predictive factors for outcome because local failure after treatment was too low (<2%) to identify potential risk factors, such as tumor size.

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Summary

Primary cutaneous anaplastic large cell lymphoma is a radiosensitive tumor with 95% complete clinical response rate. Most ILROG members used doses in the range of 30 to 39 Gy. However, lower doses also seem to be effective, regardless of T stage.

Table 1

2007 International Society for Cutaneous Lymphomas–European Organization of Research and Treatment of Cancer TNM classification of cutaneous lymphoma

Classification	Staging	Subclassification/description
T	T1 (Solitary skin involvement)	T1a: <5 cm diameter T1b: >5 cm diameter
	T2 (Regional skin involvement limited to 1 or 2 contiguous body regions)	T2a: <15 cm diameter T2b: >15 and <30 cm diameter T2c: >30 cm diameter
	T3 (Generalized skin involvement)	T3a: multiple lesions involving 2 noncontiguous body regions T3b: multiple lesions involving ≥3 body regions
N	N0	No clinical or pathological involvement
	N1	Involvement of 1 peripheral lymph node
	N2	Involvement of 2 or more peripheral lymph nodes
	N3	Involvement of central lymph nodes
M	M0	No extracutaneous non-lymph node disease
	M1	Extracutaneous non-lymph node

See reference (10). Because a diagnosis of primary cutaneous anaplastic lymphoma precludes extracutaneous disease by definition, any patient with staging other than N0 and M0 were excluded from this study.

Table 2

Characteristics of 56 patients included in analysis

Characteristic	Value
Sex (male/female), n (%)	37 (66)/19 (34)
Age (y), median (range)	66 (28–97)
Size of lesions (cm), median (range)	2.25 (0.6–12)
Site of lesions (n)	
Head/neck	17
Trunk	9
Upper extremities	17
Lower extremities	20
T Stage (n)	
T1a	34
T1b	6
T2a	10
T2b	2
T3a	3
T3b	1

Table 3

Irradiation dose and corresponding treatment response for 63 treated tumors

Dose range (Gy)	Total no. of tumors	Partial response	Complete clinical response	Complete clinical response rate (%)
<30	11	1	10	91
30–39	36	1	35	97
≥40	16	1	15	94
Total	63	3	60	95

The doses ranged from 6–45 Gy (median, 35 Gy).

Table 4

Patient outcomes

Outcome	No. of patients with complete clinical response	No. of patients with partial response	Total no. (%)of patients	Median time at last follow-up
Alive, no disease	43	2	45 (80)	4.2 y
Alive, with disease	6	1	7 (13)	3 y
Dead, intercurrent disease	3	0	3 (5)	1.7 y
Dead, pcALCL	1	0	1 (2)	7 mo

Patients who are alive with disease have experienced a relapse outside of their initial treatment fields. Time at last follow-up was calculated from last day of treatment to the most recent follow-up at which the patients' outcomes were recorded. Intercurrent disease refers to disease other than primary cutaneous anaplastic lymphoma (pcALCL).

Table 5

Studies with pcALCL patients treated primarily with RT

Authors (reference), year	N	Staging	Dose (Gy), median (range)	Response to treatment
Booken et al (8), 2012	14	T1: 12 patients T2: 2 patients	40 (40–50)	100% CCR
Yu et al (9), 2008	8	T1: 8 patients	40 (34–44)	100% CCR
Million et al (present study), 2016	56	T1: 40 patients T2: 12 patients T3: 4 patients	35 (6–45)	95% CCR 5% PR

Abbreviations: CCR = complete clinical response; pcALCL = primary cutaneous anaplastic lymphoma; PR = partial response.

Because Yu et al (9) used a different type of staging, we translated their staging to the TNM classification equivalent on the basis of the reporting that only patients with solitary lesions or tumors limited to a single anatomic site were included in the series.