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ABSTRACT

Introduction: Rotational total skin electron irradiation (RTSEI) is an effective therapy for cutaneous T cell lymphoma (CTCL). CD30 expression has been identified as a prognostic factor in CTCL. Therefore, we investigated CD30 status, treatment response, and survival

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in our cohort of patients with CTCL treated with RTSEI.

Methods: Patients with CTCL treated with RTSEI (≥ 30 Gy) between 2000 and 2013 at our institution were identified, and clinical and pathologic data were retrospectively reviewed. Primary outcomes were complete clinical response (CCR; $>90\%$ reduction of skin disease burden), relapse-free survival (RFS), and overall survival (OS).

Results: Sixty-eight patients with CTCL treated with RTSEI were identified. Median age at diagnosis was 51 years with median follow-up of 61 months. Median OS was 76 months and median RFS was 11 months. Thirteen patients (19%) had CD30+ lymphocytes on initial pathology. In the CD30+ cohort, there were no T2, eight T3, and five T4 cases. In comparison, in the CD30– cohort, there were 18 T2, 29 T3, and 8 T4 cases ($P = 0.01$). Six weeks post-RTSEI, CCR was 85% in CD30+ and 81% in CD30– cases ($P = 1$). Six months post-RTSEI, CCR was 23% in CD30+ and 50% in CD30– cases ($P = 0.083$).

Conclusion: RTSEI resulted in excellent CCR at 6 weeks in our cohort of patients with CTCL, with a median RFS of 11 months. We found

CD30+ patients presented with significantly higher T stage at time of RTSEI and trended towards decreased CCR at 6 months post-RTSEI compared with the CD30– group.

Keywords: CD30; Complete clinical response; Cutaneous T cell lymphoma; Mycosis fungoides; Overall survival; Relapse-free survival; Rotational total skin electron irradiation

INTRODUCTION

Cutaneous T cell lymphoma (CTCL) is a rare group of lymphoproliferative disorders characterized by localization of T lymphocytes to the skin with an overall incidence of 10.2 cases per million person-years [1]. It is becoming increasingly recognized that CTCL is heterogeneous, with multiple variants that have unique clinical presentations, histologic features, and therapeutic considerations [2]. The most common subtype of CTCL is mycosis fungoides (MF), which typically presents with pruritic patches and plaques in areas of skin not commonly exposed to sun, and may evolve to cutaneous tumors or erythroderma [3]. Demographic features including African-American race, male gender, and age have been found to be risk factors for CTCL, while extent of skin involvement, overall disease stage, and age are prognostic indicators [2, 3]. The prognostic significance of lymphocytic CD30 positivity in CTCL prognosis remains controversial: some have reported it as a favorable prognostic factor, [4] while others have shown it to be associated with advanced disease and independently associated with poorer survival [5].

Total skin electron irradiation (TSEI) has been shown to be an effective palliative

treatment for CTCL, even following failure with previous treatment modalities. This has been demonstrated in multiple retrospective reviews showing that conventional dose (≥ 30 Gy) TSEI achieves high clinical response rates [3, 6–11] typically using large-field/modified Stanford technique (discontinuous irradiation). However, more recent clinical series using dual-field rotational TSEI (RTSEI) technique, where a patient is rotated at a constant speed about the vertical axis while being irradiated with continuous dual-field irradiation (providing a theoretical advantage in dose homogeneity compared to its large-field/modified Stanford counterpart), showed promising results [12, 13]. Given that there have been no previous studies that have examined the response of CD30+ CTCL to RTSEI, we investigated the effect of CD30 status on treatment response and survival in our cohort of patients with CTCL treated with conventional dose RTSEI.

METHODS

Patient Population

After institutional review board (IRB) approval was obtained from Emory University for this study, we retrospectively reviewed medical records of patients treated with RTSEI identified from billing records. Patients were treated between 2000 and 2013 at Emory University, Atlanta, GA, USA. Patient electronic medical records and a previous IRB-approved dermatology database were used to ascertain information regarding demographics, diagnosis, histology, staging, treatment regimens, RTSEI treatment, clinical response, recurrence, and overall survival (OS). Eligibility criteria for the study included:

histologically confirmed CTCL and a completed first course of conventional dose (≥ 30 Gy) RTSEI. All patients were staged based on 2007 ISCL EORTC T and group stage definitions [14].

We identified patients as CD30+ based on initial pathology reports of skin biopsy. All CD30+ patients slides were reviewed by a board-certified hematopathologist (K.B.). Pathologists typically perform CD30 immunohistochemistry when there is concern for transformation with increased numbers of large lymphoid cells. CD30-not-tested cases lacked histological evidence of transformation and thus were grouped for statistical purposes with those that are known to be CD30 negative per pathology report.

Treatment Technique

RTSEI was administered using a 21EX Varian linear accelerator (LINAC; Varian, Palo Alto, CA, USA) equipped with 6 MeV high-dose total skin electron (HDTSe) mode at a dose rate of 888 MU/min. RTSEI used dual angles field at gantry angles of 241° and 299° to cover the upper and the lower halves of the patient body. In the 6 MeV HDTSe mode, our LINAC calibration was 2.99 cGy/MU at a maximum source to skin distance (SSD) of 100 cm. The patient is placed on a rotating platform at an extended SSD (315 cm) from the gantry. Both arms are raised overhead and are positioned on the rotator vertical bars. The platform rotates at a constant speed of four revolutions per minute to ensure adequate surface dose buildup.

All patients were treated using a standard method: 36 Gy delivered at 1.5 Gy per fraction, administered three times weekly, typically on a Monday–Wednesday–Friday schedule (4.5 Gy/week). Eye shields were used upon treatment initiation. Finger/toe nail shields were added after 12 Gy. A one-week mid-treatment break

was allowed after delivery of 18 Gy. Optically stimulated luminescent dosimeter (OSLD) measurements at typically under-dosed areas including but not limited to scalp, palms, inner thighs, and bottom of feet were taken prior to the mid-treatment break. Approximately 84% of patients received additional boost to these under-dosed regions based on clinical assessment of disease response at the end of RTSEI. In total, the total RTSEI regimen required 9 weeks followed by a 2–3-week boost portion.

Covariates

The overall study cohort was compared across the following covariates: sex, age at diagnosis, age at RTSEI, histology, T stage at start of RTSEI, pre-RTSEI CTCL treatments (therapies received prior to primary RTSEI course including topical, systemic antineoplastic, systemic dermatologic, and phototherapies), maintenance therapy (systemic or topical therapy started within 3–6 months after RTSEI), time from diagnosis to RTSEI, and recurrence.

Outcome Measures

Primary outcome measures were complete clinical response (CCR) rate, relapse-free survival (RFS), and OS. CCR rate was defined as the proportion of follow-up patients with at least 90% reduction in cutaneous tumor burden. Patients considered non-complete responders (non-CR) included those with partial response ($>50\%$ reduction but less than 90%), stable disease, recurrence, progression, or death at each of three time points: (1) end of RTSEI treatment, (2) 6 weeks post-RTSEI, and (3) 6 months post-RTSEI. Patients with no previous record of recurrence, those who did not follow-up or had no recorded clinical response at one of the time points were not included in

the CCR proportion. Response rates were compared across CD30 status and by T stage using Chi-square or Fisher's exact test, as appropriate.

RFS was calculated as the number of days between start of RTSEI and the date of recurrence. In the case of patients who did not have recurrence, RFS was censored at the date of last follow-up or date of death. OS was the number of days between diagnosis and the date of death or last known follow-up. RFS and OS distributions were estimated using the Kaplan–Meier method. Both RFS and OS were compared across race, T stage, and previously mentioned covariates, using log-rank tests and Cox proportional hazards models. Multivariate Cox models were fit, adjusting for T stage pre-TSEI, and the proportional hazards assumption was checked for all models. The cutoff for statistical significance for all analyses was set at the two-sided alpha error of 0.05. All analysis was done in SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Characteristics

Medical records of 110 patients treated with RTSEI identified from billing records were retrospectively reviewed. After excluding 42 patients who either had a primary diagnosis of leukemia cutis or did not complete conventional dose RTSEI, 68 eligible patients remained. Individual case summaries of all CD30+ patients are shown in Table 1. Patient characteristics of the study cohort, stratified by CD30 status, are summarized in Table 2. Sixty-eight patients were treated with conventional dose RTSEI (range 30–36 Gy). Median age at time of diagnosis was 51 years.

Median follow-up was 61 months. Median time from diagnosis until RTSEI was 35 months. Six patients (46%) received maintenance therapy following RTSEI. Seven patients (42%) recurred following RTSEI. Median follow-up time for these patients was 80.2 months.

Pathology confirmed 13 (19%) CTCL patients as CD30+. CD30% expression ranged from 5% to 30% in tumor cells. An example photomicrograph of a CD30+ transformed CTCL case is shown in Fig. 1. For the CD30+ patients, 7 (54%) were female and 6 were male (46%), and 7 were AA (54%) and 6 were white (46%). CD30+ patients had a significantly more advanced T stage disease prior to RTSEI (62% T3, 39% T4) compared to CD30– patients (33% T2, 53% T3, 15% T4; Table 2). There were no significant differences between CD30 subgroups in regard to sex, race, age at diagnosis, time from diagnosis to RTSEI, treatments prior to RTSEI, maintenance therapy, follow-up time, or proportion that recurred after RTSEI.

Clinical Response Rates

Table 3 summarizes CCR rates by CD30 status. CD30+ patients had overall CCR rates of 85% at end of RTSEI, 85% at 6 weeks follow-up, 23% at 6 months follow-up. CD30– patients had overall CCR rates of 95% at the end of RTSEI, 79% at 6 weeks follow-up, and 50% at 6 months follow-up. Chi-square and Fisher's exact tests revealed no significant differences in CCR rate between CD30 status subgroups following end of RTSEI ($P = 0.24$) or six weeks ($P = 0.44$), but did trend toward significance at 6 months post-TSEI ($P = 0.083$). This trend was driven by a significantly poorer response at 6 months for CD30+ T3 disease compared to CD30– T3 patients ($P = 0.04$). Further comparisons between CD30 status groups across respective

Table 1 Summary of CD30+ cases

Case	Age at RTSEI (years)	Sex	Race	CTCL histology	T stage pre-RTSEI	CD30+ lymphocyte	Transformation status	Time from Dx to RTSEI (months)	Response at end of RTSEI	Response at 6 weeks	Response at 6 months
1	53	Female	AA	MF	T4	10%	Equivocal	35	CR	CR	CR
2	41	Female	AA	MF	T3	5%	No	40	CR	CR	Non-CR
3	54	Female	White	MF	T3	<5%	No	30	CR	CR	Non-CR
4	61	Female	White	MF	T3	10%	No	27	CR	CR	Non-CR
5	67	Male	White	LyP	T3	*Diffuse**	Unknown	14	CR	CR	Non-CR
6	71	Male	AA	MF	T4	<5%	No	18	CR	CR	CR
7	86	Male	AA	MF	T4	*CD30+**	Unknown	18	CR	CR	Non-CR
8	49	Female	AA	MF	T4	5%	No	3	CR	CR	Non-CR
9	54	Male	AA	MF	T4	30%	Yes	2	Non-CR	Non-CR	Non-CR
10	51	Female	AA	MF	T3	5%	No	4	CR	CR	CR
11	72	Male	White	PCPTCL NOS	T3	5%	No	93	CR	CR	Non-CR
12	46	Male	White	CTCL NOS	T3	*Diffuse**	Equivocal	10	Non-CR	Non-CR	Non-CR
13	53	Female	White	CTCL NOS	T3	10%	No	17	CR	CR	Non-CR

AA African-American, CR complete response (<90% reduction in skin disease), CTCL cutaneous T cell lymphoma, LyP lymphomatoid papulosis, non-CR non-complete response, NOS not otherwise specified, PCPTCL primary cutaneous peripheral T cell lymphoma
 * Slides not available for review, CD30+ description based off previous pathology reports

Table 2 Patient characteristics

Covariate	CD30 status		P value
	CD30– (n = 54)	CD30+ (n = 14)	
Sex, n (%)			
Female	26 (47.3)	7 (53.9)	0.67
Male	29 (52.7)	6 (46.2)	
Race, n (%)			
White	27 (50.9)	6 (46.2)	0.76
African-American	26 (49.1)	7 (53.9)	
Age, mean	52.4	56.2	
Time (months) from diagnosis to RTSEI			
Median	16.8	35.4	0.30
Mean	27.2	35.8	
Pre-RTSEI tumor (T) stage, n (%)			
T2	18 (32.8)	0 (0.0)	0.01
T3	29 (52.7)	8 (61.5)	
T4	8 (14.6)	5 (38.5)	
Pre-RTSEI CTCL treatment			
Previous use of topical agents, n (%)			
No	25 (45.5)	5 (38.5)	0.65
Yes	30 (54.6)	8 (61.5)	
Previous use of systemic antineoplastic agents, n (%)			
No	27 (49.1)	6 (46.2)	0.85
Yes	28 (50.9)	7 (53.9)	
Previous use of systemic dermatologic agents, n (%)			
No	43 (78.2)	12 (92.3)	0.44
Yes	12 (21.8)	1 (7.7)	
Previous use of phototherapy, n (%)			
No	29 (52.7)	6 (46.2)	0.67
Yes	26 (47.3)	7 (53.8)	
Maintenance therapy post-RTSEI, n (%)			
No	35 (63.6)	7 (53.9)	0.54
Yes	20 (36.4)	6 (57.1)	

Table 2 continued

Covariate	CD30 status		P value
	CD30– (n = 54)	CD30+ (n = 14)	
Recurrence following RTSEI, n (%)			
No	18 (32.7)	6 (46.2)	0.42
Yes	37 (67.3)	7 (53.9)	

CTCL cutaneous T cell lymphoma, RTSEI rotational total skin electron irradiation
 Bold P values are statistically significant (P < 0.05)

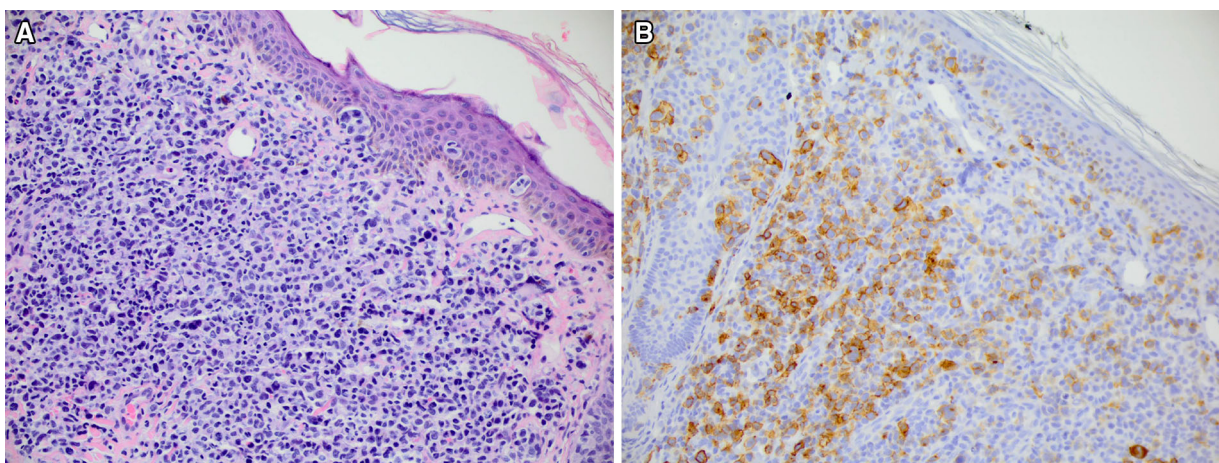


Fig. 1 Transformed cutaneous T cell lymphoma (Case #9 from Table 1). **a** Large transformed lymphoma cells with focal epidermotropism (H&E stain, original magnification

×200). **b** Approximately 30% of lymphoma cells are positive for CD30 (original magnification ×200)

Table 3 Complete clinical response rates (>90% reduction in tumor burden), stratified by T stage pre-RTSEI and CD30 status

T stage pre-RTSEI	Follow-up period								
	End of RTSEI			Six weeks post-RTSEI			Six months post-RTSEI		
	CD30 status			CD30 status			CD30 status		
	CD30+ n (%)	CD30– n (%)	P value	CD30+ n (%)	CD30– n (%)	P value	CD30+ n (%)	CD30– n (%)	P value
All T stages	11 (85)	52 (95)	0.24	11 (85)	42 (79)	1	3 (23)	24 (50)	0.083
T2	–	18 (100)	–	–	15 (88)	–	–	5 (42)	–
T3	7 (88)	27 (93)	0.53	7 (88)	22 (79)	1	1 (13)	16 (57)	0.044
T4	4 (80)	7 (88)	1	4 (80)	5 (62.5)	1	2 (40)	3 (38)	1

Bold P values are statistically significant (P < 0.05)

T stages at all other follow-up time points showed no significance difference in CCR rates.

Relapse-Free Survival

As seen in Table 4, CD30+ patients had a median RFS of 12.1 months (8.3 and 13.2 for T3 and T4 disease, respectively, not significantly different). CD30– patients had a median RFS of 9.9 months (14.3, 11.3, and 6.0 months for T2, T3, and T4 disease, respectively, with no significant difference between stages T3 and T4). Kaplan–Meier RFS curves comparing CD30 groups and CD30+ patients by T stage are shown in Fig. 2.

On multivariate analysis, controlling for T stage, CD30 status was not associated with RFS ($P = 0.75$). Maintenance therapy following RTSEI was associated with significantly improved RFS in CD30– group [hazard ratio (HR) = 2.79; 95% confidence interval (CI) 1.17–6.66; $P = 0.021$]. This association was not observed in the CD30+ group ($P = 0.383$). All other covariates such as race, sex, T stage, histology, age at diagnosis, time from diagnosis to start of TSEI, and pre-RSTEI treatment did not have a clinically significant association with RFS on univariate or

multivariate analyses in either CD30+ or CD30– groups.

Overall Survival

As seen in Table 4, CD30+ patients had a median OS of 103.3 months overall with no significant difference in OS between stages T3 and T4 ($P = 0.65$). CD30– patients had a median OS of 74.5 months with a trend towards poorer survival for T4 compared to T3 patients (103.3 months for T3, 30.5 months for T4, $P = 0.09$). There was no significant difference in OS across CD30 status ($P = 0.57$), T3 ($P = 0.95$), or T4 ($P = 0.10$) subgroups. Kaplan–Meier OS curves for comparing CD30 groups and CD30+ patients by T stage are shown in Fig. 2.

On univariate analysis, CD30 status was not associated with OS ($P = 0.57$). In the CD30+ group, non-MF histology (compared to MF histology) was associated with poorer OS in univariate analysis (HR = 10.65; $P = 0.025$). However, after controlling for T stage pre-RTSEI, this observed effect only trended towards significance ($P = 0.080$). In the CD30– group, lower T stage (HR = 0.26; $P = 0.049$) in univariate analysis was associated with

Table 4 RFS and OS, stratified by T stage pre-RTSEI and CD30 status

T stage pre-RTSEI	Median RFS (months)			Median OS (months)		
	CD30–	CD30+	<i>P</i> value	CD30–	CD30+	<i>P</i> value
All T stages	9.9	12.1	0.75	74.5	103.3	0.57
T2	14.3	–	–	–	–	–
T3	11.3	8.3	0.64	103.3	90.7	0.95
T4	6.0	13.2	0.51	30.5	–	0.10

OS overall survival, RFS relapse-free survival, RTSEI rotational total skin electron irradiation

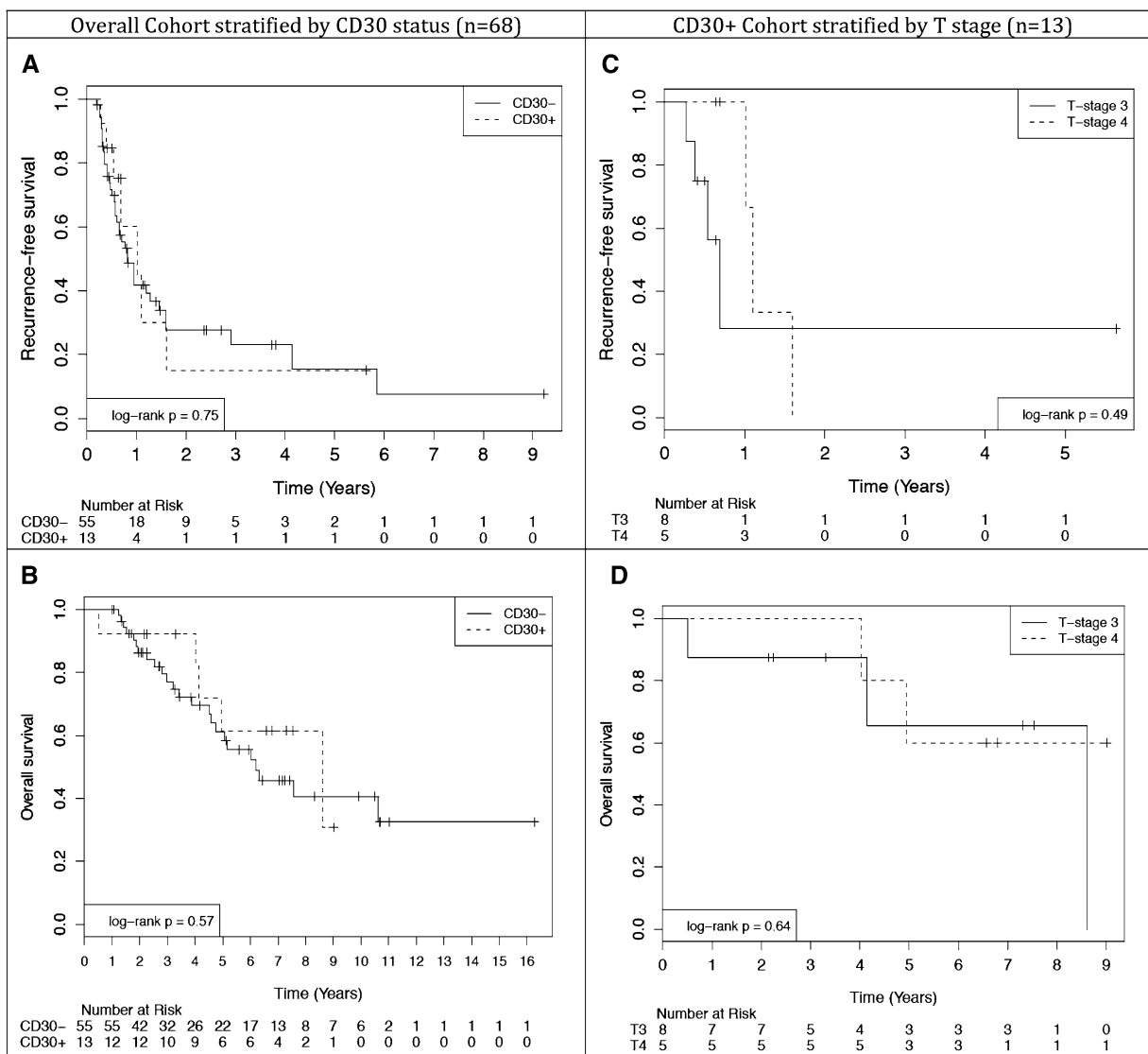


Fig. 2 Survival outcomes. **a** RFS comparing CD30+ vs. CD30- patients. **b** OS comparing CD30+ vs. CD30- patients. **c** RFS for CD30+ patients comparing stage T3 and T4 pre-RTSEI. **d** OS for CD30+ patients comparing

stage T3 and T4 pre-RTSEI. OS overall survival, RFS relapse-free survival, RTSEI rotational total skin electron irradiation

improved OS. In multivariate analysis, increased time from diagnosis to RTSEI (HR = 0.98, $P = 0.017$) and younger age at RTSEI (HR = 1.06; $P = 0.003$) were associated with a significantly improved OS. Maintenance

therapy failed to show any significant improvement in OS in both CD30+ ($P = 0.998$) and CD30- ($P = 0.242$) in multivariate analysis controlling for T stage pre-RTSEI.

DISCUSSION

At present there is no long-term curative treatment for CTCL. Management is difficult as there are no standardized treatment regimens, there is prognostic heterogeneity even within group stages, and high-quality trials are lacking due to disease rarity. There is an urgent need to identify patients at high or low risk for disease progression or mortality to aid in clinical decisions about treatment including escalation/de-escalation of radiation dose or initiation/holding of systemic agents. Since treatment for CTCL, especially advanced-stage disease, is palliative, improved prognostication would help avoid treatment toxicity in cases at low risk for progression. Recently, the prognostic Cutaneous Lymphoma International Prognostic index (CLIPi) was developed for early- and late-stage MF using a cohort of 1502 UK patients and validated in a set of 1221 patients treated at MD Anderson Cancer Center (MDACC; Houston, TX, USA); however, this has yet to be validated in a prospective manner [15–17]. The Cutaneous Lymphoma International Consortium (CLIC) developed a prognostic score for advanced MF stage IIB to IV and Sezary syndrome (SS) with 1394 patients from 29 centers worldwide including the following factors: stage IV disease, age greater than 60 years, large cell transformation, and elevated serum lactate dehydrogenase [18].

CD30 is a member of the tumor necrosis receptor family, and is found on activated T and B cells. A recent study of 47 non-transformed MF cases from the University of Pittsburgh (Pittsburgh, PA, USA) reported that patients were found to have worse survival, higher stage at diagnosis, and higher maximum stage if dermal cells are CD30+ (>4.7%) [5]. A study of 51 patients with large cell transformation of

MF at Memorial Sloan Kettering Cancer Center (New York, NY, USA) reported that predominance of CD30 in the epidermis rather than dermis was associated with poorer survival [19]. However, a retrospective analysis of 100 patients with transformed MF from the Netherlands showed that CD30 negativity was associated with multivariate analysis with reduced disease-specific survival (DSS) and OS [4]. In a long-term outcomes study, CD30 was found to have no significant effect on OS, DSS, and progression-free survival (PFS) in 1263 MF/SS patients at MDACC [17]. The CLIC reported that when CD30 is scored positive above 10% of tumoral cells, it is not statistically significant for OS but is associated with worse OS in the subset of patients with T3 disease [18]. Finally, CD30 is also targetable with brentuximab vedotin, a monoclonal chimeric antibody conjugated to antitubulin agent monomethyl auristatin E. A recent phase 2 study found that brentuximab vedotin has significant objective global response 70% (21/30) in treatment patients with refractory or advanced MF/SS who have a range of CD30 expression levels [20]. Similarly, another phase 2 trial found overall response of 73% (35/48) in patients with CD30+ lymphoproliferative disorders treated with brentuximab vedotin [21].

Based on the varying reports of the prognostic significance of CD30, we sought to assess the response and survival of our cohort of patients treated with RTSEI. We found 13 of 68 patients were CD30+ (range 5% to 30%); they presented with significantly higher T stage at time of RTSEI and trended towards decreased CCR at 6 months post-RTSEI compared with the CD30– group. One patient in our cohort had 1% CD30+ lymphocytes on pathology and was classified as negative for CD30; however, when this patient was added to the CD30+ cohort (data not reported in results) the CCR was

significantly reduced at 6 months ($P = 0.05$). Regardless, the difference in 6 month CCR was primarily driven by those with T3 stage disease. Overall, CD30+ patients had excellent CCR rates of 85% at end of RTSEI but most had progressive disease at 6 months. Maintenance therapy including topical, systemic antineoplastic, systemic dermatologic, and phototherapies failed to show any significant improvement in RFS in the CD30+ group. Additionally, maintenance therapy failed to show any significant improvement in OS in both CD30+ and CD30– groups. Although direct comparison is not possible without further study, our rates of clinical response are comparable to those recently reported for brentuximab vedotin.

Additionally, CD30+ patients may benefit from the addition of novel targeted agents such as Brentuximab vedotin to radiation, perhaps concurrently or sequentially. Recently, the concept of combined radiation and immunotherapy to enhance clinical outcomes has advanced. To date there is no trial of the safety of brentuximab vedotin with radiation. We feel prospective trial development of combined brentuximab vedotin and radiation for CTCL should proceed based on the results of recent phase 2 trials.

Our analysis is limited by small sample size; however, this is the largest report of CD30+ patients, and their response to radiotherapy. More specifically, the small sample size precluded us from examining in more detail the role of maintenance systemic and dermatologic agents. In addition, if a patient did not follow up or did not have a recorded clinical response at the specified time points without record of recurrence by other providers, they were excluded from CCR analysis which further decreased patient numbers in the present analysis. Additionally, as this was a

retrospective review, many patients had incomplete clinicopathological information, information from outside hospitals, or were lost to follow-up. Incomplete data regarding CD30 status increases confounding as patients deemed by clinicians to have aggressive disease or transformation often have more thorough workup. Strengths of our study included documentation of clinical response across multiple post-treatment time points, single institution experience with standardized RTSEI delivery and dosing, and all CD30+ cases were reviewed by a hematopathologist to confirm CD30 status.

CONCLUSIONS

In this retrospective study, RTSEI for CTCL resulted in excellent CCR at 6 weeks, with a median RFS of 11 months. This is consistent with and improves upon treatment results reported previously. CD30+ patients receiving RTSEI were found to have higher T stage and trended towards decreased CCR at 6 months post-RTSEI compared with the CD30– patients. Maintenance therapy including topical, systemic antineoplastic, systemic dermatologic, and phototherapies failed to show any significant improvement in RFS in the CD30+ group. Future work should examine quality of life metrics, the role of maintenance systemic or targeted treatments, and combination RTSEI and brentuximab vedotin in CD30+ patients with CTCL.

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Compliance with Ethics Guidelines. Institutional review board (IRB) approval was obtained from Emory University for this study

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