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Multi-institutional Investigation: Circulating CD4:CD8 ratio is a prognosticator of response to total skin electron beam radiation in mycosis fungoides

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Abstract

Background and purpose: A lower proportion of CD8+ tumor infiltrating lymphocytes in mycosis fungoides (MF) patients is associated with worse survival. However, it is not known whether circulating CD4:CD8 ratio is a prognosticator of response to total skin electron beam therapy (TSEBT).

Methods and materials: We identified 126 MF patients treated with TSEBT from 2001 to 20014 at two high-volume academic centers. Circulating CD4:CD8 ratio was obtained within 1 week before TSEBT. TSEBT was delivered with 6–9mEV electrons with low (12 Gy) or conventional (≥12 Gy) doses. Treatment response was assessed with the modified Severity Weighted Assessment Tool (mSWAT). Post-treatment mSWAT decrease of ≥75% was classified as near complete response (CR) while mSWAT decrease of <75% was considered partial response (PR). Receiver operating characteristic analysis determined an optimal CD4:CD8 threshold value

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Conflict of interest statement

The authors have no conflicts or interest or disclosures to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.12.003.

to predict TSEBT response in the derivation cohort and was applied to an external validation cohort.

Results: 71.4% and 28.6% of patients achieved CR and PR after TSEBT. Higher CD4:CD8 ratio predicted poorer response: median CD4:CD8 in patients with PR vs. CR was 4.84 vs. 1.97 (p = 0.002). A threshold CD4:CD8 of 4.42 optimally discriminated in the discovery cohort patients with PR vs. XR (sensitivity 90%, specificity 59%, area under curve (AUC) = 0.71; p = 0.002). Within an independent test cohort (n = 32), 73.9% of patients with CD4:CD8 <4.42 achieved CR vs. 33.3% of those with CD4:CD8 ≥4.42 (p = 0.033). Among all patients with CD4:CD8 <4.42 (n = 73), 74% achieved CR with low-dose TSEBT *vs.* 93% with conventional dose TSEBT (p = 0.02). On multivariable logistic regression, CD4:CD8 remained a significant independent predictor of TSEBT response in all patients (OR = 0.107, 95% CI 0.395–0.290, p < 0.001).

Conclusion: Peripheral blood CD4:CD8 ratio was a significant independent predictor of TSEBT response of MF patients as validated in an independent cohort at separate academic center. The potential for CD4: CD8 ratio as a biomarker to inform radiation treatment dosing warrants further investigation.

Keywords

Mycoses fungoides; Total skin electron therapy; Biomarker

Cancer cells often are able to overcome host immune surveillance and evade immune mediated eradication [1]. Mycosis fungoides (MF) arises from cells of lymphoid lineage [2], a key component of adaptive immunity. Although relatively rare compared to other lymphomas, MF is the most common type of primary cutaneous T cell lymphoma with an incidence rate of 6.4 per 1,000,000 persons in the United States [2].

Radiotherapy plays an important role in the management of MF [3,4]. The delivery of ionizing radiation to the tumor not only causes direct cytotoxic damage to neoplastic lymphoid cells but can also generate systemic inflammatory responses that promote anti-tumor immunity [5,6]. Total skin electron beam therapy (TSEBT) is one of the single most effective skin-directed therapy for MF, especially for wide spread skin involvement (at least Stage IIB), and or highly symptomatic plaques or tumors particularly refractory to other local therapies. Although historically TSEBT doses were escalated up to 36 Gy to improve the clinical complete responses (CR) rate of patients, the dose-dependent toxicity profiles of TSEBT has promoted recent investigation of lower dose delivery to achieve similar clinical outcomes [7].

Previous studies have identified multiple clinicopathological factors that can predict treatment responses of MF patients to radiation, serving as potential prognostic biomarkers [8,9]. The patho-physiology of MF is thought to be due in part to dysregulated CD4+ T cells, with only approximately 20% of cases displaying a CD8+ phenotype [10]. Normally, CD4+ T cells (helper T cells) are responsible for activating other immune cells including CD8+ T cells (cytotoxic T cells). However, examination of circulating lymphocyte profiles and its correlation with patient outcomes after TSEBT has not been explored. In MF, the pathologic CD4+ undergoes clonal expansion, potentially leading to abnormally elevated

CD4:CD8 T-cell ratio in the peripheral blood. Given the distinctive role of CD4+ helper and CD8+ cytotoxic T cells in regulating cellular immunity, we set out to determine whether levels of these immune cell phenotypes within the peripheral blood predict for response to radiation treatment in MF patients.

Materials and methods

Study population

This study was approved by the institutional review boards (IRB) at MD Anderson Cancer Center (MDACC) and Yale-New Haven Hospital (YNHH) with informed consent waiver granted. We identified patients with histologically confirmed MF who had received TSEBT from 2008 through 2014. Patients with evidence of elevated circulating Sézary cells were excluded to retain a relatively homogeneous group of patients and minimize confounding from patients with Sézary Syndrome. Other inclusion criteria included the availability of complete blood analytical results prior to the initiation of TSEBT. Patients who underwent stem cell transplant (SCT) after TSEBT were eligible for inclusion.

Treatment details

TSEBT was administered using a modified Stanford 6-dual field technique according to each respective institution [11]. This included possible variation in the daily fractionation, dose per fraction, methods of supplementing. MDACC patients received 12–32 Gy fractionated radiotherapy at 2 Gy/fraction while YNHH patients received a total of 2 Gy over 2 days for each total-skin treatment cycle, with a median dose of 36 Gy. Supplemental radiation was administered to the perineum, soles, any other “shadowed” sites involved with disease and to discrete tumors. Low-dose TSEBT was defined as <12 Gy.

Clinical assessment and laboratory analysis

Clinical response in the skin was performed using the mSWAT score, a quantitative means of assessing extent and type of MF lesion by summation of body surface area involved by each lesion multiple by weighting of lesion type (1 for patch, 2 for plaque, and 3 or 4 for tumor) [12,13] with complete or near complete responders classified as a decrease of ≥75% in mSWAT scores and those with <75% as incomplete responders. This definition was based on dichotomization of published definition of partial response (50–99% decrease in mSWAT) in order to gauge binary treatment outcome [14]. Clinical assessments were performed at baseline prior to the start of TSEBT and at each follow up visit after completion of radiation treatments. For patients who underwent SCT post TSEBT, only mSWAT scores recorded prior to SCT were recorded for the determination of responses. Twenty-one patients were documented to have eventually received SCT after TSEBT. The CD4: CD8 cell ratio in the peripheral blood was collected prior to the initiation of TSEBT.

Statistical analysis

Chi-square or Fisher’s exact tests were used to compare all categorical variables, and *t* or Mann–Whitney’s tests were used to compare continuous variables where applicable. Receiver-operating characteristics (ROC) curve was used to evaluate the effect of CD4:CD8 ratio for differentiating clinical responses of patients to TSEBT. Odds ratios (ORs) were

computed with the corresponding confidence intervals. Multivariate logistic regression for disease response was performed with adjustment for covariates including baseline mSWAT, disease stage, and TSEB dose. To assess heterogeneity of odds ratios across strata, the Breslow–Day test was employed. The Breslow–Day test assesses the homogeneity of the odds ratio across contingency tables and has an approximate chi-squared distribution. All tests were 2-sided, and s <0.05 was considered statistically significant. All statistical analyses were done with IBM SPSS software (V22.0).

Results

Study populations

A total of 94 MDACC patients with histologically confirmed MF without evidence of elevated circulating Sézary cells were used as the discovery cohort. The median age for this cohort was 63.5 years (range 21–86) with 58.5% male. The median baseline mSWAT score and CD4:CD8 ratio were 40.1 (range 3.5–174.1) and 2.25 (range0.1–45.9), respectively. The median radiation dose delivered was 28 Gy (range 12–36). Other detailed demographic, clinicopathological and treatment related information regarding the patient cohort is listed in Table 1. The YNHH test cohort consisted of 32 patients with median age 61.6 years (range 20–79), 65.6% male, with median baseline mSWAT score of 59.5 (5.0–113.0) and CD4:CD8 ratio of 3.25 (0.52–81) (Table 1).

Clinical outcomes

Among MDACC patients, a total of 74.5% patients ($n = 70$) achieved CR after TSEBT, of which 34 patients had complete clinical response (36.2%). Median time to maximal response was 54.5 days (25–75% 34–115 days). When examining the baseline CD4:CD8 lymphocyte ratio stratified by patient responses, the CD4:CD8 ratio was significantly elevated in the incomplete responders as compared to patients with CR (median 4.9, interquartile range: 1.6–13.3 vs. median 2.0, interquartile range: 1.1–3.0, $p = 0.002$). Receiver operating characteristic analysis showed significant discriminative utility of CD4:CD8 ratio when compared to reference line of no discrimination (AUC = 0.713, $p = 0.002$) (Fig. 1). The cut-point for CD4:CD8 ratio was found to be ≥4.42, which corresponds to a detection sensitivity of 90% and specificity of 59% for predicting treatment responses. When the 4.42 cut-point was applied to an independent YNHH test cohort ($n = 32$), 73.9% of patients with CD4:CD8 <4.42 while 33.3% of CD4:CD8 ≥4.42 patients with demonstrated complete response ($p = 0.033$).

Patient outcomes stratified by CD4:CD8 ratio

When we stratified MDACC cohort patient using the CD4:CD8 ratio cut-off point of 4.42 obtained previously, patients with a high CD4:CD8 ratio (≥4.42, $n = 21$), both low dose TSEBT (≤12 Gy) and conventional dose (>12 Gy) resulted in similar CR rates ≥ (30% vs. 36%, OR 1.33, 95% CI: 0.22–8.29, $p = 0.76$). However, among patients with low CD4:CD8 (<4.42, $n = 73$), 93% achieved CR when treated with conventional dose TSEBT as compared to 74% with low dose TSEBT ($p = 0.02$). Examination for homogeneity across strata revealed no evidence (Breslow–Day $p = 0.26$) that heterogeneity was observed in the OR estimates among different CD4: CD8 ratio groups.

TSEBT outcomes by radiation dose

On univariate analysis of the MDACC cohort, both radiation dose and CD4:CD8 ratio were significantly correlated with likelihood of achieving a near-complete clinical response to TSEBT (Table 2). Adjusting for potential confounders, multivariate logistic regression was performed for both the MDACC (Table 3) and YNHH cohorts (Table 4). When cohorts were combined on analysis, radiation dose by itself was not significantly correlated with CR response rates to TSEBT (Supplemental Table 2). However, higher dose of radiation was significantly correlated with likelihood of achieving a near-complete clinical response among patients with low CD4:CD8 ratio (OR 5.12, 95% CI 1.17–22.34, $p = 0.03$) (Supplemental Table 3). In contrast, increasing radiation dose beyond 12 Gy did not demonstrate a significant improvement in the likelihood of achieving near-complete clinical response in patients with elevated CD4:CD8 ratios (OR 1.47, 95% CI 0.22–9.87, $p = 0.69$) (Supplemental Table 4).

Discussion

We observed that a lower baseline circulating CD4:CD8 ratio prognosticated for better clinical response to TSEBT. When an empirically derived CD4:CD8 ratio cut-point of 4.42 was applied to an independent, external validation cohort, this cut-point was still able to discriminate a significant difference in response to treatment. Retrospective evidence from our study further suggests that higher circulating CD4:CD8 levels also predicts for worse response to radiotherapy, and, moreover, less detectable benefit from radiation dose escalation. Our study observed a complete response rate of 27% that is comparable to previously published pooled analyses of multiple clinical trials using 12-Gy low dose TSEBT [2]. Similarly, for patients receiving a TSEBT dose of >12 Gy, approximately 82% of the patients achieved CR, which is similar to the expected CR rate of 75% reported for those receiving conventional dose TSEBT (>30 Gy) [3,15].

Others have tried to identify immunological biomarkers (such as intralesional CD4 or CD8 counts) to diagnose MF and predict clinical responses with mixed results [16]. In one study, no differences were observed in tissue samples among MF patients and benign inflammatory dermatoses patients [17]. Similarly, some have suggested that an intratumoral CD4:CD8 ratio >2, or a low percentage of CD8+ population in CD3+ T cells are suggestive of MF diagnoses [18]. The CD4:CD8 ratios in both tumor tissues and peripheral blood have been shown to impact patient outcomes in solid tumors and cutaneous T cell lymphomas. For instance, when Sézary counts are not available, one EORTC definition of Sézary Syndrome require both the presence of clonal T-cell receptor rearrangement and a CD4:CD8 ratio >10 [19]. In the setting of erythrodermic cutaneous T cell lymphomas, elevated CD4:CD8 ratio closely correlates with the extent of disease burden and act as a negative prognostic factor [20]. However, how peripheral blood CD4:CD8 ratio predicts TSBT responses of MF had not been previously investigated.

Patients with elevated CD4:CD8 ratio had similar clinical response rate to standard or low-dose TSEBT in our study. However, in patients with low CD4:CD8 ratio, high dose TSEBT was associated with improved clinical response compared to low dose TSEBT. The implications of our findings impact both good- and poor-prognosis MF patients when

considering the use of targeted total skin radiation for symptomatic relief. While patients with high circulating CD4:CD8 levels may not benefit appreciably from dose escalation, given possibly less comprehensive response and less temporally durable response, patients with low circulating CD4:CD8 levels may in fact be a better subgroup to benefits from dose escalation. In the setting of continued consideration of TSEBT dose de-escalation to reduce dermatological toxicities, our results suggest investigation into a more individualized consideration maybe warranted, especially in a highly selected patient population where the clinical benefit could overweigh the potential risks of toxicities.

Notably, TSEBT dose escalation in low CD4:CD8 patients would represent a potential paradigm shift in treatment approach since historically many have considered disease burden as the most important indication for dose escalation. Therefore, further investigation is needed before more widespread adoption of dose escalation in this cohort, especially since minimizing long-term toxicity of total skin radiotherapy is an important goal because higher complete remission does not translate to longer survival. Rather, than a priori dose escalation approach in all low CD4-CD8 patients, an alternative plan may use an initial low dose of TSEBT with only higher doses in case CR was not observed. Nonetheless, our data suggest that a different risk–benefit ratio – in which the toxicities of high-dose TSEBT for only a minimally durable skin response may not be a the most value-added treatment approach – especially in the era of other available targeted and systemic therapy options.

Given the retrospective nature of our study, inherent limitations exist including selection bias and potential confounders not recorded and accounted for in our models. Furthermore, there was notable variation in clinical staging between the two institutional cohorts, with 23.4% Stage IB patients in MDACC vs. 37.5% in Yale. This difference likely reflects institutional biases regarding patient selection for TSEBT, with Yale clearly offering TSEBT more commonly to those with diffuse patch and plaques. Still, that we find prognostic value in CD4:CD8 in both cohorts despite variation in staging suggests the robustness of its predict value. Additionally, while the sensitivity of 59% associated with CD4:CD8 cutoff of ≥4.42 in the initial MDACC cohort appears low, in context of specificity of 90%, it is clinical safer for putative biomarker to offer reduce risk of false positive over false negatives for medical decision making regarding which patients benefit most from low-dose TSEBT. Thus, especially given the consistent findings between two independent institutions, our results raise the interesting possibility that circulating lymphocyte counts and ratios can be used as a predictive biomarker to select potential patient populations that are most likely to benefit TSEBT.

In summary, we observed that MF patients who exhibit high base-line CD4:CD8 ratios are more likely to demonstrate poor clinical responses to radiation treatment as compared to those with low CD4:CD8 ratios. Furthermore, among patients with low CD4: CD8 ratios at baseline, conventional TSEBT with dose >12 Gy appeared to provide improved clinical response rate as compared to low dose TSEBT, which was not observed in patients with high CD4:CD8 ratios. Therefore, our study raises the question as to whether the CD4:CD8 ratio may serve as a prognostic and predictive biomarker for TSEBT responses in MF patients and suggests further investigations into its use to inform radiation treatment decisions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

YA, WJ, TYA, SL performed data collection.

YA, WJ, LDW, BSD designed the researched study.

YA, WJ, LDW, and BSD wrote the manuscript.

JPR, ZAY, MD, NMD, SAM, CCP, YO, GLS, LDW, BSD contributed to study design and data analysis.

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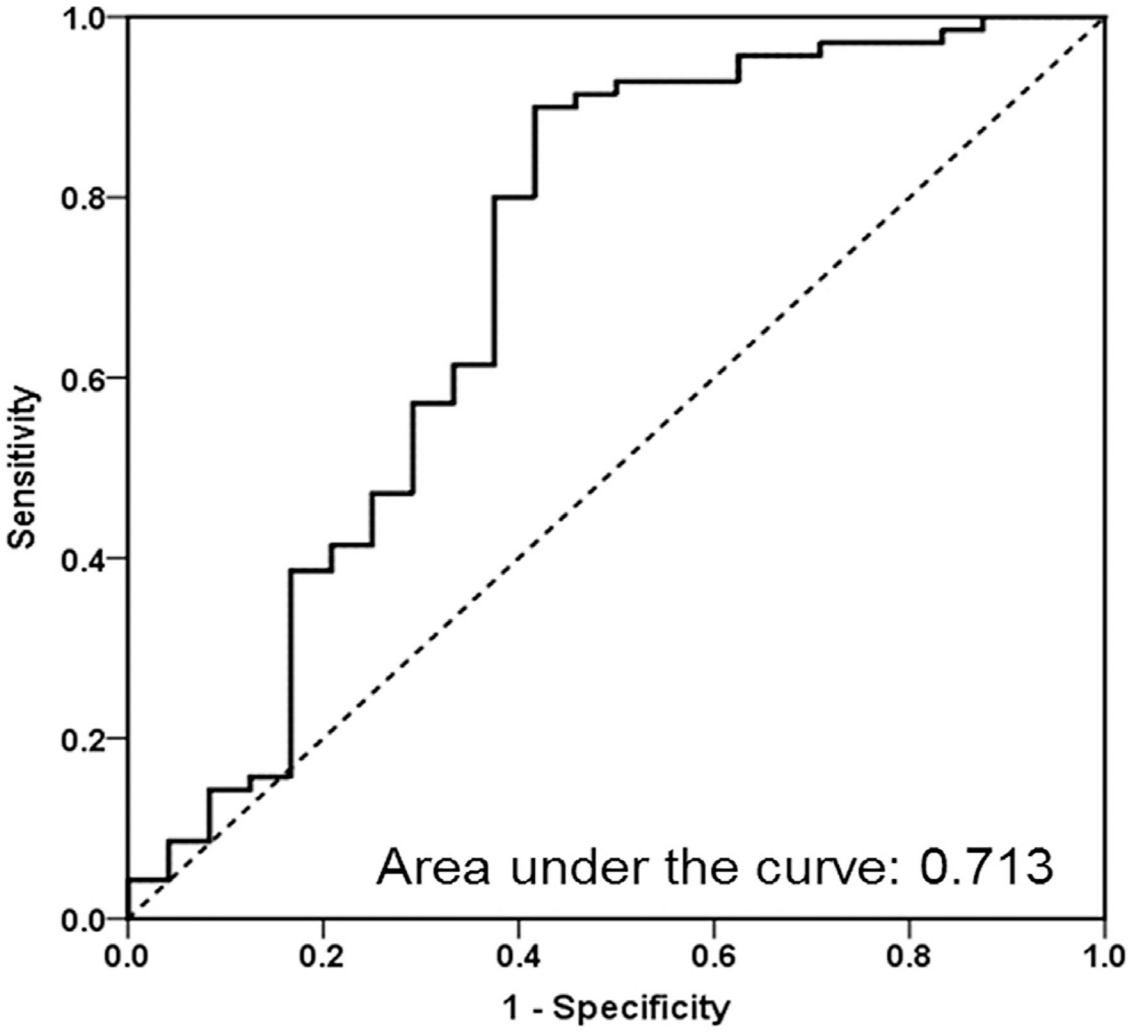

Fig. 1.

Receiver operating characteristic curve of CD4:CD8 ratio as predictor of clinical response rate in MDACC patients with MF who underwent TSEBT.

Table 1

Patient characteristics.

Characteristics	MDACC All Patients (*n* = 94)	Yale All Patients (*n* = 32)
Age, years		
Median (range)	63.5 (21–86)	61.6 (20–79)
Sex		
Male	55 (58.5)	21 (65.6%)
Female	39 (41.5)	11 (34.4%)
Clinical stage		
IB	22 (23.4)	12 (37.5%)
IIA	7 (7.5)	9 (28.1%)
IIB	40 (42.6)	7 (21.9%)
IIIA	1 (1.1)	3 (9.4%)
IVA	16 (17.0)	1 (3.1%)
IVB	8 (8.5)	0
CD4:CD8 ratio (range)	2.25 (0.11–104.4)	3.25 (0.52 – 81)
Baseline mSWAT (range)	40.1 (3.5–174.1)	59.5 (5.0 – 113.0)
RT dose (range)	28 (12–36)	36 (11–38)
SCT after TSEBT	16	5

Table 2

Univariate analysis of achieving CR after TSEBT for patients.

Co-variates	OR	95% CI	*P* value
Age	0.99	0.97–1.03	0.80
Gender	1.25	0.48–3.24	0.65
Stage	0.81	0.64–1.02	0.07
Histology			
Folliculotropic	0.71	0.2–2.5	0.60
Large cell	0.63	0.18–2.16	0.46
Others	1.00	–	–
Baseline mSWAT			
<40	1.00	–	–
≥40	0.80	0.32–2.04	0.64
RT dose			
≤12 Gy	1.00	–	–
>12 Gy	2.86	1.10–7.42	0.03
CD4:CD8 ratio			
<4.42	1.00	–	–
≥4.42	0.08	0.03–0.25	<0.001

Table 3

Multivariate analysis of achieving CR after TSEBT for MDACC patients.

Co-variates	OR	95% CI	*P* value
Stage	0.677	0.189–2.42	0.549
Baseline mSWAT			
<40	1.00	–	–
≥40	1.26	0.393–4.03	0.700
RT dose			
≤12 Gy	1.00	–	–
>12 Gy	3.06	0.993–9.44	0.052
CD4:CD8 ratio			
<4.42	1.00	–	–
≥4.42	0.084	0.025–0.289	<0.001

Table 4

Multivariate analysis of achieving CR after TSEBT for Yale patients.

Co-variates	OR	95% CI	P value
Stage	0.580	0.036–9.24	0.700
Baseline mSWAT			
<40	1.00	–	–
≥40	3.62	0.580–22.6	0.169
RT dose			
≤12 Gy	1.00	–	–
>12 Gy	4.08	0.200–83.0	0.361
CD4:CD8 ratio			
<4.42	1.00	–	–
≥4.42	0.20	0.033–1.47	0.119