Original Article

Comparison of Referring and Final Pathology for Patients With T-Cell Lymphoma in the National Comprehensive Cancer Network

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BACKGROUND: T-cell lymphomas (TCLs) are uncommon in the United States. The accurate diagnosis of TCL is challenging and requires morphologic interpretation, immunophenotyping, and molecular techniques. The authors compared pathologic diagnoses at referring centers with diagnoses from expert hematopathology review to determine concordance rates and to characterize the usefulness of second-opinion pathology review for TCL. **METHODS:** Patients in the National Comprehensive Cancer Network non-Hodgkin lymphoma database with peripheral TCL, not otherwise specified (PTCL-NOS), angioimmunoblastic TCL (AITL), and anaplastic lymphoma kinase (ALK)-positive and ALK-negative anaplastic large cell lymphoma (ALCL) were eligible if they had prior tissue specimens examined at a referring institution. Pathologic concordance was evaluated using available pathology and diagnostic testing reports and provider progress notes. The etiology of discordance and the potential impact on treatment were examined. **RESULTS:** Among 131 eligible patients, 57 (44%) had concordant results, totaling 64% of the 89 patients who were referred with a final diagnosis. Thirty-two patients (24%) had discordant results, representing 36% of those who were referred with a final diagnosis. The rates of discordance among patients with of PTCL-NOS, AITL, ALK-negative ALCL, and ALK-positive ALCL were 19%, 33%, 34%, and 6%, respectively. In 14 patients (44% of discordant results), pathologic reclassification could have resulted in a different therapeutic strategy. Forty-two patients (32%) were referred for classification with a provisional diagnosis. **CONCLUSIONS:** In a large cohort of patients with TCL who were referred to National Comprehensive Cancer Network centers, the likelihood of a concordant final diagnosis at a referring institution was low. As current and future therapies target TCL subsets, these data suggest that patients with suspected TCLs would benefit from evaluation by an expert hematopathologist. ***Cancer*** **2014;120:1993–9**. © *2014 American Cancer Society.*

KEYWORDS: lymphoma, T-cell lymphoma, diagnosis, outcomes research, pathology.

INTRODUCTION

Peripheral T-cell lymphomas (TCLs) comprise an uncommon group of diseases that were recently updated in the World Health Organization (WHO) classification of non-Hodgkin lymphomas (NHLs). The accurate diagnosis of TCL is challenging, requiring morphologic interpretation, immunophenotyping, and molecular techniques. Establishing a precise diagnosis in TCL is critical for determining prognosis and has the potential to impact both therapeutic decisions and clinical trial enrollment.

Although TCLs are generally associated with poor outcomes, the prognosis varies with disease subtype. Patients with anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) have the most favorable prognosis,[1]

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Presented in part as Abstract 1610 at the 54th Annual Meeting of the American Society of Hematology; December 8-11, 2013; Atlanta, Georgia.

We acknowledge the hematopathologists at each National Comprehensive Cancer Network institution who reviewed the cases included in this analysis. We thank the Clinical Research Associates at each site for their assistance with assembling all of the review materials.

DOI: 10.1002/cncr.28676, **Received:** December 23, 2013; **Revised:** February 4, 2014; **Accepted:** February 20, 2014, **Published online** April 4, 2014 in Wiley Online Library (wileyonlinelibrary.com)

although some studies suggest that outcomes in ALCL depend on age rather than ALK status.[2] Most patients with TCL receive anthracycline-based induction combination chemotherapy; however, with the exception of ALK-positive ALCL, relapse rates are high, and a subset of patients may benefit from consolidation with autologous hematopoietic stem cell transplantation (HSCT).[3-7] In recent years, several novel therapies, including histone deacetylase inhibitors,[8,9] pralatrexate,[10] and the novel CD30 antibody-drug conjugate, brentuximab vedotin,[11,12] have demonstrated significant promise in treating TCLs. Thus, as new targeted therapies become available, accurate classification of TCL will be crucial for determining appropriate candidates for clinical trial enrollment and treatment.

Despite the use of advanced techniques, prior studies evaluating the diagnostic accuracy of expert hematopathologists using both older classification systems and the newer WHO classification for TCLs have produced suboptimal rates of agreement with consensus diagnoses. Historic studies evaluating expert hematopathologist agreement rates with consensus panel diagnoses for TCLs have demonstrated similar diagnostic accuracy, ranging from 72% for angioimmunoblastic T-cell lymphoma (AITL) and peripheral TCL-not otherwise specified (PTCL-NOS) to 85% for ALCLs.[13-15] In a series of recent studies in 1314 patients with peripheral TCL and natural killer cell/TCL (NKTCL) by the International T-Cell Lymphoma Project, the agreement rates between the diagnoses assigned by individual expert hematopathologists and the consensus diagnoses assigned by panels of expert hematopathologists were in the 66% to 97% range for various TCL subtypes. The agreement rates for the more common TCL histologies—PTCL-NOS, AITL, ALK-negative ALCL, and ALK-positive ALCL—were 75%, 81%, 74%, and 97%, respectively.[1,16,17] In addition, in a recent study of upfront autologous HSCT for TCL by the Nordic Lymphoma Group, referral pathology was reanalyzed by national reference center pathologists with an agreement rate of 87%.[6] In another study from the United Kingdom, all lymphomas diagnosed within a hospital network underwent central review by an expert hematopathologist, and the agreement rate also was 87% for TCLs.[18]

Although the studies described above suggest that consensus expert panel hematopathology review of TCLs is beneficial, convening an expert panel for each case of suspected TCL is not feasible. Instead, when a community pathologist is unsure of a diagnosis of TCL, the biopsy specimen is referred for second-opinion review, often to a tertiary center. In real-world practice, expert hematopathology review (often with departmental consensus review) is the standard of care for TCL diagnosis. Although concordance between community and expert hematopathology review has been evaluated in B-cell NHLs,[19] little data exist regarding the rates of agreement between referring diagnoses and expert review for TCLs in the United States and the potential impact of pathologic reclassification on treatment recommendations. We evaluated the rate of diagnostic concordance between referring center diagnoses and expert hematopathology review for 4 subtypes of TCL at 7 tertiary centers in the National Comprehensive Cancer Network (NCCN).

MATERIALS AND METHODS

The NCCN NHL Outcomes Project is a multicenter, prospective registry of comprehensive clinical, treatment, and outcome data for patients with NHL that was established on July 1, 2000. Data collection for patients with TCLs was initiated on April 1, 2007. Seven institutions contributed patients to this analysis: City of Hope Cancer Center (Duarte, Calif), Dana-Farber Cancer Institute (Boston, Mass), Fox Chase Cancer Center (Philadelphia, Pa), Robert H. Lurie Comprehensive Cancer Center of Northwestern University (Chicago, Ill), University of Michigan Cancer Center (Ann Arbor, Mich), The University of Texas MD Anderson Cancer Center (Houston, Tex), and Roswell Park Cancer Institute (Buffalo, NY). The institutional review boards at all participating centers approved the data-collection protocol. When required, we obtained written informed consent for medical record review.

All patients with TCL who presented to participating NCCN centers between April 1, 2007 and June 15, 2012 were eligible for inclusion. Additional inclusion criteria included a documented pathologic review at a referring center before expert hematopathology review and a final diagnosis of 1 of the following 4 TCL WHO subtypes: PTCL-NOS, AITL, ALK-negative ALCL, and ALK-positive ALCL.[20]

The pathologic diagnosis from the referring center was compared with the final WHO diagnosis at the NCCN center to establish pathologic concordance rates. Pathologic concordance was defined as the same pathologic diagnosis at both the referring center and the NCCN center, considering all supporting documentation, including pathology reports, immunohistochemistry (IHC), flow cytometry, fluorescence in situ hybridization (FISH) and cytogenetics, T-cell gene rearrangement studies, and physician progress notes. Review of the records of all patients

was performed by 3 of the authors (A.F.H, A.C.-T., and A.S.L.) to determine pathologic concordance.

Pathology results were separated into the following categories: 1) concordant, with the same referral and NCCN diagnoses; 2) provisional diagnosis before second-opinion referral with further workup suggested; and 3) discordant, with different referral and NCCN diagnoses. Patients who were referred with a provisional diagnosis to a non-NCCN tertiary academic referral center or commercial hematopathology service before the NCCN presentation were placed in the same provisional diagnosis category as those who had a provisional referral diagnosis and were referred directly to an NCCN center for diagnosis. Patients who had a provisional diagnosis before second-opinion referral in which an additional biopsy was necessary at the NCCN center to make a final diagnosis were included in the provisional diagnosis category.

To characterize the etiology of discordance, reviewers assigned each patient with pathologically discordant results to 1 of the following categories: 1) discordant final referral diagnosis based on the NCCN center's interpretation of existing data, or 2) discordant final referral diagnosis based on additional studies performed at the NCCN center. Finally, 5 situations were identified in which pathologic reclassification might influence a patient's treatment: 1) benign diagnosis changed to TCL, 2) malignancy other than NHL changed to TCL, 3) B-cell NHL or classical Hodgkin lymphoma changed to TCL, 4) NKTCL changed to TCL, and 5) incorrect or undefined ALK status in patients with ALCL. Patients who had discordant pathologic diagnoses and met 1 of these criteria were considered as potentially having experienced a change in treatment based on pathologic reclassification.

When reported in the materials reviewed, information was collected regarding the type of biopsy performed (core-needle or excisional biopsy), the materials received for review by the NCCN center (the number of paraffin-embedded tissue blocks and/or slides), the number and type of studies performed at the referring and NCCN centers (eg the number of immunostains, T-cell receptor [TCR] gene rearrangement studies), the duration of the pathology review at the referring and NCCN centers, and the number of pathologists involved with the case review. Descriptive statistics were used to estimate concordance rates, rates of potential treatment difference, and rates of additional testing among groups and subgroups. Analyses were performed using the Fisher's exact test, *t* test, or Wilcoxon rank sum test, as appropriate, to evaluate whether the type of biopsy or the number or type of ancillary testing performed at the referring center was associated with pathologic concordance or with the referring center arriving at a final diagnosis.

RESULTS

In total, 175 patients with TCL were included in the NCCN NHL database between April 1, 2007 and June 15, 2012. Twenty-four of those patients had a primary presentation to a NCCN center and, thus, had no referring pathology and were ineligible for the study. Twenty patients had incomplete or insufficient data for analysis—usually unavailable referral pathology reports for comparison—and were excluded.

Of 131 eligible patients, 89 were assigned a final diagnosis at the referring center (Fig. 1). Fifty-seven patients (44%) had pathology results that were concordant with the NCCN center diagnosis, and 32 (24%) had discordant pathology results. Forty-two patients (32%) were referred for a second opinion with a provisional diagnosis and with further workup or additional biopsy suggested. The rates of pathologic discordance among patients with PTCL-NOS, AITL, ALK-negative ALCL, and ALK-positive ALCL were 19%, 33%, 34%, and 6%, respectively (Table 1). Among patients who were referred for a second opinion with a final diagnosis, the overall discordance rate was 36%, and the discordance rates among patients with PTCL-NOS, AITL, ALK-negative ALCL, and ALK-positive ALCL were 38%, 50%, 38%, and 7%, respectively. Table 1 lists the various referring and final diagnoses assigned to patients who were diagnosed with TCL at the NCCN centers.

Of the 32 patients with discordant results who were referred to an NCCN center with a final diagnosis, 15 (47%) were reclassified based on a different interpretation of the same data or noncontributory additional studies. Noncontributory additional studies represented either studies performed at the NCCN center that were not performed originally at the referring center and were negative or studies that were repeated at the NCCN center that had been performed originally and merely confirmed positivity. In the remaining 17 patients (53%) with discordant results, additional studies were performed at the NCCN center that led to a different diagnosis. Additional IHC led to a reclassification in 14 patients, a positive TCR result led to 1 reclassification, an additional biopsy with repeat TCR testing led to 1 reclassification, and a negative FISH test for a 9q34 abnormality supported a reclassification based on morphology from enteropathy-associated TCL to PTCL-NOS. Of the patients who were reclassified because of additional IHC analyses, 2 patients had ALCLs in which ALK staining had not been

TABLE 1. Referral and Final NCCN Diagnoses for Patients With T-Cell Lymphoma (n = 131)

Referral Diagnosis	NCCN Diagnosis: No. of Patients				Total
	PTCL NOS	AITL	ALK+ ALCL	ALK− ALCL	
PTCL-NOS	15	4	0	3	22
AITL	0	11	0	0	11
ALK+ ALCL	0	0	13	0	13
ALK− ALCL	1	0	0	18	19
ALCL, no ALK status	0	0	0	2	2
Anaplastic T-cell/NK-cell lymphoproliferative neoplasm	0	0	0	1	1
DLBCL	1	1	0	0	2
EMZL	0	1	0	0	1
Classical Hodgkin lymphoma	1	1	0	3	5
EATL	1	0	0	0	1
TCL without WHO designation	4	1	0	1	6
Atypical lymphoid proliferation	1	1	0	0	2
Benign/reactive	0	2	1	0	3
No definitive diagnosis rendered	0	0	0	1	1
Final referring diagnosis	24	22	14	29	89
Provisional referring diagnosis	24	11	4	3	42
Total patients evaluated at NCCN centers	48	33	18	32	131
Discordant cases: No. (%)	9 (19)	11 (33)	1 (6)	11 (34)	32 (24)

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALK, anaplastic lymphoma kinase; ALK− ALCL,anaplastic lymphoma kinase-negative anaplastic large cell lymphoma; ALK+ ALCL,anaplastic lymphoma kinase-positive anaplastic large cell lymphoma; DLBCL, diffuse large B-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; EMZL, extranodal marginal zone lymphoma;NCCN, National Comprehensive Cancer Center; NK-cell, natural killer cell; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; TCL T-cell lymphoma; WHO, World Health Organization.

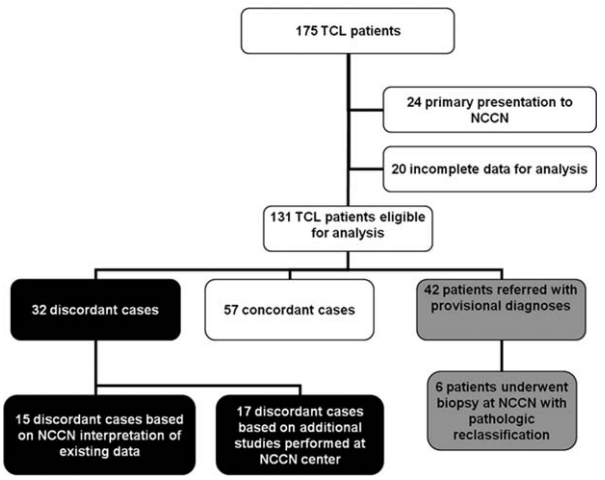

Figure 1. Comparison of referral and NCCN pathology results in patients with T-cell lymphoma (TCL). NCCN indicates National Comprehensive Cancer Network.

performed at the referring center; 5 patients had chemokine (C-X-C motif) ligand 13 (CXCL13), and/or programmed cell death 1 (PD-1), and/or cluster of differentiation 21 (CD21) stains performed that led to a reclassification to AITL; in 3 patients, B-cell–specific activator protein/paired box protein Pax-5 (BSAP/PAX5) stains, usually in concert with repeat CD15, CD30, and (on 1 occasion) octamer-binding transcription factor 2 (OCT2) and B-cell octamer binding protein 1 (BOB1) stains led to a reclassification from classic Hodgkin lymphoma to ALCL. The remaining 4 patients were reclassified based on IHC for standard T-cell markers or CD30.

In 14 patients (11% overall, 16% of patients who were referred with a final diagnosis, and 44% of patients who had discordant results), pathologic reclassification may have resulted in a change in treatment. Three patients who were referred with benign diagnoses were diagnosed with TCL at an NCCN center and required treatment. Eight patients were referred with a diagnosis of B-cell NHL or classic Hodgkin lymphoma and were reclassified to TCL. One patient who was referred with a diagnosis of NKTCL was reclassified to TCL. Two patients were diagnosed with ALCL without evaluation of ALK status.

In total, 112 patients (86%) had an excisional biopsy sample from the referring center submitted for NCCN hematopathology review. In 19 patients (14%), a core-needle biopsy sample or other type of sample represented the primary tissue sample referred for NCCN hematopathology review. Among 42 patients who were referred to an NCCN center with a preliminary diagnosis, 9 had a core-biopsy sample or other type of sample referred for review, and 33 had an excisional biopsy sample. Of the 89 patients who were referred with a final diagnosis, 10 were referred with a core-biopsy sample or other type of sample, and 79 had an excisional biopsy sample. Of the 10

TABLE 2. Number and Type of Studies Performed at Referring Centers in Patients Referred with a Final Diagnosis

Type of Study Performed at Referring Institution	No. of Patients (%)	
	Concordant Diagnoses, n = 57	Discordant Diagnoses, n = 32
IHC		
Yes	54 (95)	29 (91)
No/not mentioned	3 (5)	3 (9)
Flow cytometry		
Yes	32 (56)	17 (53)
No/not mentioned	25 (44)	15 (47)
TCR gene rearrangement		
Yes	19 (33)	13 (41)
No/not mentioned	38 (67)	19 (59)
FISH		
Yes	5 (9)	0 (0)
No/not mentioned	52 (91)	32 (100)
IHC and flow cytometry	31 (54)	16 (50)
IHC, flow cytometry, and TCR	15 (26)	6 (19)
Median no. of referring IHC stains [range]	14 [0–35]	11 [0–31]

Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemical staining; TCR, T-cell receptor.

patients referred with a final diagnosis from a core-biopsy sample or other type of sample, there was 1 patient with a discordant pathologic diagnosis and 9 patients with concordant pathologic diagnoses. Of the patients who were referred with an excisional biopsy sample and a final diagnosis, there were 48 concordant diagnoses and 31 concordant diagnoses. There was no association between biopsy type and pathologic concordance among the patients who were referred with a final diagnosis ($P = .18$) or between biopsy type and whether a final diagnosis was rendered at the referring center ($P = .09$).

Additional testing beyond histologic evaluation of biopsy material was performed at the referring institution before the second-opinion referral in 95% of all eligible patients. IHC stains, flow cytometry, TCR gene rearrangement testing, and FISH testing (usually for *ALK* rearrangement) were performed in 84%, 52%, 36%, and 6% of patients, respectively. Table 2 describes the studies performed at the referring center in patients who had a final diagnosis conferred, separated into those with concordant or discordant results. There was no association between pathologic concordance or discordance and the number of IHC stains performed ($P = .23$) or the type of study performed: IHC ($P = .66$), flow cytometry ($P = .83$), TCR gene rearrangement testing ($P = .5$), the combination of IHC and flow cytometry ($P = .825$), or the combination of IHC and flow cytometry plus TCR testing ($P = .6$).

The median number of paraffin-embedded tissue blocks and slides received for review at the NCCN centers was 0 (range, 0-10 blocks) and 19 (range, 0-65 slides), respectively. The median duration of time spent reviewing a case at the NCCN center was 5 days (range, 1-34 days). From the available documentation, in 72% of the NCCN pathology reviews, a single NCCN hematopathologist reportedly reviewed the case. In 28% of cases, it was reported that cases were referred for intradepartmental consultation by at least 1 hematopathologist or were reviewed at an intradepartmental conference. Comparatively, in 76% of referring center pathology reviews, it was reported that cases were reviewed by 1 pathologist; and, in 24% of cases, it was reported that cases were referred for intradepartmental consultation by at least 1 pathologist or were reviewed at an intradepartmental conference. At the NCCN center, additional IHC stains, flow cytometry, TCR gene rearrangement testing, and FISH testing were performed in 53%, 18%, 18%, and 6% of patients, respectively. The median number of IHC stains performed at the NCCN centers was 2 (range, 0-29 stains) compared with 11 (range, 0-35 stains) performed at the referring centers. In 31 patients, a median number of 10 IHC stains (range, 1-40 IHC stains) were performed at an institution other than the referring institution before NCCN referral.

DISCUSSION

Our review of second-opinion pathology in the NCCN demonstrated a high rate of pathologic discordance for most TCL subtypes that were included in the current study with the exception of ALK-positive ALCL. The discordance rates were particularly high for patients who were assigned a "final" diagnosis at the referring center. Compared with other studies reporting central review of clinical trial participant specimens or central review of all patients with lymphoma in a geographic region, the discordance rates in our study are high.[6,18] We also observed that, in 44% of the patients with discordant pathology results, the pathologic reclassification may have impacted treatment.

Unlike a previous study by our group in which we demonstrated a high rate of pathologic concordance between referring and NCCN centers for B-cell NHLs,[19] the lower rate of agreement between referring and NCCN centers suggests that community pathology review is not equivalent to expert hematopathology review of TCLs. Often, referring pathologists did not assign a specific diagnosis according to the WHO classification. There was no association between the type of biopsy performed or the number or types of studies performed at the referring center and pathologic concordance or discordance. In fact, in

47% of patients with discordant pathology, NCCN hematopathology review of already available diagnostic testing resulted in a pathologic reclassification. The other half of patients were reclassified based on additional testing performed at the NCCN center. The most common additional testing performed was IHC, including novel stains like CXCL13 and PD-1 that may not be available in the community. Common reclassifications included a referral diagnosis of PTCL-NOS reclassified as AITL or ALK-negative ALCL and a referral diagnosis of classical Hodgkin lymphoma reclassified as ALK-negative ALCL. Notably, 3 patients who originally were diagnosed with benign conditions were reclassified with TCL at NCCN centers, which would have resulted in a major difference in treatment. Two of those patients ultimately were diagnosed with AITL, an aggressive TCL that is notoriously difficult to accurately diagnose and to distinguish from nonmalignant lymphoid proliferations. Thus, as new advanced diagnostic tools, including molecular profiling of TCLs,[21] become available to enhance the diagnostic accuracy of TCLs, patients will require review at centers capable of performing and interpreting these analyses.

It is noteworthy that several patients were referred for a second opinion without a final diagnosis from the referring institution or were referred immediately for a second opinion with only a provisional diagnosis. Referring pathologists frequently recognized atypical lymphoid populations and, sometimes, lymphoid proliferations suggestive of TCL, but they often referred patients for expert hematopathology review for final diagnosis and classification. The considerable proportion of patients referred with a provisional diagnosis likely reflects how infrequently TCLs are encountered in the community and the inherently challenging nature of accurately diagnosing TCLs. The high early referral rate suggests that it may already be common practice for community pathologists to refer these complicated cases to a tertiary center.

Our study has limitations. First, the numbers of patients with each subtype of TCL are small. Second, we compared community pathology review with expert hematopathology review at a tertiary center. For the purposes of this analysis, we assumed that the diagnosis rendered by the NCCN hematopathologist was the "correct diagnosis." Prior studies evaluating expert hematopathology review against consensus expert panels have demonstrated diagnostic accuracy rates in the 72% to 97% range for the lymphoma subtypes included in this study.[1,14,16,17] Therefore, there may be an inherent discordance rate in the expert review that should be considered when interpreting the data.

Next, because our study population was entirely composed of patients who were referred to tertiary centers for further management and pathologic review, our population may have been enriched for patients with complex pathology who were more challenging to accurately diagnose. This may explain the higher discordance rate in our study relative to studies that evaluated all patients in a geographical region or all individuals enrolled on a specific clinical trial. In addition, in estimating the impact of pathologic reclassification, we did not examine the actual therapy received by patients in the study. Finally, the hematopathologists at NCCN centers were not blinded to the referring pathology, which may have influenced their decisions regarding a final pathologic diagnosis. Nevertheless, awareness of a previously assigned diagnosis should have biased the hematopathologists toward a concordant diagnosis and should not have altered the high discordance rates demonstrated in this study.

Establishing a precise diagnosis by differentiating between different TCL subtypes is important for determining prognosis and has an impact on both therapeutic decisions and clinical trial eligibility. Prognosis and response to standard chemotherapy differs between TCL subtypes; for instance, ALK-positive ALCL is associated with higher remission rates and improved survival after induction chemotherapy.[1,6] Because of the poor prognosis associated with non-ALK-positive ALCL TCLs, many of these patients are considered for up-front consolidation with autologous HSCT. Recent data suggest that there may be differences in outcomes after autologous HSCT according to TCL subtype, with increased progression-free and overall survival among patients who have ALK-negative ALCL compared with patients who have other TCL subtypes.[6] In addition, several currently available therapies for relapsed or refractory TCLs have differential activity across different TCLs, with patients who have AITL less likely to respond to pralatrexate and exhibiting longer duration of responses to romidepsin.[8-10] Thus, accurate TCL histologic classification is critical for making treatment decisions in these patients and will become increasingly important as we continue to learn about the differences in outcomes according to TCL subtype after HSCT and various therapies. Furthermore, with the evolution of clinical trials examining the activity of novel agents among TCL subtypes, such as brentuximab vedotin, the anti-CD30 antibody drug conjugate, proper classification will be important for understanding and identifying these differential responses. The low rate of pathologic concordance observed in our study stresses the

importance of centralized expert hematopathology review in these trials.

In summary, 36% of patients with TCL who were referred to NCCN centers for a second opinion with a final diagnosis were reclassified at the NCCN center. Approximately 1 in 10 patients with TCL in the NCCN NHL Outcomes Project database had a pathologic reclassification at the NCCN center that may have had an impact on their treatment. The NCCN NHL Outcomes Project database is one of the largest reported TCL series to date using the WHO classification. Given the frequency of pathologic reclassification for TCLs we observed, our data support obtaining expert hematopathology review for any patient suspected of having TCL as well as centralized hematopathology review for TCL clinical trials. Indeed, TCLs are uncommon and are difficult to diagnose accurately. Thus, as current and future therapeutic approaches target subsets of TCLs, accurate diagnosis and distinguishing between TCL subtypes promises to become even more important.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

Dr. Rodriguez reports research funding from Pfizer, Glaxo-Smith Kline, and Amgen unrelated to the submitted work.

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