Received: 5 November 2019 | Revised: 16 December 2019 | Accepted: 18 December 2019

DOI: 10.1002/hon.2705

WILEY

ORIGINAL RESEARCH ARTICLE

Survival benefit in patients with peripheral T-cell lymphomas after treatments with novel therapies and clinical trials

Helen Ma[1] | Bin Cheng[2] | Lorenzo Falchi[1] | Enrica Marchi[3] | Ahmed Sawas[3] | Govind Bhagat[4] | Owen A. O'Connor[3]

[1]Division of Hematology and Oncology, New York Presbyterian Hospital, Columbia University Irving Medical Center, New York, New York

[2]Department of Biostatistics, Columbia University Irving Medical Center, New York, New York

[3]Center for Lymphoid Malignancies, Columbia University Irving Medical Center, New York, New York

[4]Department of Pathology and Cell Biology, Columbia University Irving Medical Center, New York, New York

Correspondence
Helen Ma, MD, Division of Hematology and Oncology, New York Presbyterian Hospital, Columbia University Irving Medical Center, 177 Fort Washington Ave, MHB 6GN-435, New York 10032, NY.
Email: hm2715@cumc.columbia.edu

Present Address
Lorenzo Falchi, Memorial Sloan-Kettering Cancer Center, New York, New York.

Funding information
American Cancer Society, Grant/Award Number: Research Professorship (OAO); Columbia Lymphoma Research Fund

Peer Review
The peer review history for this article is available at https://publons.com/publon/10.1002/hon.2705.

Abstract

The peripheral T-cell lymphomas (PTCL) are rare and heterogeneous diseases characterized by an unfavorable prognosis. Chemotherapy is standard upfront treatment in most patients, but responses are short-lived with few FDA-approved "novel" agents available. We sought to define the impact of these novel agents as single agents or in clinical trials on the outcomes of patients with PTCL. From January 1994 to May 2019, adult patients with PTCL who were managed at our institution were included in this analysis. In addition to patients with incomplete data, those diagnosed with large granular lymphocytic leukemia and cutaneous T-cell lymphoma (CTCL) except for transformed mycosis fungoides were excluded. Statistical analyses were performed using SAS version 9.4. There were 219 patients included in the analysis. The median age at diagnosis was 56 years (range, 18-90 years). First line therapies mostly consisted of combination chemotherapy (75%). There was a statistical difference among patients who received chemotherapy, novel agents alone and in chemotherapy-free combinations, other, and no treatment ($P < .0001$). In patients who were treated with second line chemotherapy, novel agents alone and in combination without chemotherapy, or other, there was a still a survival benefit favoring novel agents ($P = .0417$). In the third line, there was no statistical difference among the three groups ($P = .569$). All patients who received novel therapies and underwent autologous stem cell transplant (autoSCT) achieved a complete response (CR) and had a better survival compared with patients who underwent chemotherapy who had a 70% CR rate prior to autoSCT ($P = .046$). Exposure to FDA-approved novel agents, immunoepigenetic trials, and clinical trials in general was associated with an overall survival (OS) benefit ($P = .003$, $P = .04$, and $P = .006$, respectively). These data suggest that patients who receive novel agents have superior outcomes compared with patients without exposure to novel therapies who receive chemotherapy-predicated treatments.

KEYWORDS

belinostat, clinical trial, histone deacetylase inhibitor, outcomes, peripheral T-cell lymphoma, pralatrexate, romidepsin

1 | INTRODUCTION

The peripheral T-cell lymphomas (PTCL) are rare and heterogeneous non-Hodgkin lymphomas (NHL) originating from mature, post-thymic T- and NK-cells. The 2016 World Health Organization (WHO) Classification now recognizes 29 distinct subtypes.[1] The subtypes encountered in the United States include PTCL not otherwise specified (PTCL-NOS, 34%), angioimmunoblastic T-cell lymphoma (AITL, 16%), anaplastic large T-cell lymphomas (ALCL), which are typically divided into ALK-positive (8%) and ALK-negative (16%) subtypes, enteropathy-type (6%), extranodal NK/T-cell lymphoma (ENKTCL, 5%), hepatosplenic T-cell lymphoma (HSTCL, 3%), and adult T-cell leukemia/lymphoma (ATLL, 2%).[2] Given the rarity and heterogeneity, treatment approaches for these diseases have been largely extrapolated from the management of aggressive B-cell lymphomas and revolve around CHOP-based chemotherapy (consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone with or without etoposide).[3,4] Depending on subtype, the 5-year overall survival (OS) worldwide ranges from 14% (ATLL), 32% (PTCL-NOS, AITL, NKTCL), 49% (ALK- ALCL), to 70% (ALK+ ALCL).[2] The phase III ECHELON-2 trial only recently demonstrated an improvement in the outcome of patients with CD30-positive ALCL who were treated with frontline Brentuximab vedotin (Bv), an antibody drug conjugate targeting CD30, in combination with cyclophosphamide, doxorubicin, and prednisone.[5]

Patients with PTCL who present with relapsed or refractory (R/R) disease have an especially poor prognosis with the median time from diagnosis to relapse or progression of disease of 6.7 months after primary therapy, while the median OS and progression free survival (PFS) were only 6.5 and 3.1 months, respectively.[6] These dismal statistics signify an unmet need in the care of patients with PTCL, especially because studies establish that overall response rate (ORR), complete response (CR), PFS, and duration of response (DOR) decline as the lines of therapy increase.[6,7] In the United States, there are four approved agents approved in various countries for the treatment of R/R PTCL, including (a) pralatrexate, the first drug approved for patients with R/R PTCL in 2009 with an ORR of 29%; three histone deacetylase inhibitors (HDACi) including (b) romidepsin, approved in 2009 for R/R cutaneous T-cell lymphomas (CTCL) and in 2011 for R/R PTCL with ORR of 25%; (c) belinostat, approved in 2014 for R/R PTCL with ORR of 26%; and (d) Bv, which was approved in 2011 for R/R CD30-positive systemic ALCL with ORR of 86% and in 2017 for CD30-positive CTCL.[8-11] Additionally, chidamide, another HDACi, was approved in China in 2014 with ORR of 28%, and forodesine, an oral purine nucleoside phosphorylase inhibitor, was approved in Japan in 2016 with ORR of 22%.[12,13] To better understand how the these "novel" agents influenced the natural history of PTCL, we identified patients diagnosed with mature T-cell lymphomas and managed at our institution to analyze their outcomes as a function of different treatments.

2 | MATERIALS AND METHODS

Using data captured through the electronic medical record and pathology department database, patients with a diagnosis of T-cell lymphoma were identified at New York Presbyterian Hospital-Columbia University Irving Medical Center. We included patients 18 years of age and older with the diagnosis of a mature T-cell lymphoma. Diagnoses were confirmed and classified by a hematopathologist (G.B.) in accordance with the 2016 WHO classification.[1] Due to the drastically different disease characteristics and treatment standards, we excluded patients with T/NK large granular lymphocytic leukemia and CTCL, with the exception of transformed mycosis fungoides (tMF), given its similar outcomes to other PTCL subtypes (mean 5-year OS of 20%).[14]

Treatment categories were defined as follows: (a) conventional chemotherapy, such as anthracycline-containing regimens like CHOP, CHOEP, or EPOCH; (b) novel therapy, which included FDA approved single agents, such as romidepsin, pralatrexate, belinostat, and Bv, as well as multi-agent combinations without chemotherapy such as romidepsin and pralatrexate or hypomethylating agents with or without immune checkpoint inhibitors, as well as single agent clinical trials of experimental drugs such as alisertib, AFM13 (NK-cell engager), TTI-621 (SIRPαFc fusion protein), AGS67E (antibody drug conjugate targeting CD37), navitoclax (Bcl-2 inhibitor), ACY1215 (HDAC6 inhibitor); and mogamulizumab (CCR4 monoclonal antibody); (c) other, which consisted of skin-directed therapies (ultraviolet B, denileukin diftitox, bexarotene, photopheresis, and topical therapies), systemic steroids, radiation, interferon, and drugs that did not fit any other categories, for example, alemtuzumab; and (d) no therapy.

OS was calculated from the time of diagnosis to death from any cause. Kaplan-Meier curves for overall survival were compared based on the log-rank test. Cox proportional hazard models were used to investigate the impact on overall survival by adjusting for age, gender, diagnosis, International Prognostic Index (IPI), Prognostic Index for T-cell Lymphoma, Unspecified (PIT-U) in PTCL-NOS patients, International Peripheral T-Cell Lymphoma Project (IPTCLP) score, and type of treatments. The analysis was performed using SAS version 9.4. A P value <.05 was considered statistically significant. The research reported herein was conducted and reported in accordance with the Declaration of Helsinki and a protocol approved by our Institutional Review Board.

3 | RESULTS

3.1 | Patient characteristics

Our analyses included 219 patients who were diagnosed with PTCL and managed at our institution from January 1, 1994, to May 31, 2019, as shown in Figure 1; the median follow up time was 1.7 years (range, 0.01 to 16.5 years). Table 1 summarizes the patient characteristics, including the time-period during which the diagnosis was made, median age, gender, race, ethnicity, central nervous system (CNS) involvement, IPI, PIT-U, IPTCLP, subtypes of PTCL, and the types of first line treatments received. The median time to initiation of treatment was 3 weeks (range, 0-208 weeks), and the

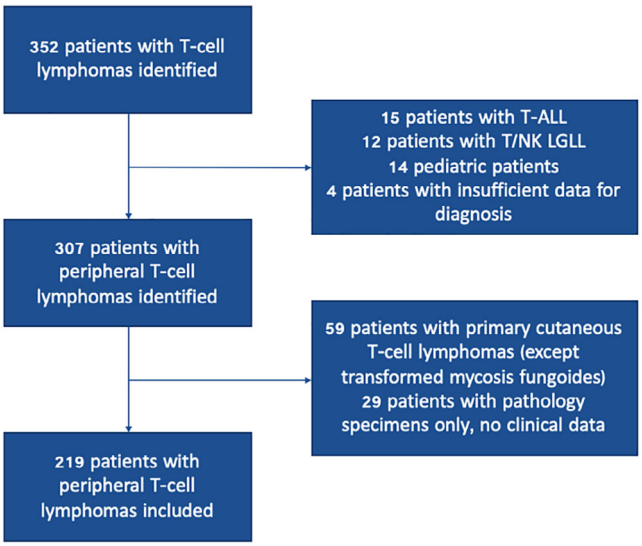

FIGURE 1 Schema of patients included in the analysis. Abbreviations: T-ALL, T-acute lymphoblastic leukemia; T/NK LGLL, T/NK cell large granular lymphocytic leukemia

median number of treatments was 2 (range, 0-11). The IPI, PIT-U, and IPTCLP predicted worse survival for higher risk disease that was statistically different among risk stratifications ($P < .001$). With a median IPI of 3, the data indicate that this study population was predominantly composed of higher risk patients.

3.2 | Treatment factors influencing overall survival

Era of diagnosis impacted OS among the 114 patients diagnosed before 2010 with a median OS of only 1.71 years (range, 0.82-2.34 years), compared with 4.29 years (range, 2.62-not reached, NR) among the 105 patients diagnosed in 2010 and later ($P = .002$). This difference was highly statistically significant, and Figure 2 reveals the OS as a function of the era. Patients younger than 65 had a median OS of 3.61 (range, 2.03-5.60 years) compared with patients 65 and older, who had a median OS of 1.99 years (range, 0.99-2.82), and although clinically meaningful, these differences were not statistically significant ($P = .051$). Gender and race did not seem to impact survival ($P = .53$ and .49, respectively). Patients who identified as Hispanic/Latino demonstrated an inferior survival compared with those who did not ($P = .006$).

Most patients had PTCL-NOS, and their median OS was 3.13 years (range, 1.29-5.60 years). The poorest OS was noted for patients with ATLL who exhibited the shortest median OS of only 0.69 years (range 0.37-1.49), highlighting the need for better treatments in this subgroup. Patients with AITL had a median OS of 3.83 years (range, 2.23 years-NR). The aggressive intestinal T-cell lymphomas had a worse median OS compared with the ITCLPD of the gastrointestinal tract, with OS of 0.84 years (range, 0.43-1.16 years) and 11.68 years, (range, 0.46 years-NR), respectively. From the date of documented pathologic transformation, patients with tMF had a median OS of 4.29 years (range, 1.07 years-NR). Patients with ALK-positive ALCL did better than patients with ALK-negative disease with a median OS of 5.77 years (range, 0.83 years-NR) compared with 2.82 years (range, 0.57-7.38 years), respectively. Patients with HSTCL demonstrated a median OS of 2.91 years (range, 0.28 years-NR). While not well represented, patients with ENKTCL, SPTCL, PTCL-NOS TFH, BI-ALCL, and T-PLL exhibited the highest median OS (not reached).

3.3 | Impact of therapy choice during each line of therapy

In the front-line setting, 164 (75%) of patients received chemotherapy-containing treatment summarized in Table 1. Twenty-three patients received the second most common treatment, which was other, followed by 20 patients who received novel agents. Ten patients received no treatment, which was associated with the worst outcome compared with patients who were treated, shown in Figure 3A ($P < .0001$). In the front-line setting, the median OS for patients was as followed: 2.94 years (range, 1.89-4.51 years) with chemotherapy, not reached (NR) (range, 1.00 years-NR) with novel, 2.23 years (range, 1.35-11.68 years) with other treatments, and 0.12 years (range, 0.01-0.40 years) with no treatment ($P < .001$).

After frontline therapy, 57 of 134 patients received novel therapy compared with 62 of patients who received chemotherapy. The remaining patients received other treatments. Figure 3B summarizes the survival curves for patients who received these therapies. The median OS for patients who received second-line treatments was as followed: 2.53 years (range, 1.49-3.63 years) with chemotherapy, 3.83 years (range, 2.34-9.97 years) with novel therapies, and less than a year (0.99 year; range, 0.25-5.18 years) with other treatments ($P = .0417$).

In the 95 patients who received third line treatment, 40 patients received novel drugs compared with the 37 patients who received chemotherapy. The median OS for patients was as followed: 2.62 years (range, 1.49-5.65 years) with chemotherapy, 5.25 years (range, 2.32-12.72 years) with novel agents, and 3.30 years (range, 1.70 years-NR) with other treatments, shown in Figure 3C ($P = .569$).

In our study population, a total of 43% received an FDA approved novel agents alone or in combination during their treatment course, and this was associated with improvement in survival, shown in Figure 4A ($P = .003$). Exposure to romidepsin and the associated survival benefit is shown in Figure 4B ($P = .027$). Figures 4C demonstrates that participants in any clinical trial (n = 77) experienced a longer median OS compared with those who did not ($P = .006$). Patients who received any of the above novel therapies had similar responses and long-term outcomes irrespective of lines of treatment. In addition, patients with ITCLPD of the GI tract did not respond to any chemotherapy or novel therapy reported.

TABLE 1 Patient characteristics in the first line setting

Number of Patients	Overall, n = 219 (%)	Chemotherapy, n = 164 (%)	Novel Agents, n = 22 (%)
Time period diagnosed (%)			
1991-2009	114 (52)	90 (55)	1 (5)
2010-2019	105 (48)	74 (45)	21 (95)
Median age (range)	56 (18-90)	53 (18-86)	61 (36-87)
Age diagnosed (%)			
< 65	147 (67)	119 (73)	11 (50)
≥ 65	72 (33)	45 (27)	11 (50)
Male gender (%)	121 (55)	86 (52)	13 (59)
Race (%)			
White	115 (53)	80 (49)	11 (50)
Black	44 (20)	36 (22)	4 (18)
Declined/unknown	45 (21)	35 (21)	5 (22)
Asian/Pacific Islander	11 (5)	9 (5)	2 (9)
Other	4 (2)	4 (2)	0
Ethnicity			
Not Hispanic/Latino	127 (58)	95 (58)	14 (64)
Declined/unknown	47 (21)	36 (22)	7 (32)
Hispanic/Latino	45 (21)	33 (20)	1 (5)
International prognostic index (%)			
Low risk (0-1)	42 (19)	27 (16)	5 (22)
Low-intermediate risk (2)	42 (19)	33 (20)	5 (22)
High-intermediate risk (3)	63 (29)	48 (29)	9 (41)
High risk (4-5)	49 (22)	36 (22)	3 (14)
Unknown	23 (11)	20 (12)	0
Prognostic index for PTCLU (%)	PTCL-NOS (n = 49)	PTCL-NOS (n = 42)	PTCL-NOS (n = 2)
Low risk (0)	4 (8)	4 (10)	0
Low-intermediate risk (1)	12 (24)	10 (24)	2 (100)
High-intermediate risk (2)	17 (35)	16 (38)	0
High risk (3-4)	10 (20)	8 (19)	0
Unknown	6 (12)	4 (10)	0
International PTCL project score (%)			
Low risk (0)	85 (39)	65 (40)	10 (45)
Low-intermediate risk (1)	55 (25)	43 (26)	5 (22)
High-intermediate risk (2)	42 (19)	28 (17)	5 (22)
High risk (3)	15 (7)	8 (5)	2 (9)
Unknown	22 (10)	20 (12)	0
Histology (%)			
PTCL-NOS	49 (22)	42 (26)	2 (9)
ATLL	44 (20)	36 (22)	1 (5)
AITL	43 (20)	30 (18)	8 (36)
Transformed MF	14 (6)	5 (3)	6 (27)
Aggressive intestinal TCL	13 (6)	8 (5)	0
ENKTCL	13 (6)	13 (8)	0
ALK-negative ALCL	11 (5)	10 (6)	0
HSTCL	9 (4)	8 (5)	1 (5)
ALK-positive ALCL	6 (3)	6 (4)	0

(Continues)

TABLE 1 (Continued)

Number of Patients	Overall, n = 219 (%)	Chemotherapy, n = 164 (%)	Novel Agents, n = 22 (%)
ITCLPD of the GI tract	6 (3)	1 (0.6)	0
SPTCL	6 (3)	4 (2)	2 (9)
PTCL-NOS, TFH	2 (1)	0	2 (9)
BI-ALCL	2 (1)	1 (0.6)	0
T-PLL	1 (0.5)	0	0
Central nervous system involvement			
No involvement	198 (90)	144 (88)	22 (100)
At diagnosis	9 (4)	9 (5)	0
At progression during natural history	12 (6)	11 (7)	0
Median number of treatments (range)	2 (0-11)	2.5 (1-11)	2 (1-7)
First line therapies			
Chemotherapy (%)	164 (75)	164 (100)	0
CHOP-based	77	77	0
EPOCH	30	30	0
CHOEP/CHEP/COEP	11	11	0
Other	46	46	0
Other (skin directed, steroids, radiation)	23 (11)	0	0
Novel	22 (10)	0	22 (100)
No treatment	10 (5)	0	0
Exposure to novel agents during treatment course (%)			
Clinical trial	77 (35)	5 (3)	16 (73)
Pralatrexate	68 (31)	0	6 (27)
Any HDACI	57 (26)	0	15 (68)
Romidepsin	51 (23)	0	15 (68)
Brentuximab in CD30+ (n = 34)	12/33 (36)	0	0
Transplant during treatment course (%)			
Autologous transplant (autoSCT)	37 (17)	34 (21)	2 (9)
Allogeneic transplant (alloSCT)	19 (8.7)	16 (10)	1 (5)
Exposure to radiation (%)	34 (16)	25 (11)	3 (14)

Abbreviations: PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; ATLL, adult T-cell leukemia lymphoma; AITL, angioimmunoblastic T-cell lymphoma; MF, mycosis fungoides; ENKTCL, extranodal NK/T-cell lymphoma; ALCL, anaplastic large cell lymphoma; HSTCL, hepatosplenic T-cell lymphoma; TCL, T-cell lymphoma; BI-ALCL, breast implant-associated anaplastic large cell lymphoma; T-PLL, T-cell prolymphocytic leukemia; ITCLPD, indolent T-cell lymphoproliferative disorder; GI, gastrointestinal; CHOP/EPOCH/CHOEP/CHEP/COEP-C, cyclophosphamide; H, doxorubicin; O, vincristine; P, prednisone; E, etoposide.

3.4 | Impact of stem cell transplant

Thirty-eight (17%) out of 219 patients received an autologous stem cell transplant (autoSCT) and 19 (8.7%) received an allogeneic stem cell transplant (alloSCT). In our study population, all eight patients who received novel therapies and underwent autoSCT had a CR with a survival advantage compared with those who received chemotherapy and underwent autoSCT as shown in Figure 4D (P = .0462). In the chemotherapy group, 21 achieved CR and nine still had residual disease prior to transplant. When controlled for patients who obtained a CR, the difference was no longer significant between patients who had novel therapies compared with chemotherapy (P = .202). There was no difference in survival between patients who received novel therapies and chemotherapy prior to alloSCT (P = .498).

4 | CONCLUSION

Since the PTCL represent a rare and heterogeneous group of diseases, experiences capturing the varied histology and treatments such as the one reported here can help us better understand the merits of different treatment decisions. The ability to analyze lymphoma datasets from large referral centers over long periods of time offers an opportunity to interrogate important issues, albeit often in a retrospective

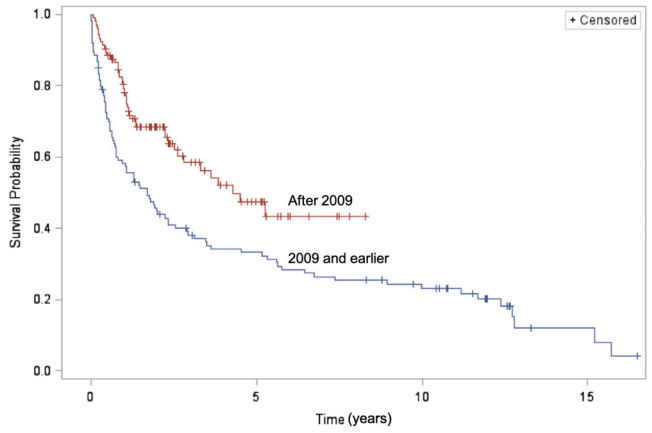

FIGURE 2 The impact of time: Survival curves of patients based on time period of diagnosis. Survival curves of 219 patients based on (A) diagnosis ≤2009 (n = 114): median overall survival 1.71 years (range, 0.82 to 2.34) and ≥ 2010 (n = 105): median overall survival 4.29 years (range, 2.62 to not reached), *P* = .0017

manner. In this 25-year experience, ATLL patients experienced inferior OS compared with those with other types of PTCL, consistent with the literature.[2] It was unclear why Hispanic patients did more poorly, even when controlling for confounding factors, but one consideration may be that Hispanics from the Caribbean are more likely to be diagnosed with ATLL, which portends worse outcomes. More research needs to be done as we could not interrogate the impact of other determinants, including socioeconomic status, adherence to therapy, and insurance status, on outcomes in this data set.

The study population presented herein is notable for the large fraction of patients who have been treated by novel agents and/or on clinical trials, which were associated with a survival benefit. One of the first analyses suggests that patients who were diagnosed in 2010 and later experienced a superior OS to those diagnosed and treated before 2010. While there are certainly a host of factors that might contribute to this, the most obvious relates to the approval of new drugs during and after 2009. The notion that these outcomes after 2010 are attributed in part to the approval of new drugs is further supported by the finding that patients who received novel drugs or care on clinical trials experienced an outcome superior to those who did not in our data and further reinforced by other published reports.[15] Chihara et al[16] at MD Anderson published that treatment with pralatrexate was associated with a significantly longer OS when incorporating PIT risk factors, duration to first line therapy, and eventual transplant in a multivariate analysis. A second study reported by O'Connor et al[17] demonstrated that in a Case Match Control Analysis, patients treated on the PROPEL study experienced a superior OS compared with those who were matched for the eligibility criteria but had not received pralatrexate. Pralatrexate-treated patients were found to have an improved survival of 15.2 months compared with 4.07 months in the control population with a hazard ratio of 0.43 (95% CI, 0.30-0.63). These data also underscored a trend toward greater clinical efficacy as the drug moved earlier in the lines of treatment.

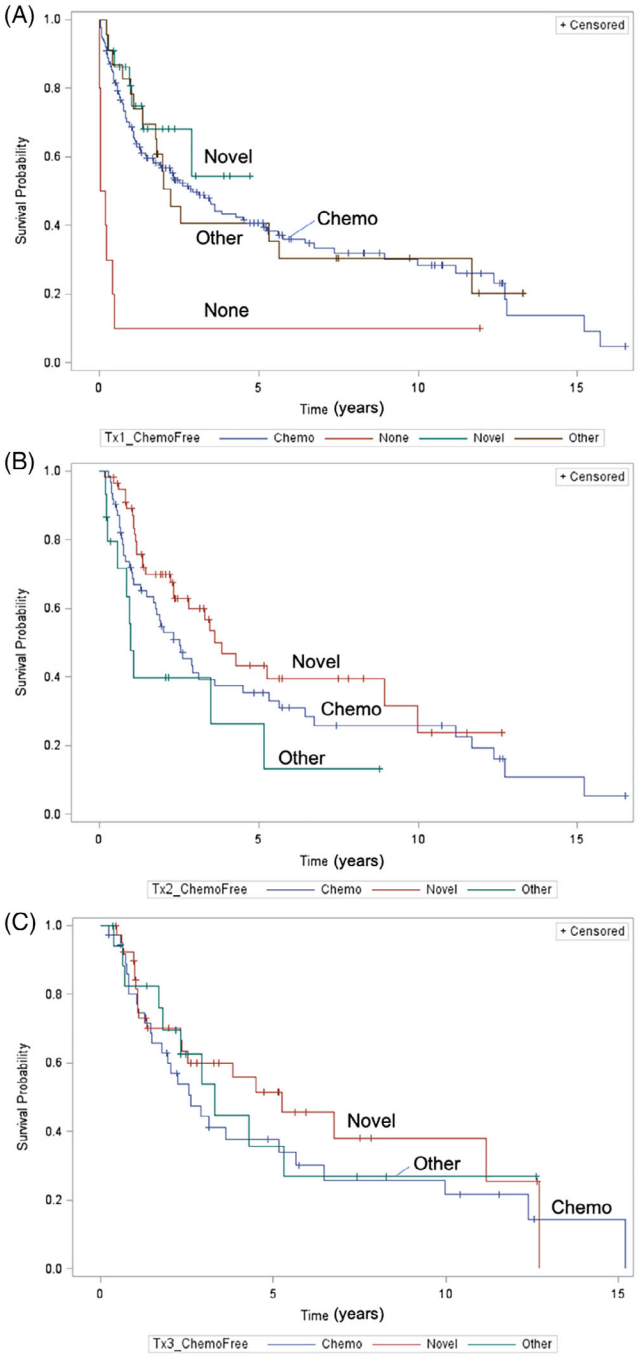

FIGURE 3 Survival curves of patients based on types of therapies according to first, second, or third line of therapy. (A) Survival curves of patients (n = 219) based on first line use of chemotherapy (Chemo), Novel agents alone and in combination (Novel), other, and no treatment (None) (*P* < .0001); (B) Survival of patients (n = 134) based on second line use of the above treatments (*P* = .0417); and (C) Survival of patients (n = 95) based on third line treatments (*P* = .569)

When it comes to treatment, many patients continue to receive chemotherapy throughout the natural history of the disease, despite the suboptimal outcomes of these therapies in the disease. These data suggest that patients are usually exposed to novel agents late during the course of their disease, despite data from the MD Anderson and

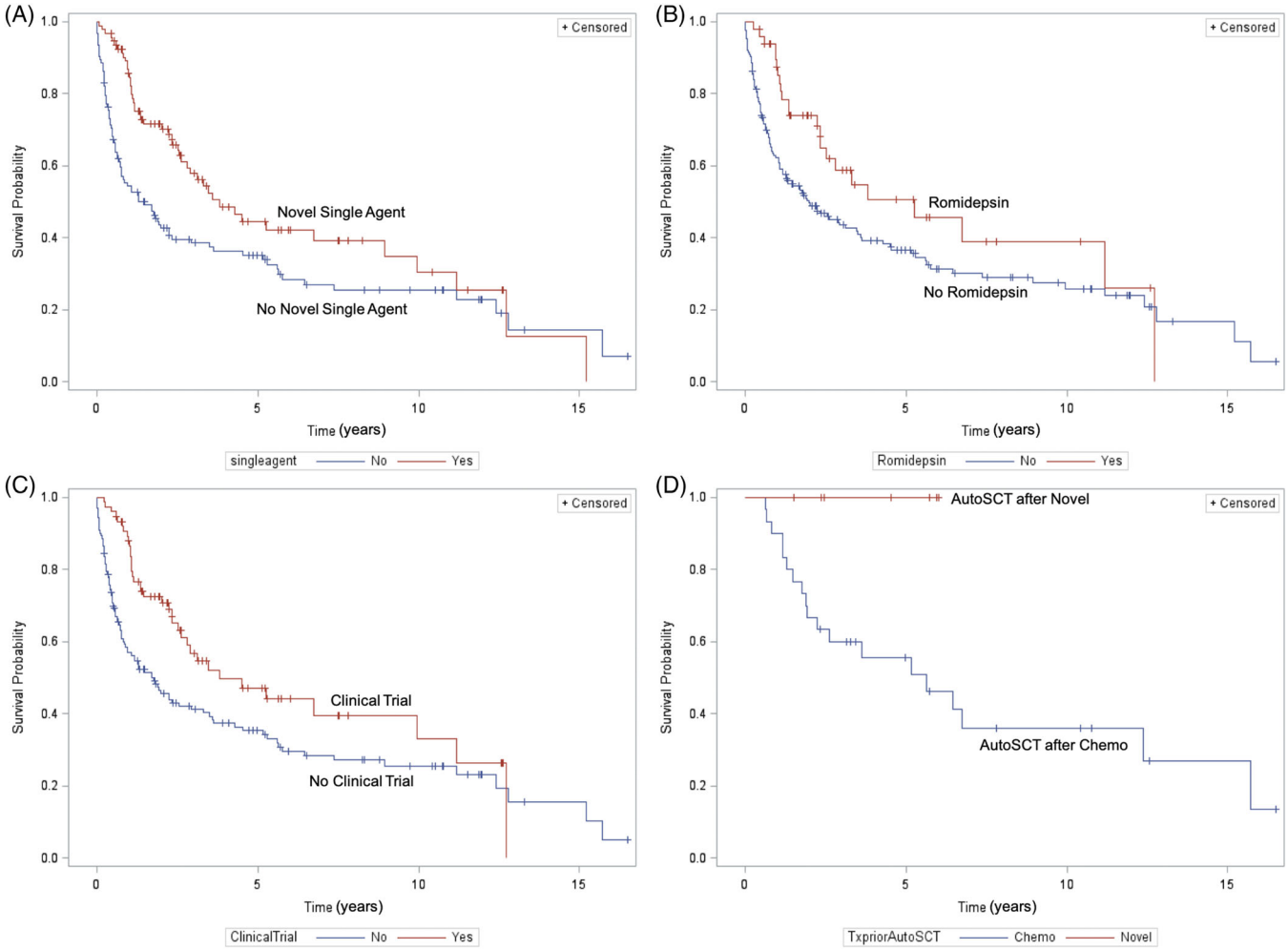

FIGURE 4 Survival curves of patients who received novel therapies compared with patients who did not. Survival curves of patients (n = 219) based on exposure to the following: (A) FDA approved single agents: pralatrexate, HDACi, brentuximab vedotin in CD30-positive patients compared with no FDA approved single agents (P = .003); (B) romidepsin compared with no romidepsin (P = .027); (C) clinical trials compared with no enrollment into clinical trials (P = .006); and (D) autologous stem cell transplant (autoSCT) after novel therapies compared with chemotherapy (P = .0462)

the Case Match Control analyses suggesting that use of these agents sooner is better. Patients who do not respond to chemotherapy in the front line rarely respond to chemotherapy as salvage treatment, highlighting the resistance to additional lines of chemotherapy and the need for earlier use of novel agents alone, in combination, or in clinical trial-based therapy.

Since 1995, there are mixed reports about the impact of frontline autoSCT on survival in patients with PTCL.[18,19] In our population, patients who received novel therapies prior to autoSCT had a longer survival than patients who received chemotherapy. When controlled for patients who proceeded to autoSCT after CR with any type of therapy, the survival advantage was no longer significant, but all patients who had novel therapies achieved CR compared with the 70% of patients who received chemotherapy and achieved CR. Consistent with the International T-Cell Lymphoma Project, patients who received a transplant had a better outcome compared with patients who did not, which may be related to patient, disease or treatment characteristics.[20] Recently, there has been a report that autoSCT and allogeneic stem cell transplant (alloSCT) have no difference in OS or event-free survival, but alloSCT is associated with higher treatment related mortality.[21]

Limitations of the study include systematic error based on the retrospective nature of these analyses, especially with the varied documentation over the span of 25 years. We limited selection bias by confirming diagnoses with our hematopathologist. The 22 patients who underwent novel therapies frontline were older but did not have CNS involvement compared with 164 patients who received chemotherapy, with 4% of patients who had CNS involvement, suggesting more aggressive disease. For patients with limited data, we excluded to minimize information bias, and we censored patients who were lost to follow-up. Understanding that there are limits to the methods of this study, we have insights that can lead to action. We know that patients with ATLL have a worse prognosis and warrant further studies in their disease. We know that patients who undergo autoSCT

after complete remission at any point in their treatment course have an improvement in overall survival with our data suggesting the likelihood is increased with novel therapies compared with chemotherapy, although this warrants further study. Finally, we know patients who enroll in clinical trials have better outcomes, which support improving enrollment rates.

AUTHOR CONTRIBUTIONS

H.M. conceived the idea, performed the literature search, gathered the patient data, and wrote the manuscript. L.F., E.M., A.S., O.A.O. provided cases and clinical care to patients and contributed to the manuscript. G.B. provided cases, confirmed the histologic diagnoses, and contributed to the manuscript. B.C. performed the statistical analysis. All authors analyzed the data, critically reviewed the manuscript, and approved the final version.

ACKNOWLEDGEMENTS

C.K.N. inspired this work. The authors would like to thank the patients and their families who entrusted us with their care.

CONFLICT OF INTEREST

H.M., B.C., L.F., and G.B. have nothing to report. E.M. received research support from Celgene, Merck, and Spectrum and has a scientific advisory role for Mundipharma, Verastem, and Spectrum. A.S. received research support from Affimed and consultancy fees from Seattle Genetics, Gilead, and Daiichi Sanko. O.A.O. received research funding from Affimed, Agensys, Celgene, Merck, Seattle Genetics, Spectrum, TG Therapeutics, and Trillium and has a scientific advisory role for Celgene (Data Safety Monitoring Committee), Mundipharma, and TG Therapeutics (Travel support only).

ORCID

Helen Ma https://orcid.org/0000-0002-0416-5115

REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-2390.
2. Vose J, Armitage J, Weisenburger D, International TCLP. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol*. 2008;26(25):4124-4130.
3. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med*. 1993;328(14):1002-1006.
4. Schmitz N, Trumper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German high-grade non-Hodgkin lymphoma study group. *Blood*. 2010;116(18):3418-3425.
5. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet*. 2019;393(10168):229-240.
6. Mak V, Hamm J, Chhanabhai M, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. *J Clin Oncol*. 2013;31(16):1970-1976.
7. Lansigan F, Horwitz SM, Pinter-Brown LC, et al. Outcomes for relapsed and refractory peripheral T-cell lymphoma patients after front-line therapy from the COMPLETE registry. *Acta Haematol*. 2019;1-11. https://doi.org/10.1159/000500666
8. O'Connor OA, Horwitz S, Masszi T, et al. Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: results of the pivotal phase II BELIEF (CLN-19) study. *J Clin Oncol*. 2015;33(23):2492-2499.
9. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *J Clin Oncol*. 2011;29(9):1182-1189.
10. Coiffier B, Pro B, Prince HM, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol*. 2012;30(6):631-636.
11. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol*. 2012;30(18):2190-2196.
12. Shi Y, Dong M, Hong X, et al. Results from a multicenter, open-label, pivotal phase II study of chidamide in relapsed or refractory peripheral T-cell lymphoma. *Ann Oncol*. 2015;26(8):1766-1771.
13. Maruyama D, Tsukasaki K, Uchida T, et al. Multicenter phase 1/2 study of forodesine in patients with relapsed peripheral T cell lymphoma. *Ann Hematol*. 2019;98(1):131-142.
14. Salhany KE, Cousar JB, Greer JP, Casey TT, Fields JP, Collins RD. Transformation of cutaneous T cell lymphoma to large cell lymphoma. *A Clinicopathologic and Immunologic Study*. *Am J Pathol*. 1988;132(2):265-277.
15. Stuver RN, Khan N, Schwartz M, et al. Single agents vs combination chemotherapy in relapsed and refractory peripheral T-cell lymphoma: results from the comprehensive oncology measures for peripheral T-cell lymphoma treatment (COMPLETE) registry. *Am J Hematol*. 2019;94(6):641-649.
16. Chihara D, Fanale MA, Miranda RN, et al. The survival outcome of patients with relapsed/refractory peripheral T-cell lymphoma-not otherwise specified and angioimmunoblastic T-cell lymphoma. *Br J Haematol*. 2017;176(5):750-758.
17. O'Connor OA, Marchi E, Volinn W, Shi J, Mehrling T, Kim WS. Strategy for assessing new drug value in orphan diseases: an international case match control analysis of the PROPEL study. *JNCI Cancer Spectrum*. 2018;2(4):pky038.
18. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med*. 1995;333(23):1540-1545.
19. Sharma M, Pro B. Bone marrow transplantation for peripheral T-cell non-Hodgkins' lymphoma in first remission. *Curr Treat Options Oncol*. 2015;16(7):34.
20. Bellei M, Foss FM, Shustov AR, et al. The outcome of peripheral T-cell lymphoma patients failing first-line therapy: a report from the prospective, international T-cell project. *Haematologica*. 2018;103(7):1191-1197.
21. Shmitz N, Truemper L, Ziepert M, et al. First-line therapy of T-cell lymphoma: allogeneic or autologous transplantation for consolidation—final results of the AATT study. *J Clin Oncol*. 2019;37(15_suppl):7503.

How to cite this article: Ma H, Cheng B, Falchi L, et al. Survival benefit in patients with peripheral T-cell lymphomas after treatments with novel therapies and clinical trials. *Hematological Oncology*. 2020;38:51–58. https://doi.org/10.1002/hon.2705