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Management of Angioimmunoblastic T-Cell Lymphoma (AITL) and other T Follicular Helper Cell lymphomas (TFH PTCL)

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ABSTRACT

Despite the remarkable improvements in the treatment and outcome of patients with aggressive B-cell lymphoma, the peripheral T-cell lymphomas (PTCL) continue to carry a poor prognosis with the presently available treatment options. The PTCL are very rare diseases that account for only 10,000 to 15,000 new cases per year in the United States. The World Health Organization's 2016 classification describes 29 distinct subtypes of PTCL, thus making these both rate and incredibly heterogenous. The 2 most common forms of PTCL, for example, peripheral T-cell lymphoma-not otherwise specified and angioimmunoblastic T-cell lymphoma , have an incidence of only 2500 and 1800 cases per year respectively, in the United States

Recently, molecular insight into the pathogenesis of the PTCL has revealed that the PTCL are characterized by recurring mutations in epigenetic genes governing DNA methylation, including *TET2, IDH2,* and *DNMT3*. Interestingly, the mutations in epigenetic genes are most pronounced in select subtypes including angioimmunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphoma T follicular helper cell (PTCL TFH) subtypes.

Over the past 30 years, CHOP (ie cyclophosphamide, doxorubicin, vincristine and prednisone) and CHOP-like regimens have been considered the standard of care for patients with PTCL based on clinical experiences that were largely extrapolated from patients with aggressive B-cell malignancies. It should then come as no surprise that patients with PTCL exhibit a much worse outcome and clearly represent an unmet need.

In the relapsed or refractory setting, pralatrexate and histone deacetylase (HDAC) inhibitors, including romidepsin and belinostat, have been FDA-approved now for nearly a decade. Despite the improved understanding of the underlying pathogenetic mechanisms and the availability of new drugs, treatment is still agnostic to the disease subtype, save a few well-known examples (eg anaplastic large cell lymphoma and CD30-positive PTCL).

Interestingly, several lines of recent data have suggested that the treatment of patients with novel drugs and/or on a clinical trial may be associated with superior outcomes compared to conventional chemotherapy. These retrospective analyses have led to a number of innovative prospective studies exploring the merits of novel drug combinations in PTCL. Additionally, unplanned retrospective subset analyses not powered to identify relationships between subtype vulnerability to 1 drug or another have demonstrated that AITL and PTCL TFH might have a greater vulnerability to HDAC inhibition. These findings, all largely predicated on combinations with HDAC inhibitors, are beginning to suggest that select subtypes of PTCL, namely AITL and PTCL TFH subtype, appear to exhibit a provocative sensitivity to these platforms. Herein, we will review the scope of this evidence, discussing the merits of both conventional and novel drugs, in an effort to define the most efficacious strategies now available to treat patients with AITL and PTCL TFH subtype.

Historic overview

Angioimmunoblastic T-cell lymphoma (AITL) is a lymphoid malignancy characterized by intense inflammatory and immune reactions that in the 1970s was described as "immunoblastic disease" [1], "angioimmunoblastic lymphadenopathy with dysproteinemia" [2], or "immunoblastic lymphoadenopathy" [3]. Subsequently, a proportion of cases described as angioimmunoblastic lymphadenopathy with dysproteinemia and immunoblastic lymphoadenopathy were considered to actually be malignant lymphomas of either B-cell or T-cell origin [4]. By the end of the 1980s, the scientific community reached the consensus that these entities were in fact malignant lymphomas of T-cell origin. The term "an-

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gioimmunoblastic T-cell lymphoma" was finally introduced by the Revised European and American Classification of Lymphoid Neoplasm in 1994 [5] and subsequently the World Health Organization (WHO) classification. By the early 2000s, with the development of gene expression profiling techniques, the normal counterpart of the malignant T-cell was identified as a T-follicular helper cell. It was only in 2016 that the WHO defined a new umbrella category, "AITL and other nodal T-cell lymphomas of TFH origin," that presently includes 3 diseases: [1] AITL, [2] follicular T-cell lymphoma and [3] a newly defined nodal PTCL with TFH phenotype (PTCL-TFH) [6]. The recognition of this novel category was largely based on the identification of genetic mutations in epigenetic factors (eg *TET-2, DNMT3A, IDH2,* and *RHOA*) clustering in these specific new entities.

Epidemiology

Each year, only 10,000 to 15,000 cases of PTCL are diagnosed in the United States [7]. To date, with nearly 30 distinct subtypes, the PTCL are a group of both rare and heterogeneous diseases with some of the poorest outcomes of any hematologic malignancy (6). According to the International Peripheral T-cell and Natural Killer/T-cell Lymphoma study, AITL typically accounts for 21.1% of PTCL making it the second most common subtype of (PTCL) worldwide after peripheral T-cell lymphoma not otherwise specified (PTCL NOS) [7]. The disease exists most commonly in Europe (28.7%), Asia (17.9%), and North America (16%).

AITL has been traditionally considered a PTCL subset characterized by marked chemotherapy resistance and a very poor prognosis with expected 5-year overall OS of 32%, compared with, for example, 70% in patients with ALK-positive anaplastic large cell lymphoma (ALCL) [7]. While there is a clear unmet medical need in AITL, recent insight into its pathogenesis, along with promising pre-clinical and early clinical data, have firmly established that drugs targeting the AITL epigenome may hold particular promise.

Clinical manifestations and diagnosis

AITL is characterized by constitutional symptoms, lymphadenopathy, hepatosplenomegaly, and dysgammaglobulinemia, especially in older patients [2]. Clinically, patients with AITL generally present with acute onset illness characterized by diffuse lymphadenopathies, hepatosplenomegaly, rash and systemic symptoms including fever, unintentional weight loss and night sweats. Interestingly, AITL is also often associated with autoimmune hemolytic anemia, vasculitis, polyarthritis, rheumatoid arthritis, and thyroid disease along with immunologic laboratories abnormalities including plasmacytosis, polyclonal hypergammaglobulinemia, and a positive Coombs test [8,9].

A lymph node biopsy is mandatorily required to make the diagnosis. AITL is characterized by partial or total effacement of the lymph node architecture, often with perinodal infiltration but sparing of the peripheral cortical sinuses. Cytologically, the neoplastic T-cells of AITL are small to medium-sized lymphocytes, with clear to pale cytoplasm, distinct membranes and minimal cytological atypia [6]. They form frequently small clusters, often adjacent to high endothelial venules. Vascularity is prominent. Typically, the neoplastic cells are present in a polymorphous inflammatory background containing variable numbers of reactive lymphocytes, hystiocytes, plasma cells, and eosinophils. The immunophenotype of the neoplastic cells is positive for the pan-T antigens including CD3, CD2, and CD5 and in the vast majority of cases are positive for CD4. Surface CD3 might be reduced or absent by flow cytometry. Variable numbers of reactive CD8-positive T cells can be present. Characteristically, the tumor cells show the immunophenotype of normal TFH cells, expressing CD10, CXCL13, ICOS, BCL6, and PD1 in 60-100% of cases [6]. These findings are also useful in distinguishing AITL from atypical paracortical hyperplasia and other PTCL, which have been shown to be consistently upregulated in the AITL. These findings suggest that the cell of origin is the germinal center TFH cell [10-23]. Other subtypes with similar clinic-pathologic characteristics and cell of origin have emerged in the last 3-5 years.

Molecular pathogenesis

"The strange case" of AITL has demonstrated that often times the development of new treatments does not follow the sequence of identification of deranged molecular pathways prior to discovery and development of novel effective therapeutics but quite the opposite. If there is a recurring theme that seems to be consistent in the molecular pathogenesis of AITL and PTCL TFH, it surely relates to the gross epigenetic dysregulation seen across these particular subtypes. The first clue into this biology emerged empirically from the clinic following the approval of a number of HDAC inhibitors for the treatment of PTCL [24-26]. As a class of drugs, the HDAC inhibitors exhibit consistent and reproducible activity of an overall response rate (ORR) of approximately 25% in the diverse spectrum of PTCL [24-26]. PTCL are the only disease for which HDAC inhibitors are approved as a single agent, with four different HDAC inhibitors approved around the world for the disease. Though only 25% of patient can expect a response to an HDAC inhibitor, the duration of response seen across these drugs across the diversity of the PTCL is impressive, usually lasting more than a year [24-26].

Despite the well-established clinical activity of HDAC inhibitors in these diseases, it was only in the mid-2010s that it became clear that epigenetic dysregulation was a common feature seen in the pathogenesis of AITL and PTCL - TFH. Many lines of genetic data demonstrated several recurring mutations in genes governing a host of epigenetic functions, including *DNMT3A, IDH2, TET2, MLL2, KMT2A, KDM6A, CREBBP,* and *EP300* [27-32]. Most of these mutations occurred in genes involved in DNA methylation, predominantly including *IDH2, TET2,* and *DNMT3* [33,34]. These mutations, which appear to be more commonly found in AITL and PTCL TFH, conspire to produce genome wide hypomethylation and gene silencing of likely tumor suppressor genes. While heterozygous mutations in *IDH2* have been found in many different cancers, including solid tumors (glioblastoma multiforme; GBM) and hematologic malignancies (especially acute myeloid leukemia; AML), they have been found in only approximately 20% (17/85) of AITL cases, making it the second most common mutation found in AITL [35]. A confirmatory study exploring these mutations found that 45% (10/22) of AITL cases carry the *IDH2* mutation [33]. Interestingly, the spectrum of mutations seen in AITL was different from other neoplasms. *IDH1* mutations were not found in AITL, though they were seen in glioma and AML, and the mutations detected were at a different locus, namely R172 [33,35,36]. Also different is the finding that *IDH2* mutations appear to have no impact on overall survival (OS) of patients with AITL or AML, though they do seem to portend a more favorable OS in patients with gliomas [37]. This biology appears unique to the T-cell neoplasms, as *IDH* mutations are typically not found in patients with B-cell or Hodgkin lymphoma. Biochemically, wild type IDH2 converts isocitrate to α-ketoglutarate (α-KG), which is a critical co-factor in α-KG dependent enzymes (oxidative demethylases) such as TET2 and KDM, which normally promote demethylation of DNA and histone proteins [38,39]. Mutant IDH2 converts isocitrate to R-2-hydroxyglutarate (2-HG) which impairs α-KG dependent enzymes leading to increased genome wide methylation [33].

Another unanswered question in AITL revolves around the role that Epstein-Barr virus (EBV) infection plays into the pathogenesis of the disease. Curiously, EBV viral RNA has been detected in 71% to 96% of cases of AITL [40,41]. Though EBV is often de-

tected, the virus has not been determined to be the causative agent in pathogenesis, but rather an opportunistic infection in the setting of immunodeficiency even though contrasting theories have been explored [42]. Occasionally, the immunosuppression related to AITL leads to EBV reactivation that progresses to produce both monoclonal and polyclonal populations of large CD20-positive B-cells [43,44]. Composite AITL and EBV-associated B-cell lymphomas have been described and are likely due to the uncontrolled infection associated with immunosuppression from the lymphoma and/or treatment of the disease [45-49]. Despite the correlation between EBV and AITL, the impact on prognosis and treatment approach remains unclear. EBV-positivity has been reported as having no impact as well as having an improved prognosis in younger patients with EBV-positive AITL [50,51]. The addition of the monoclonal antibody targeting CD20, rituximab, to CHOP chemotherapy has been studied to treat AITL, though there was no clear benefit in this disease entity [52].

As these and other data begin to fill in the gaps in our knowledge of these diseases, our improved understanding of the genomic landscape in PTCL holds the prospect of refining the diagnosis, prognosis, and management of PTCL. Treatment approaches for patients with PTCL are moving away from the so-called "standard" combination chemotherapy towards T-cell specific platforms that will leverage the improved knowledge of pathogenetic mechanisms with the availability of novel drugs and drug combination in these challenging diseases.

First line treatment

Combination chemotherapy

In the landmark study establishing CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) as standard first line therapy for patients with aggressive lymphomas, Fisher et al. enrolled histologies according to the Non-Hodgkin's Lymphoma Pathologic Classification Project, which included aggressive lymphomas [53]. This broad category included patients with aggressive B- and T-cell malignancies, with little detail regarding the discrete histologic features of the treated patient population. Given the limitation in diagnostic tools at the time in which this trial was conducted and the historic trial design, it has not been possible to discern precisely the outcomes for patients with PTCL as a function of the 4-arms in the study. By default, CHOP became the *de facto* standard of care for patients with PTCL despite the lack of disease-specific analysis of the trial results. It should then come as no surprise that CHOP has produced inferior results in patients with PTCL. A large multicenter cohort showed that PTCL patients treated with CHOP-like therapy experienced a 3-year progression free survival (PFS) and OS of only 32% and 55%, respectively [54]. Based on the experience reported by Pautier et al., 33 patients with AITL who had been treated with CHOP had an overall ORR of 61% and a 5-year OS of only 36.2%. These reports appear consistent with the data published by the International Peripheral T-cell and NK-cell Lymphoma Study [8]. In trying to build on the efficacy of CHOP, a multicenter, international, phase III trial comparing six cycles of romidepsin plus CHOP (Ro-CHOP) with the standard of care (CHOP) was initiated. Unfortunately, the addition of the HDAC inhibitor to the combination chemotherapy backbone led to high rates of treatment related adverse events limiting treatment administration without improvement in response rates, PFS, or OS [7,55]. Despite the association with EBV and CD20-positive B-cell lymphomas, the addition of rituximab to CHOP also did not show clear benefit in a phase 2 trial (NCT00169156) as previously mentioned. The ORR of the combination was 80% (CR 44%) with an overall survival of 62% after a follow up of 2 years [52]. Based on these lines of evidence, it has become clear that that the so-called standard of care with CHOP for patients with PTCL leads to unsatisfactory results, producing an urgent need for more effective treatments. As a testament of this recognition, the scientific community in the most recently published National Comprehensive Cancer Network guidelines recommends enrollment in clinical trials for newly diagnosed PTCL.

While advances have come slowly to the field, the recently published results of the ECHELON-2 trial have now changed the front-line standard of care for patients with ALCL, raising new questions regarding the universal applicability of the regimen across other PTCL subtypes not necessarily characterized by an abundance of CD30 expression. The Bv-CHP regimen (brentuximab vedotin [the antibody drug conjugate linking a monoclonal antibody targeting CD30 and antimitotic agent monomethyl auristatin E], cyclophosphamide, doxorubicin, and prednisone) has received FDA approval for all newly diagnosed patients with CD30-positive PTCL, despite the fact that non-ALCL patients comprised only a minority of the trial population compared to ALCL [56]. The ECHELON-2 trial was designed to have 75% target accrual of patients with ALCL and was not powered to perform any subgroup analysis in any other PTCL subtypes. Interestingly, only 54 of 452 patients carried a diagnosis of AITL and were randomly assigned to receive either Bv-CHP versus CHOP. While the study demonstrated a survival benefit for the population, though there was no statistically significant advantage seen in the particular subtypes including AITL and/or PTCL-NOS with CD30 expression. Nonetheless, Bv-CHP is now considered an accepted front-line therapy for patients with CD30 positive AITL, though some have suggested this should be restricted to the ECHELON population where 10% or greater CD30 expression was required for study entry.

Second line approved treatments

Inevitably, approximately 70% of patients with PTCL will develop relapsed or refractory disease. These patients have an especially poor prognosis. In an analysis by the British Columbia Cancer Agency Lymphoid Cancer database, 191 patients with relapsed and refractory (R/R) PTCL had an extremely short median PFS of 3.1 months and median OS of 5.5 months [57]. In AITL specifically, the MD Anderson Cancer Center published data revealing that the failure free survival and OS of patients with each subsequent progression or relapse was associated with progressively worse outcomes [58]. Patients with AITL ($n = 105$) had a median failure free survival after frontline therapy, second line therapy, and third line therapy that was reported to be 5.5 months, 2.9 months, and 2.3 months, respectively. The OS after frontline, second line, and third line therapy was 15 months, 8.3 months, and 6 months, respectively [58].

Chemotherapy is commonly used in subsequent lines of therapy after failing frontline CHOP but both retrospective and prospective registries have shown that combination chemotherapy may be associated with an inferior survival compared to novel, targeted therapies [59,60]. In an analysis by Ma et al., 134 R/R PTCL patients, there was a survival benefit favoring novel agents, including HDAC inhibitors, pralatrexate, and clinical trials, over second line chemotherapy (median OS 3.8 years compared to 2.5 years, $P = .0417$) [59]. The COMPLETE database also reported that PTCL patients receiving second line therapies had higher response rates as well as longer median OS with novel agents, such as HDAC inhibitors, pralatrexate, brentuximab vedotin, compared to combination chemotherapy with additional details listed below [60].

Although there is no standard of care for patients with any R/R PTCL including AITL, there are many novel therapies approved for these patients including the following: [1] pralatrexate, [2] romidepsin, [3], belinostat, [4] brentuximab vedotin in CD30-positive ALCL and mycosis fungoides, [5] chidamide only in China, and [6] forodesine only in Japan. Table 1 lists the response rates to var-

Table 1
Response rates in relapsed or refractory PTCL versus angioimmunoblastic T-cell lymphoma patients treated with single agent therapy.

Trial	Number of overall patients	ORR overall	Number of AITL patients	ORR AITL	Reference
Alisertib (phase 3)	138	33%	31	32%	[75]
Pralatrexate (phase 2)	109	29%	13	8%	[62]
Romidepsin (phase 2)	130	25%	27	33%	[24,68]
Belinostat (phase 2)	120	25.8%	22	45.5%	[25,69]
Chidamide (phase 2)	79	28%	10	50%	[26]
Brentuximab vedotin (phase 2)	35	41%	13	54%	[71]
Duvelisib (phase 1)	16	50%	3	66%	[74]

ious single agent treatments in PTCL cohorts as well as in the AITL subsets.

As mentioned above, multiple lines of evidence in support of novel drugs, including pralatrexate, HDAC inhibitors, and brentuximab vedotin, in PTCL have been recently published [59,60]. One analysis demonstrated that any exposure to novel agents during a patient's treatment course was associated with improvement in OS compared to patients without exposure to novel therapy [59]. While the numbers are small, a higher proportion of patients who received novel therapies (8/8) achieved CR prior to autologous stem cell transplant compared to patients who received combination chemotherapy (21/30). Among patients who underwent autologous stem cell transplant, achieving a CR was the most important predictor of prolonged survival regardless of whether patients received chemotherapy or novel agents. In addition, the COMPLETE database revealed that in the relapsed or refractory setting, there was an increase in response rate in patients who received single agents, including pralatrexate, HDAC inhibitors, and brentuximab vedotin, compared to combination chemotherapy (41% vs 19%, $P = .02$) as well as median OS (28.9 months vs 17.1 months, $P = .02$) [60]. This analysis also demonstrated a higher percentage of patients receiving single agents proceeded with autologous stem cell transplant compared to patients who received combination chemotherapy.

Though the various novel agents represent a vast repertoire of different mechanisms of action, they share many clinical similarities including lineage selectivity, overall and complete response rates and survival benefit across the heterogeneity of PTCL subtypes. Pralatrexate, the first drug ever approved for patients with relapsed or refractory PTCL, is a folate analogue that binds the reduced folate carrier , which internalizes the drug where it inhibits dihydrofolate reductase (DHFR) [61]. Gene expression profiling revealed that pralatrexate exhibits a very unique gene expression profiling pattern compared to methotrexate, suggesting that the exquisite sensitivity of PTCL to this drug could be related to the modulation of pathways unrelated to DHFR including lymphocyte activation, methylation, cytokine response [unpublished data]. PROPEL was an international single arm Phase 2 study conducted in patients with R/R PTCL. Of note, the PROPEL patient population remains the most heavily treated population ever studied in this setting, with a median number of prior therapies of 3, and 20% of patients receiving more than 5 lines of prior treatment. PROPEL demonstrated an ORR of 29% with a CR rate or unconfirmed complete response (CRu) rate of 11%, with an updated PFS and duration of response (DOR) of 3.5 and 12.4 months. The PROPEL study led to U.S. FDA accelerated approval of pralatrexate in patients with R/R PTCL in 2009. In order to gain a better understanding of the drug's activity in this setting, O'Connor et al. conducted a number of analyses on the PROPEL dataset. The first observation relates to an analysis of primary and secondary endpoints as a function of the line of therapy. These data demonstrated that for patients with 3 or more lines of prior therapy ($N = 57$), the ORR, CR, PFS, and DOR were 29.8%, 7%, 1.7 months and 8.2 months, respectively. For patients with 2 lines of prior therapy, those same metrics were 24.1%, 10%, 3.2 months and 10 months, respectively, while for patients with only 1 line of prior therapy the same metrics were 35%, 17%, 8 months and not reached at 2 years. These data suggest that using pralatrexate earlier in the natural history of the disease may produce a greater clinical benefit. While randomized studies are the gold standard to determine OS benefit, single arm studies are more often than not the only data regulatory agencies have to assess clinical benefit in orphan diseases. Given the paucity of patients, time required to conduct these studies, and the cost, sponsors are often left trying to make decisions regarding the merits of randomized studies in orphan diseases, where commercial return on investment is substantially less than it is for other diseases. In an effort to understand the OS impact of pralatrexate, a case matched control analysis of the PROPEL dataset was performed [62]. An international database of 859 patients with PTCL was assembled from 4 international institutions who maintained well annotated registries of their respective patient populations. About 386 of the original 850 patients were considered eligible for matching against the PROPEL criteria. The analysis used a propensity score matching algorithm and demonstrated an OS benefit for the PROPEL population versus historical cohort, with a median OS of 4.07 versus 15.24 months (hazard ratio of 0.432). Highly statistically significant improvements in survival were noted for the PROPEL population with regard to all variables explored, including the subtype of PTCL (save ALCL where the curves were superimposable, suggesting equivalency), and age, where elderly (> 65 years of age) exhibited one of the most significant benefits. While not a prospective randomized study, the analysis does provide another layer of information about how to assess drug benefit in a more rigorous statistical setting.

In the scientific community, some have suggested that pralatrexate activity in AITL appears inferior compared to other PTCL subtypes. A post-hoc pooled analysis in a subset of twenty-nine patients with R/R AITL drawn from 2 prospective registration trials completed in China and Japan was performed to provide insight on efficacy of pralatrexate monotherapy in this subtype. After a median of 2 prior lines of therapy, the overall response rate was 52% (15/29 patients; 95% CI 0.34, 0.70). The estimated median DOR, PFS and OS were 6.4, 5.0, and 18.0 months, respectively. These results of this analysis, along with data from 2 United States retrospective cohorts, supported the potential benefits of pralatrexate monotherapy also in patients with R/R AITL [64].

Confirming the findings made by O'Connor et al., Chihara et al. collected data on 105 AITL patients who had relapsed after or were refractory to first line therapy. Subsequent lines of therapy included chemotherapy, HDAC inhibitors, pralatrexate, and investigational drugs. What is particularly notable is that in a multivariate analysis, treatment with pralatrexate at any time during the clinical course of the AITL patients was associated with a survival benefit (hazard ratio of 0.39, 95% confidence interval: 0.16-0.97, $P = .044$) [63]. These studies suggested that earlier use of pralatrexate is likely to be more effective than when used in later lines of

treatment. Interestingly, some have suggested that pralatrexate has less activity in AITL compared to other drugs approved in this setting. It is important to recognize that the studies reported to date were never intended to support subset analyses of this sort. In fact, the earlier activity noted with romidepsin in AITL demonstrated an ORR of only 8%. Despite the small numbers, and lack of any comparative studies, the National Comprehensive Cancer Network has suggested that pralatrexate should not be considered in AITL. Testament to the point, recent pooled analysis on the activity of pralatrexate from two registration trials in China and Japan demonstrate an ORR, median DOR, median PFS, and median OS in AITL specifically of 52%, 6.4 months, 5.0 months, and 18.0 months, respectively [64]. It is unlikely these differences are explained by ethnic differences, and likely reflects a growing experience with the drug, and possibly more familiarity with the use of leucovorin as a supportive care medication which has been shown to reduce the risk of mucositis by the drug [65].

The PTCL are uniquely sensitive to HDAC inhibitors. Presently, there are four HDAC inhibitors that are approved for the disease as follows: romidepsin, belinostat, chidamide (only in China) and vorinostat (only in cutaneous T-cell lymphomas; CTCL). Impressively, across all drugs in the class, there is a higher response rate seen among the patients in the AITL subgroup, suggesting a possible association between the epigenetic dysregulation and likelihood of response to an epigenetic targeted treatment. In the international registration-directed phase II study in patients with R/R PTCL, Coiffier et al.reported that romidepsin produced an ORR of 25% with a median DOR of 28 months [24,66,67]. Subsequent analysis of AITL patients (n = 27) from this trial showed an ORR of 33% compared to 25% overall [68]. The BELIEF study was a phase II registration study of belinostat in patients with R/R PTCL (n = 129), and demonstrated an ORR of 26% with a median DOR of 13.6 months (95% CI 4.5-29.4) [25]. Patients with AITL (n = 22) again seem to have exhibited an improvement in the response rate with an ORR of 45.5% compared to the 26% seen in the entire cohort [69]. Treatment of R/R PTCL patients (n = 79) with chidamide in China produced an ORR of 29% with a median DOR of 9.9 months, similar to the other HDAC inhibitors [26]. In the subgroup analysis, patients with AITL (n = 10) again exhibited an ORR of 50%, which was higher than that seen with any other histology.

Interestingly, a recently published retrospective multicenter analysis showed that patients with PTCL TFH treated with HDAC inhibitors also had a higher ORR (56.5% overall, 54.2% as single agent, and 61.1% in combination therapy) compared to patients with PTCL non-TFH phenotype (29.4% overall, 31.5% as single agent, and 25% in combination therapy), furthering the notion that specific PTCL subtypes, such as AITL and PTCL TFH, might exhibit increased sensitivity to treatment with epigenetic modifiers [70].

Other novel therapies have been studied in R/R PTCL with variable efficacy. Brentuximab vedotin has been studied in relapsed or refractory CD30-positive PTCL NOS (n = 22) and AITL (n = 13) patients [71]. Historically, CD30 expression of 1+ or more by immunohistochemistry ranges from 42.8% to 63% in AITL [72,73]. In this study, the ORR was 41% in the entire cohort whereas the ORR was 54% in the AITL subset, suggesting improved efficacy as single agent in this subset. Duvelisib is an inhibitor of phosphatidylinositol 3-kinase, which may play an important role in lymphoid malignancies, and has been shown to have an ORR of 50% in 16 patients with PTCL, including 3 patients with AITL [74]. The phase III LUMIERE trial compared physician's choice with alisertib, an aurora A kinase inhibitor, which was associated with an ORR, median PFS, and median OS of 33%, 3.8 months, and 13.7 months in patients with R/R PTCL [75]. Based on the success obtained treating other hematological malignancies and solid tumor, treatment with immune checkpoint inhibitors as single agent in PTCL has limited success so far. Pembrolizumab was shown to have an ORR of 33% in 15 patients with R/R PTCL and 25% (1/4) in follicular T-cell lymphomas including AITL [76]. The trial was terminated early due to futility. Nivolumab, another PD1 inhibitor, was associated with an ORR of 33% (4/12) in all comers and 1/6 in AITL but also with hyperprogression during treatment in 10 of 12 patients, including those with AITL [77]. The trial was also terminated early due to futility and safety concerns. It is likely that, as with many drugs with a primary immunologic effect, these agents might be substantially more active with other rational combinations, like HDAC inhibitors and hypomethylating agents. Additional trials that are employing immune checkpoint inhibitors in combination with epigenetic modifiers are not confirming the occurrence of hyperprogression, suggesting that the mechanism of action of these drug could be still be advantageous in this disease. Lastly, Inducible T-cell costimulator (ICOS) has been targeted due to its expression in T follicular lymphomas, and treatment with MEDI-570, an anti-ICOS antibody, is associated with ORR of 33% (4/12) in AITL [78].

Given the stable ORR in the treatment of PTCL with single agent therapies, the field has looked to improve outcomes by tailoring treatments in a disease-specific fashion or by combining synergistic and complementary drugs.

The utility of autologous and allogeneic stem cell transplant is controversial given the lack of systematic, prospective, randomized clinical trials. Autologous stem cell transplant did not show improvement in OS or PFS in 39 patients with AITL in the prospective COMPLETE registry, though there was a trend toward improved OS in those who underwent transplant after first CR [79]. A large retrospective study consisting of 207 Japanese patients with AITL showed a 5-year OS of 41% overall and 47% in 27 patients treated with autologous transplant as first line therapy [80]. No comparison could be made between those who received transplant versus those who did not. As with all retrospective studies, conclusions are limited because data may be confounded with unmeasured patient and disease characteristics. Randomized, prospective clinical trials studying the role of autologous transplant are indicated. Allogeneic stem cell transplant has been retrospectively studied in 45 AITL patients registered in the European Group for Blood and Marrow Transplantation database [81]. Patients had a median age of 48 years (range 23-68 years), 34 patients (76%) had 2 or more prior lines of therapy, and 27 (60%) had chemotherapy-sensitive disease [81]. With a median follow up time of 29 months, estimated 3-year OS, relapse rate at 3 years, and non-relapse mortality at 12 months were 64%, 20%, and 25%, respectively [81]. With high treatment related mortality, the risks and benefits must be weighed in this hard-to-treat patient population, and allogeneic transplant should be reserved for further study in clinical trials.

Tailoring treatment to the disease

Given better insights into the biology of AITL, translational research and clinical trials are in development for disease specific treatment. With the understanding that T-cell lymphomas derived from TFH cell origin have profound epigenetic dysregulation, hypomethylating agents such as azacytidine may have promising activity as shown in a small case series of 12 patients [82]. To further improve clinical efficacy and duration of response, preclinical models testing the combinations of HDAC inhibitors and hypomethylating agents have demonstrated synergistic cytotoxicity across T-cell lymphoma cell lines and murine models [83-85]. As a result, 2 multicenter trials were rationally designed from these data: [1] romidepsin plus oral azacytidine (NCT01998035), and [2] romidepsin plus pralatrexate (NCT01947140). In patients with R/R PTCL, treatment with pralatrexate and romidepsin resulted in an ORR of 71% though the median PFS was short-lived at 4.4 months [86]. Evaluable patients with both treatment naïve and R/R PTCL (n = 23) were treated with oral azacytidine and romidepsin. These trials ex-

Table 2
Response rates in relapsed or refractory PTCL versus angioimmunoblastic T-cell lymphoma patients treated with combination therapy.

Trial	Number of Overall Patients	ORR Overall	Number of AITL patients	ORR AITL	Reference
Panobinostat and bortezomib (phase 2)	23	43%	8	50%	[89]
Romidepsin and azacytidine (phase 2)	23	61%	15	80%	[87]
Romidepsin and pralatrexate (phase 1)	14	71%	0	Not Evaluable	[86]
Pralatrexate and bortezomib (case series)	5	40%	2	50%	[90]

hibited an ORR of 61% with 43% of the patients achieving a CR. Patients with AITL or PTCL TFH (n = 15) had an ORR of 80%, which speaks to the potential of improved clinical efficacy when tailoring treatments to the biology of the disease [87]. Patients with AITL had a median OS that was not reached after a median follow up of 13.5 months compared to 9.4 months in patients with other histologies (HR 0.2, 95% CI 0.03-1, $P = .03$) [87]. These results are astonishing when compared to historic data published by Mak et al.: the combination of azacytidine and romidepsin in the treatment of R/R PTCL more than doubled the PFS and OS, 8 months and 20.6 months, respectively [57,87]. Patients with treatment naïve disease had a median PFS and OS that were not reached after a median follow up of 13.5 months (range, 2.3-33.5 months), suggesting that the combination of epigenetic modifiers could be explored in the frontline setting [87].

Preclinical studies also showed synergistic effects of combining HDAC inhibitors or pralatrexate with proteosome inhibitors [88,89]. Panobinostat, an HDAC inhibitor, and proteosome inhibitor bortezomib produced ORR of 43% in 23 patients with R/R PTCL [89]. A case series showed that the combination of pralatrexate with bortezomib produced an ORR of 2 out of 5 elderly patients with R/R PTCL [90]. One patient with AITL had a complete response whereas another patient with PTCL NOS had a partial response. Table 2 lists the response rates in PTCL cohorts treated with combination therapy as well as the AITL subsets. Though these are steps made in the right direction, more work needs to be done to improve outcomes for patients with AITL.

Currently, numerous clinical trials are investigating various novel backbones of novel agents and immune checkpoint inhibitors. These immune-epigenetic trials explore the value of adding different PD-1 and PD-L1 inhibitors to epigenetic doublet based on preclinical data that showed induction of expression of cancer testis antigens after treatment with azacytidine and romidepsin. The EMBOLDEN and DURABILITY trials have been initiated to study different combinations of immune checkpoint inhibitors with romidepsin, pralatrexate, and hypomethylating agents in R/R PTCL (NCT03240211 and NCT03161223). Preliminary data presented at a scientific meeting in 2020 showed that out of 12 patients treated so far, treatment has been safe and efficacious, especially in the triplet arms [91]. Now building on the established backbone of azacytidine and romidepsin, adding new agents to improve the combination in the treatment of patients with R/R PTCL is a logical next step as with the addition of lenalidomide (NCT04447027) and others to come. In addition, romidepsin and pembrolizumab have been studied in a phase I/II study of 20 patients with R/R PTCL [92]. In the phase II (n = 14), the ORR was 50%, including patients with AITL and PTCL TFH [92]. This study found that PD-L1 expression correlated with response, highlighting potential for a biomarker-driven approach.

With the understanding that chemotherapy-based treatments may be insufficient, there are other trials with other chemotherapy-free combinations, such as romidepsin and carfilzomib – a proteosome inhibitor (NCT03141203), chidamide with a PD-1 inhibitor (NCT04512534), chidamide and lenalidomide (NCT04329130), chidamide, PD-1 blockade with lenalidomide and gemcitabine (NCT04040491); a bispecific antibody combining PD-1 and CTLA-4 (NCT04444141); nivolumab with cabiralizumab, a monoclonal antibody against CSF-1R (NCT03927105). There is a plethora of new targeted agents as the field develops more understanding of PTCL pathogenesis. Studies have built on the chemotherapy backbone by adding various targeted agents based on next generation sequencing results compared to placebo in an umbrella trial (NCT04480099), chidamide (NCT03023358), vorinostat (NCT00601718), decitabine (NCT03553537), nivolumab (NCT03586999), and thalidomide (NCT02879526).

The future of AITL treatment may lie in epigenetic targeted therapies rather than nonspecific combination chemotherapy. With better understanding of the biology, clinical trials are being developed specifically for AITL in the frontline setting: combining CHOP with lenalidomide (NCT01553786, completed 2019 with results pending), azacytidine (NCT03542266), chidamide (NCT03853044), as well as other combinations such as thalidomide with fludarabine and cyclophosphamide (NCT00958854). In an abstract presented at ASH 2020, CHOP and azacytidine resulted in an ORR of 85% (CR 76.5%) in 20 evaluable patients with untreated PTCL. Of the 15 evaluable out of 17 patients with AITL or PTCL TFH, 86.7% achieved CR. After a median follow up of 7 months (range, 4-25 months), the one-year PFS and OS for AITL and PTCL TFH were 61.1% and 88.9%, respectively [93]. Next generation sequencing revealed expected mutations in *TET2, RHOA, DNMT3A*, and *IDH2*. *TET2* mutations were associated with higher rates of CR as well as more improved PFS and OS compared to unmutated *TET2*, suggesting a role for *TET2* mutations as a predictive biomarker. In the relapsed or refractory setting, trials are highlighting the epigenetic dysregulation seen in AITL by comparing azacytidine with investigator's choice (NCT03593018, NCT03703375), or testing AG-221 in patients with *IDH2* mutations (NCT02273739). As more and more therapeutics are being developed at a rapid pace in a constantly changing paradigm, better understanding of biomarkers will be important to determining which patient should get which treatment.

Conclusions

It took two decades for a standard of care to be developed from the discovery of AITL as a disease entity in the 1970s to the development of combination chemotherapy in 1990s. After an additional 20 years, novel therapies such as pralatrexate and HDAC inhibitors were approved to treat PTCL in the relapsed and refractory setting, finally revealing some insights into the pathophysiology of the disease. Though it is true that PTCL are incredibly rare and heterogeneous, limiting robust phase III clinical trial data to guide treatment decisions, there are creative ways around these circumstances. The field is continually developing as more is understood about the complex lymphomagenesis derived from the pleiotropic effects of epigenetic dysregulation. Now, almost fifty years after the first published reports of AITL, the treatment paradigm is shifting away from combination chemotherapy toward classes of drugs known to mitigate the underlying disease processes. In the past, AITL was a disease that was mostly described without many treatment options. With this evolving knowledge, clinical trials studying new drugs are being developed to target proteins that had previ-

ously only been reported as positive stains by immunohistochemistry, such as PD1 and ICOS. AITL had traditionally been a subtype of PTCL with a worse prognosis but clinical trials have shown that given the right treatment, patients can do well. Ideally, this targeted approach will increase efficacy and decrease toxicity in the treatment of this group of orphan diseases.

Given the rarity of the disease, international and multicenter consortiums and collaborations will be vital in enrolling patients to clinical trials so that key questions are answered in a timely manner. These answers will guide how novel treatment platforms are developed and how AITL patients can derive the most benefit from these efforts.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

Helen Ma declares no competing interests. Owen A. O'Connor has received research support from Spectrum, Celgene, Merck, Affimed, and Seattle Genetics; and has had a scientific advisory role with Mundipharma. Enrica Marchi has received research funding from Merck, Celgene, and Astex; and has had a scientific advisory role with Myeloid Therapeutic and Kyowa Kirin.

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