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EVOLVING STRATEGIES IN T-CELL LYMPHOMA

Background

Peripheral T-cell lymphomas (PTCL) are derived from post-thymic, mature T-cells and represent a clinically and biologically heterogeneous group of diseases. A common feature of the majority of PTCLs is a poor prognosis compared to their aggressive B-cell counterparts. Additionally, due to the rarity of the disease, the optimal therapy remains unknown. A large proportion of patients present with multiple poor risk factors as per the International Prognostic Index (IPI) and are rarely cured.¹⁻³ The one exception is ALK positive anaplastic large cell lymphoma (ALCL), a group of diseases that has a much more favourable prognosis; however, those patients with ALCL and multiple IPI factors have a similar poor prognosis.⁴ CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like chemotherapy has been the mainstay of therapy for aggressive lymphomas, including PTCLs. However, response rates for most PTCLs are inferior to those observed in aggressive B-cell lymphomas and relapses are frequent. In a meta-analysis of 31 studies of patients with PTCL treated with anthracycline based chemotherapy (n=2912), excluding ALCL cases, the estimated 5-year overall survival (OS) was only 36.6%.⁵ The German High Grade Non-Hodgkin Lymphoma Group (DSHNHL) retrospectively evaluated the outcome of 289 PTCL patients included in phase II and III trials and reported that the addition of etoposide in young patients (≤ 60 years of age) with a normal lactate dehydrogenase (\leq upper value of normal) improved event-free survival (EFS) but not OS. However, the benefit appeared to be mainly in patients with ALK-pos ALCL (p=.012) with only a trend to improved 3 year event-free survival (EFS) observed in

the other common PTCL subtypes (p=.057).⁶ Importantly for patients above the age of 60, the addition of etoposide conferred no benefit.

Recently, the ECHELON2 trial reported improved progression-free survival (PFS) and OS with the addition of brentuximab to frontline therapy compared with CHOP alone in CD30+ T-cell lymphomas (75% of which were ALCL)⁷ and this regimen has become the standard frontline treatment in many jurisdictions for these lymphomas. Adverse events such as febrile neutropenia and peripheral neuropathy were similar between both groups. Other attempts at improving CHOP with the addition of a novel agent have not been as successful. A phase III randomized controlled trial (RCT) compared romidepsin-CHOP to CHOP alone in 421 untreated PTCL patients demonstrated that this combination did not result in an improved PFS or OS but was associated with more grade 3 or 4 treatment-emergent adverse events (TEAEs) such as thrombocytopenia, neutropenia, anemia and leukopenia.⁸ Similarly, the addition of alemtuzumab to CHOP did not improve survival in a cohort of elderly patients due to excessive toxicity.⁹

For patients who do have a complete response to frontline therapy, some centres proceed to consolidation with an autologous stem cell transplant (ASCT). However, there is no randomized data to support this approach, and thus it has been recommended by experts based mostly on retrospective cohort comparisons or prospective phase II trials.^{10,11} A recent Dutch nationwide population-based study identified that in patients age < 65 years of age with advanced-stage ALK- ALCL, AITL, or PTCL (ALCL,

35%; AITL, 21%; and PTCL NOS, 44%, respectively), consolidation with ASCT was associated with an improved OS (78% vs. 45%) compared with patients receiving induction chemotherapy only, including in the subgroup who achieved a complete response (CR) to frontline therapy (**Figure 1**).¹²

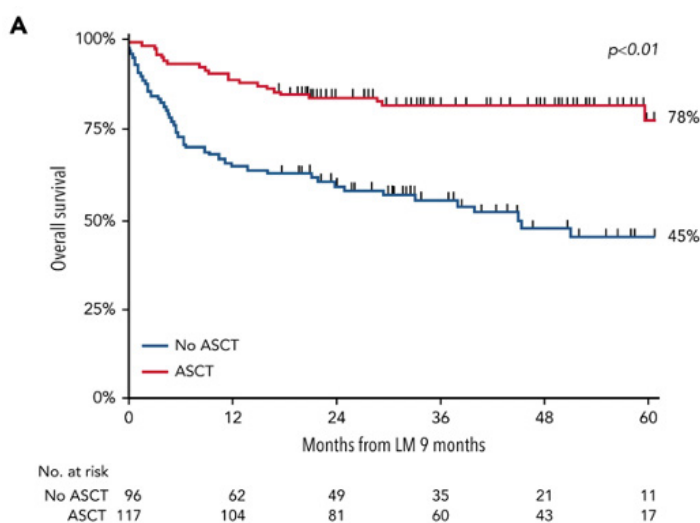


Figure 1. OS in patients aged <65 years with stage II to IV disease. (A-B) OS in patients with ALCL, AITL, or PTCL NOS treated with or without consolidation with ASCT after chemotherapy in the first-line setting, measured in months after the 9-month landmark (LM) (A); Brink et al, 2022

Relapsed/Refractory PTCL

Despite the approaches above, many PTCL patients relapse. The present approach to treatment of these patients can be divided into two categories: salvage chemotherapy with the goal of a stem cell transplant (SCT) (autologous or allogeneic) or single agent treatment, including the use of novel agents as part of clinical trials, either with a palliative intent or more rarely, as bridging with the goal of potentially reaching an allogeneic SCT in younger, fit patients. This review will focus on those available single agents beyond chemotherapy with an emphasis on evolving novel therapies.

Histone Deacetylase (HDAC) inhibitors

Mutations in epigenetic regulatory genes are common in AITL and PTCL-NOS, particularly in TET2, DNMT3A, IDH2 and KMT2D.¹³ Romidepsin is an HDAC inhibitor derived as a natural product from *Chromobacterium violaceum*. It has been investigated as monotherapy in phase 2 trials of previously treated PTCL patients, at the dose of 14 mg/m² on day 1, 8 and 15 of 28 day cycles. One trial of 47 patients of various PTCL subtypes demonstrated an overall response rate (ORR) of 38% with a CR rate of 18%, and median duration of response (DoR) of 8.9 months.¹⁴ In 2014, other researchers conducted a pivotal phase 2 trial of 130 patients, demonstrating an ORR of 25% (CR/CRu 15%), with a median PFS of 29 months in those patients who achieved a CR/CRu \geq 12 months.¹⁵ Interestingly in this study, there were long term responders having confirmed/

unconfirmed complete response (CR/CRu) who achieved DoR as long as 48 months, and among AITL patients, the median DoR was 38 months. Thus, patients achieving a good response, can stay on romidepsin until progression, with some clinicians decreasing the dosing frequency to every 2 weeks. Pre-clinical and early phase studies have demonstrated synergy between romidepsin and the DNA methyltransferase inhibitor 5-azacytidine (5-aza).¹⁶ A phase 2 trial combining 5-aza 300 mg po daily on days 1 to 14 with romidepsin 14 mg/m² on days 8, and 15, and 22 on a 35 day cycle in 25 patients who were treatment naïve or who had R/R PTCL demonstrated an ORR of 61% (CR 48%), and median PFS of 8.0 months. Seventeen patients (68%) had AITL or PTCL of T-follicular helper (tTFH) cell phenotype and the ORR in this subgroup was 80% (CR 67%), with a median PFS of 8.9 months vs. 2.3 months for other PTCL subtypes.¹⁷ The most common observed toxicity was myelosuppression (thrombocytopenia 48%; neutropenia 40%). There is an ongoing study testing this combination (NCT04747236).

Nanatinostat is an HDACi being studied in EBV-positive lymphomas, including AITL and PTCL-NOS. A phase 1b/2 study tested the combination of this drug with valgancyclovir in EBV-positive R/R-lymphoma, including 15 T/NK lymphoma patients. In total 9 of the 15 patients had a response (60%), 4 of whom had a CR.¹⁸ The phase II trial NAVAL-1 testing this combination is currently ongoing (NCT05011058).

Pralatrexate

Pralatrexate is an intravenous anti-folate with high affinity for the reduced folate carrier, resulting in higher internalization and retention in cells than methotrexate. Pralatrexate is approved in Canada for the treatment of R/R-PTCL based on data from the PROPEL trial, a phase 2 international multicenter trial of 109 evaluable patients demonstrating an ORR of 29% (CR 11%), median PFS of 3.5 months and DoR of 10.1 months.¹⁹ Cytopenias and mucositis can be severe, and, as such, patients must be pre-medicated with vitamin B12, folic acid and leucovorin. Pralatrexate has also been studied in combination with romidepsin in a phase 1 trial to determine the dose-limiting toxicities (DLTs), maximum tolerated dose, pharmacokinetic profile, and response rates, and the combination demonstrated an ORR of 71% and CR of 40% (**Figure 2**). The most common grade 3 toxicities included anemia (29%), oral mucositis (14%), thrombocytopenia (14%), and neutropenia (10%). Five grade 4 toxicities were observed, including thrombocytopenia (14%), neutropenia (10%), sepsis (7%), fever (3%), and pneumonia. These toxicities may limit the applicability of this combination in R/R PTCL patients.²⁰

Parameter	Number
Total # of Patients (evaluable)	29 (23)
All patients ORR	13/23 (57%)
All patients CR	4/23 (17%)
All patients PR	9/23 (39%)
non-TCL ORR	3/9 (33%)
non-TCL CR	0/9 (0%)
non-TCL PR	3/9 (33%)
T-Cell ORR	10/14 (71%)
T-Cell CR	4/10 (40%)
T-Cell PR	6/10 (60%)

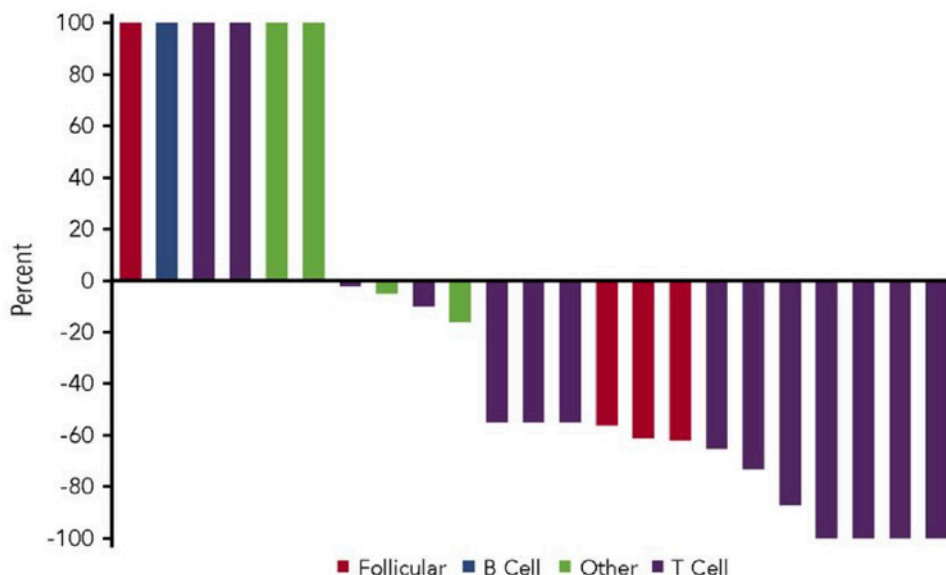


Figure 2. Summary of response rates across study population for patients treated with romidepsin and pralatrexate. (A) Response rates by disease subtype. (B) Waterfall plot representing the percentage change in tumor growth following treatment depicted by disease subtype. ORR, overall response rate; TCL, T-cell lymphoma; Amengual et al, 2018

Duvelisib

Duvelisib is an oral dual inhibitor of phosphatidylinositol 3-kinase (PI3K)- δ and PI3K- γ that has been well studied in PTCL patients. It is postulated to inhibit both the proliferation of lymphoma cells through its inhibition of PI3K- γ , as well as M2 tumour-associated macrophages, which leads to increased CD8⁺ cytotoxic T-cell activation. The phase 2 Primo trial in R/R-PTCL patients has completed enrollment at the expansion dose of 75 mg twice daily for two months, followed by 25 mg twice daily. An interim analysis of the first 78 patients is available and the results are very encouraging: in patients with a median of 3 prior lines of therapy, the ORR is 50% and the CR rate is 32%. Notably, patients with AITL showed a 66.7% ORR with a 47.6% CR rate.²¹ Patients did have TEAEs, leading to 18% of patients discontinuing treatment, with the most common grade 3 or greater adverse events being neutropenia (39%), ALT/AST increase (24%/21%), rash (7.7%), decrease in lymphocyte count (7.7%) and sepsis (6.4%). Recently, a phase I trial combined duvelisib with romidepsin in 64 PTCL patients. Interestingly, the rate of transaminase elevation was much lower in this study of a combination compared with the single agent duvelisib.²² An ORR of 55% (CR 34%) with a median PFS of 6.9 months in PTCL patients was observed, which is encouraging in this patient population. A similar study combining tenalisib, a highly selective PI3K δ/γ and SIK3 inhibitor with romidepsin in R/R-PTCL and CTCL patients yielded promising results, with an ORR of 75% with a CR of 50% in twelve PTCL patients.²³

Valemetostat

Valemetostat is an oral dual inhibitor of the histone methyltransferases EZH1 and EZH2, leading to increased gene expression of pro-apoptotic and tumour suppressor

genes by altering histone methylation. This mechanism of action is felt to be an important therapeutic approach, given that epigenetic dysregulation is a hallmark of T-cell lymphomas. Early data has demonstrated efficacy in R/R-adult T-cell leukemia/lymphoma²⁴, and as such a phase 1 trial was undertaken in R/R-PTCL and ATLL. In a cohort of forty-five PTCL patients treated with varying dose regimens, an encouraging ORR rate of 55.6% and CR rate of 24% was observed, with AITL patients, specifically, having an observed ORR rate of 70.6%. Significant side effects included predominantly cytopenias, dysgeusia and alopecia, but overall valemetostat is a well-tolerated treatment option.²⁵ The dose selected for the phase II evaluation was 200 mg/day, and the ongoing VALENTINE-PTCL01 study is close to completing recruitment in R/R-PTCL (NCT04703192).²⁶

Tolinapant

Tolinapant (ASTX660) is a novel oral non-peptidomimetic, small-molecule antagonist of cellular/X-linked inhibitors of apoptosis proteins. In the phase II trial, 98 patients with PTCL (45% PTCL-NOS, 34% AITL) and 51 with cutaneous T-cell lymphoma (CTCL) received tolinapant orally at 180 mg/day on Days 1 to 7, and 15 to 22 of a 28-day cycle. Treatment was well tolerated, with the most common grade ≥ 3 adverse events in PTCL patients being lipase elevation (15%), rash (8%), and amylase elevation (6%); 2 patients had grade 4 pancreatitis. The ORR for PTCL patients was 22%, including 9 complete responses (CRs) and 13 partial responses (PRs). The median PFS was only 1.8 months with a DoR of 6.5 months. The ORR in CTCL was 28% including 2 CRs and 12 PRs.²⁷ An ongoing trial combining tolinapant with oral decitabine/cedazuridine in R/R-PTCL is currently enrolling patients [NCT05403450].

Chimeric Antigen Receptor (CAR) T-cell Therapy

The development of CAR-T therapy in T-cell lymphomas has been more difficult than in B-cell lymphomas due to a number of challenges. Firstly, CAR-T therapy leads to aplasia of normal lymphocytes it is targeting along with the malignant lymphocytes. Although B-cell aplasia is a manageable side effect of CD19 directed CAR-T cell therapy, T-cell aplasia is less tolerable in the long term, and can lead to life-threatening infections.²⁸ However, approaches using either transient CAR-T cell expression or persistence, targeting T-cell subsets, or suicide genes, could be used to allow for T-cell immune reconstitution. Secondly, the killing of CAR-expressing cells by each other, known as fratricide, can undermine the generation of CAR-T cell products. Possible solutions include gene editing, knocking out the T-cell receptor on the cell surface, or using NK cells. Circulating tumor cells can contaminate leukapheresis products and be transduced with CARs during manufacturing, and this can be bypassed by using NK cells or allogeneic T-cells. Finally, identifying targets uniquely expressed on malignant but not normal T cells has been challenging. One approach has been to target molecules expressed by a subpopulation of T cells, or which are downregulated when T cells are activated. With this approach, CARs against CD4, CD5, CD7, CD30, CD37, CCR4, and the 2 alleles of the T cell receptor beta chains (TRBC1/TRBC2) have been designed.²⁸ There are several ongoing early phase clinical trials using both autologous and allogeneic T-cells, as well as NK cells for the potential treatment of T-cell lymphomas.

CTX130 is an investigational allogeneic, CRISPR/Cas9 gene-edited, anti-CD70 CAR-T cell therapy that is being studied in CD70+ R/R T-cell lymphomas. CD70 is a ligand for CD27 with transient expression on activated lymphocytes and is highly expressed in many TCLs. The outcomes of 18 patients (8 with PTCL and 10 with CTCL) were recently presented.²⁹ Median lymphoma CD70 expression was 90%. Responses occurred in PTCL (80% ORR at dose level > 3) and CTCL (60% ORR at dose level \geq 3) across disease compartments (skin, blood, organs and lymph nodes). There was no graft versus host disease, and there were no DLTs, no Grade \geq 3 cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome. However, 80% of patients in the higher cell dose cohorts had grade 1-2 CRS, and 30% grade 1-2 ICANS. Four patients (22%) experienced a Grade \geq 3 infection. This study is ongoing.

Conclusions and ongoing work

PTCL patients continue to experience poor outcomes, and despite development of new treatments in the relapsed/refractory setting, many of these newer agents only offer short remissions with a palliative intent. The early data with duvelisib and valemestostat are encouraging and further results are anticipated. However, it is likely that larger gains will be achieved with combination therapies,

and the new combinations of romidpesin and duvelisib, as well as romidepsin and 5-aza seem promising. Incorporation of these drugs into earlier lines of therapy, including frontline therapy in non-CD30 positive T-cell lymphomas needs to be explored more meaningfully in order to improve outcomes in these patients. An upfront trial through the North American Lymphoma Intergroup is ongoing, comparing the addition of either duvelisib or 5-aza to CHOEP in patients \leq 60 years of age to CHOEP alone in untreated CD30 negative T-cell lymphomas (NCT04803201). The development of CAR-T therapy is in earlier development than in B-cell lymphomas, but promising results are emerging. Recent data has confirmed that conducting phase 3 randomized trials is feasible in patients with T-cell lymphomas and will be needed to demonstrate that these therapies may lead to more durable response and improved survival for T-cell lymphoma patients.

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