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CELLULAR THERAPY IN CLL/iNHL: THERAPEUTIC AGENTS IN THE PIPELINE

Introduction

Advanced cellular therapies have been introduced in Canada over the past two years. Chimeric antigen receptor (CAR) T-cell therapy is the current standard of care for third-line large B-cell lymphoma (LBCL), relapsed/refractory (RR) acute lymphoblastic leukemia (ALL) in patients <26 years old³ and, more recently, in third-line mantle cell lymphoma.⁴ These novel therapies are now gaining more prominence in the treatment of LBCL with recent FDA approval for the second line in patients eligible for stem cell transplant, based on recent Phase 3 trials.^{5,6} Another class of novel immunotherapy agents are bispecific T-cell engagers (BiTEs) which have been studied in many B-cell malignancies but are not yet approved in Canada.

The indolent non-Hodgkin's lymphoma (iNHL) and chronic lymphocytic leukemia (CLL) landscape have been evolving over the past few years with many novel therapies being studied and becoming available. However, patients with RR iNHL, as well as patients using Bruton tyrosine kinase (BTK) and B-cell lymphoma-2 (BCL2) inhibitors for refractory CLL continue to have an unmet need for treatment. This article will focus on cellular therapy that will likely be available for use by Canadian clinicians in the near future to treat patients with iNHL and CLL.

Cellular Therapy in Indolent NHL

iNHL represents at least 35% of new cases of non-Hodgkin's lymphoma in the United States; follicular lymphoma represents the most common of these cases. iNHLs are likely underdiagnosed and their incidence may be even higher, given that a significant number of patients

with the disease are asymptomatic.⁷ The clinical course of the majority of iNHLs is very heterogeneous and many patients experience extended survival.⁸ However, many patients will likely need treatment at some point based on the clinical evolution of the disease. Particularly in follicular lymphoma, it is well known that progressive disease in the first 24 months (POD24) following standard chemoimmunotherapy is associated with a poor prognosis.⁹

Axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) are currently available in the United States and Europe and will likely be available in Canada in the near future. Axi-cel was approved based on ZUMA-5, a single arm, Phase 2 clinical trial.¹⁰ In this trial, both follicular (n=124) and marginal zone (n= 24) lymphomas were included after having failed at least two prior lines of therapy (median of three). The majority of the cohort (55%) had POD24. Despite this, the overall response rate (ORR) was 92%, with a 74% complete response (CR) rate. In the updated analysis, the 18-month progression-free survival (PFS) and overall survival (OS) were 65% and 87%, respectively. Tisa-cel was approved outside of Canada based on the ELARA study.¹¹ ELARA was also a Phase 2, single arm clinical study investigating patients having received at least two prior lines of therapy (median of 4); however, it included only follicular lymphoma. The majority of the cohort (63%) also experienced POD24 and 78% were refractory to their last line of treatment. The ORR was impressive at 92%, with a 75% CR rate. The reported 12-month PFS was 67%.

Rapid access to treatment for the high-risk disease population is the area requiring the greatest advocacy. For

the high-risk population with POD24, Axi-cel was associated with an impressive ORR of 92% with a 75% CR rate and an 18-month duration of response of 60%.¹² With Tisa-cel, the CR rate was 59% and the 12-month PFS was 61%.¹³

The primary advantage of CAR T-cell therapy is its single infusion treatment. However, it has a unique toxicity profile as compared with other therapies; the two initial side effects are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). In LBCL, CRS was reported in 58%-93% patients, with 13%-22% Grade ≥ 3 , and ICANS in 21%-64% of patients, with 12%-28% Grade ≥ 3 .^{1,2,14} In iNHL, the CRS rate was lower, at 49%-82% and 0%-7% Grade ≥ 3 . ICANS was no different, with a rate of 4.1%-59% and 1%-19% Grade ≥ 3 .^{10,11} Cytopenias, B-cell aplasia and infections are additional moderate to long-term side effects that must be considered after CAR T-cell therapy infusion.

BiTEs are another novel form of immunotherapy. The mechanism of action of these antibody therapies is based on recognition of a specific target on tumor cells with another binding site for engaging T-cells.¹⁵ Current BiTEs target CD20 and CD3; mosunetuzumab is the most advanced in terms of access process.¹⁶ Other BiTEs have been investigated in B-cell malignancies, in recently-published Phase 1 clinical studies evaluating glofitamab, epcoritamab and odronextamab.¹⁷⁻¹⁹ BiTEs have the advantage of being rapidly available compared to CAR T-cell therapy which requires apheresis of a fresh product, and a manufacturing time which reduces the time to therapy from 4-6 weeks to only 1-2 weeks at the most.

A Phase 2, single arm mosunetuzumab trial was recently published.¹⁶ Only follicular lymphomas with at least two prior lines of therapy (median 3) were included. Prior CAR

T-cell treatment was not excluded, but represented only 3% of the cohort. Fifty-two percent of the study cohort had POD24. As with the majority of BiTEs, CRS is the most common adverse event; however, it can be mitigated by the use of scheduled titration. Mosunetuzumab requires an infusion every three weeks until progression. In this clinical trial, ORR was 80%, with a 60% CR rate. CRS was confined primarily to cycle 1 with a 44% incidence in all grades but only 2% Grades 3/4. Despite a short follow-up, no unexpected major adverse events have been reported. The key characteristics of the available Phase 2 clinical trials are summarized in **Table 1**.

Cellular Therapy in Chronic Lymphocytic Leukemia (CLL)

Cellular therapy in CLL is still in its early phase. CAR T-cell and BiTEs therapy are emerging as promising treatment strategies for patients who are refractory to both BTK and BCL2 inhibitors.

Although currently there is no product approved for commercial use in Canada, the United States or Europe, several patients with CLL have been treated with cellular therapy for more than 10 years. A recent report described the characteristics of two patients who have been in remission since the infusion of their CD-19 directed CAR T-cell therapy. Data on lisocabtagene-maraleucel (liso-cel), a CD-19 directed CAR T-cell therapy which has published data on LBCL, but is not currently available in Canada in any indication, has recently been published for patients with CLL. This Phase 1 study (TRANSCEND CLL 004), involving 23 patients with standard and high-risk disease and 2-3 prior lines of therapy (including a BTK inhibitor) showed an 82% ORR and a 45% CR or CR with incomplete marrow recovery (CRi) rate. In the cohort of patients who progressed on both BTK and BCL2 inhibitors, the highest

Therapy	Phase	Histology	N	ORR (%)	CRR (%)	Median DOR (months)	Median PFS (months)	Median OS (months)
Axicabtagene ciloleucel ¹⁰	II	FL/MZL	109	92	76	NR 18 months DOR was 66%	NR 18-month PFS was 65%	NR 18-month OS was 87%
Tisagenlecleucel ¹¹	II	FL	94	87	69	NR Among patients with CR 9-month DOR was 87%	NR 12-month PFS was 67%	NR
Mosunetuzumab ¹⁶	II	FL	90	80	60	23	18	NR 18-month OS was 90%

Table 1. Phase 2 studies of cellular therapies in iNHL; courtesy of Christopher Lemieux, MD
DOR: Duration of response, FL: Follicular lymphoma, MZL: Marginal zone lymphoma, NR: not reached, PFS: progression free survival, OS: Overall survival.

ORR was 80% (60% CR/CRi); 78% achieved undetectable minimal residual disease in the blood and 67% in the marrow, which appears to be promising for those patients with a current unmet need.²⁰ In terms of toxicity, CRS occurred in 74% (9% Grade 3) of the cohort and ICANS occurred in 39% (22% Grades 3/4), which is higher than that seen in the LBCL cohort.¹⁴ Results of the Phase 2 trial will have to be followed (NCT03331198). Other early phase trials have shown comparable results in this population.²¹⁻²³ The usefulness of using a BTK inhibitor throughout the CAR T-cell treatment process remains to be determined.

The development of BiTEs in CLL currently focuses on CD3-CD20 dual targeting. Epcoritamab (NCT04623541) and mosunetuzumab (NCT05091424) studies are ongoing. Preliminary results from the EPCORE CLL-1 trial have been previously presented, however, only five patients were assessed for responses.²⁴

Conclusion

Cellular therapy has been emerging in B-cell malignancy, iNHL and CLL over the past decade. It is hoped that these novel therapies will become available for Canadian patients in the near future. Despite showing high response rates, longer-term follow up of these trial cohorts will elucidate the durability of response of these novel agents. In addition, defining the patient population for which these therapies should be available in the future might become a factor in payors' decision-making process.

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