Immuno-Oncology RESEARCH REVIEW™

Making Education Easy

Issue 7 – 2022

In this issue:

Abbreviations used in this issue

ALL = acute lymphoblastic leukaemia
axi-cel = axicabtagene ciloleucel
BCMA = B-cell maturation antigen
CAR = chimeric antigen receptor
cilta-cel = ciltacabtagene autoleucel
CNS = central nervous system
CRS = cytokine-release syndrome
DLBCL/LBCL = (diffuse) large B-cell lymphoma
liso-cel = lisocabtagene maraleucel
MRD = minimal residual disease
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
PRO = patient-reported outcome
QOL = quality of life
SCT = stem-cell transplantation
tisa-cel = tisagenlecleucel

Welcome to issue 7 of Immuno-Oncology Research Review, with a focus this issue on haematological malignancies.

We begin with a retrospective study comparing the CAR T-cell therapies axi-cel (axicabtagene ciloleucel) and tisa-cel (tisagenlecleucel) in a real-world cohort of patients with DLBCL. This is followed by two studies in LBCL, one comparing second-line liso-cel (lisocabtagene maraleucel) with standard of care in relapsed or refractory disease, and the other reporting PROs (patient-reported outcomes) associated with second-line axi-cel therapy. Other highlights in this issue include first-in-human data from patients with B-cell ALL for CAR T-cell therapy manufactured using a next-day platform, and a report on ethnicity, age and sex disparities among participants enrolled into trials of immune checkpoint inhibitors. We conclude the issue with research reporting that patients with stage III–IV Hodgkin lymphoma treated with the CD30-directed antibody-drug conjugate brentuximab vedotin combined with AVD (doxorubicin, vinblastine, dacarbazine) experienced a survival advantage over those treated with ABVD (AVD plus bleomycin).

We hope you enjoy the selected research. We invite your comments and suggestions.

Kind regards,

Dr Ahmed Kolkeila
ahmed@researchreviewmena.com

A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma

Authors: Bachy E et al.

Summary: Outcomes were reported for a retrospective cohort of 809 patients with relapsed or refractory DLBCL who after ≥2 lines of treatment had initiated CAR T-cell therapy with axi-cel or tisa-cel in France. A propensity score-matched analysis (n=418) revealed that compared with tisa-cel, axi-cel therapy was associated with superior overall and complete response rates (80% vs. 66% and 60% vs. 42%, respectively [p<0.001 for both]), as well as (after a median 11.7 months of follow-up) greater 1-year PFS and OS rates (46.6% vs. 33.2% [p=0.0003] and 63.5% vs. 48.8% [p=0.0072]), with similar findings seen using an inverse probability of treatment weighting statistical approach. Although grade 1–2 CRS was seen significantly more frequently with axi-cel than with tisa-cel, there was no significant difference for the incidence of grade 3 CRS between these CAR T-cell therapies; however, axi-cel was associated with greater incidences of grade 1–2 and grade 3 immune effector cell-associated neurotoxicity syndrome compared with tisa-cel.

Comment: This retrospective French registry study compared 'real-world' outcomes of two anti-CD19 CART-cell therapies for relapsed/refractory DLBCL. The study found a higher complete response rate and longer PFS and OS for axi-cel compared with tisa-cel. However, axi-cel was associated with a higher rate of CRS and neurotoxicity – there is no free lunch! In countries with both agents available, many clinicians favour axi-cel for younger patients without comorbidities, and tisa-cel for frailer patients with lower physiological reserve. A key difference between these two CAR T-cell therapies is that axi-cel uses a CD28 costimulatory domain, whereas tisa-cel uses a 41BB domain. We need CAR T-cell therapies that combine the efficacy of axi-cel with the favourable toxicity profile of tisa-cel.

Reference: Nat Med 2022;28:2145–54
Abstract

Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM)

Authors: Kamdar M et al., for the TRANSFORM Investigators

Summary: TRANSFORM, an open-label phase 3 study, compared liso-cel with standard of care (salvage immunochemotherapy followed by high-dose chemotherapy and autologous SCT in responders) as second-line therapy in patients with primary refractory or early (≤12 months) relapsed LBCL; this was a report of a prespecified interim analysis. Among 184 patients with follow-up of 6.2 months, median event-free survival (primary endpoint) was longer in the liso-cel group than in the standard of care group (10.1 vs. 2.3 months [p<0.0001]). No new liso-cel safety issues were identified in the second-line setting. The most common grade ≥3 adverse events in the liso-cel and standard-of-care groups were neutropenia (80% and 51%, respectively), anaemia (49% and 49%), thrombocytopenia (49% and 64%) and prolonged cytopenia (43% and 3%). Serious treatment-emergent adverse events occurred in 48% of participants from each group. No participants died in the liso-cel group and one died in the standard-of-care group, due to sepsis.

Comment: The TRANSFORM study was one of three recently-reported phase 3 trials, the others being ZUMA-7 and BELINDA, to directly compare anti-CD19 CAR T-cell therapies with standard of care (salvage chemotherapy plus autologous SCT) for primary refractory LBCL. Two of these studies, ZUMA-7 (axi-cel) and TRANSFORM (liso-cel) met their primary endpoint, favouring the CAR T-cell arm, while BELINDA (tisa-cel) did not. Differences in study design and endpoints have been thoroughly debated, but the three CAR T-cells also differ in design and manufacture. In any case, TRANSFORM and ZUMA-7 establish liso-cel and axi-cel as treatments of choice for primary refractory LBCL.

Reference: Lancet 2022;399:2294–308
Abstract

Independent commentary by Dr Robert Weinkove

Dr Robert Weinkove is a Consultant Haematologist at Te Rerenga Ora Blood & Cancer Centre in Wellington and Clinical Director at the Malaghan Institute of Medical Research. His clinical and research interests include B-cell malignancies and cancer immunotherapy. He runs a clinical and translational CAR T-cell research programme and is Principal Investigator of New Zealand's first CAR T-cell trial, 'ENABLE' (NCT04049513). He studied medicine at the University of Cambridge and Kings College London, trained in General Medicine and Haematology at Guy's and St Thomas' Hospitals in London and in Hannover, and has a PhD in the field of immunology.

Patient-reported outcomes in ZUMA-7, a phase 3 study of axicabtagene ciloleucel in second-line large B-cell lymphoma

Authors: Elsawy M et al.

Summary: These researchers reported PROs for participants from the phase 3 ZUMA-7 study of axi-cel versus standard of care as second-line therapy for relapsed/refractory LBCL; 165 axi-cel recipients and 131 participants from the standard of care arm were evaluable for the QOL analysis. Compared with standard of care, axi-cel recipients experienced statistically significant and clinically meaningful differences in mean changes from baseline for QLQ-C30 Global Health Status/QOL, Physical Functioning and EQ-5D-5L visual analogue scale scores by day 100 (respective estimated differences 18.1 [95% CI 12.3, 23.9], 13.1 [8.0, 18.2] and 13.7 [8.5, 18.8]), and for Global Health Status/QOL and EQ-5D-5L visual analogue scale scores at day 150 (9.8 [2.6, 17.0] and 11.3 [5.4, 17.1]).

Comment: PROs are increasingly valued by healthcare funders. This study compared PROs following CAR T-cell therapy or salvage chemotherapy/autograft within the randomised phase 3 ZUMA-7 trial. CAR T-cell therapy was associated with better QOL, physical, role and social functioning, and less fatigue, diarrhoea and nausea, than chemotherapy/autograft. This chimes with our preliminary experience within the NZ-based ENABLE CAR T-cell trial (NCT04049513). As this study shows, when scrutinising risks of immunotherapies, such as CRS and neurotoxicity, it is easy to discount the substantial toxicities of salvage chemotherapy and autograft. Aside from survival benefits, the patient, whānau and societal benefits of CAR T-cell therapy may be significant.

Reference: Blood; Published online July 15, 2022
Abstract

Efficacy and safety of CD19-specific CAR T cell-based therapy in B-cell acute lymphoblastic leukemia patients with CNSL

Authors: Qi Y et al.

Summary: Patients with relapsed/refractory B-cell ALL with CNS leukaemia (n=48) were treated with CD19-specific CAR T-cell-based therapy in this study. The ORR for bone marrow disease was 87.5% and the remission rate for CNS leukaemia was 85.4%. After a median 11.5 months of follow-up, median event-free survival and OS durations were 8.7 months and 16.0 months, respectively. The 12-month cumulative relapse incidence was greater for bone marrow disease than for CNS disease (31.1% vs. 11.3% [p=0.040]). Tolerability of the CAR T-cell therapy was generally good, although nine participants (18.8%) experienced grade ≥3 CRS. In addition, eleven participants (22.9%) experienced grade 3–4 neurotoxic events, which were associated with a higher pre-infusion disease burden in the CNS, and were effectively controlled with intensive management.

Comment: CNS involvement by acute leukaemia (or by an aggressive lymphoma) is very difficult to treat and is often fatal – most chemotherapies and monoclonal antibodies fail to penetrate the CNS. In many CAR T-cell trials, CNS involvement has been an exclusion, due to the risk of cytokine-mediated CAR T-cell-related neurotoxicity. However, neurotoxicity pays testament to the capability of CAR T-cells to enter the CNS and to recognise and destroy B-cells there. This publication adds to a growing literature suggesting CAR T-cells may be an important treatment modality for CNS involvement by B-cell cancers. The ideal treatment will have a proven capacity to penetrate the CNS, while exhibiting low neurotoxicity potential.

Reference: Blood 2022;139:3376–86
Abstract

Next-day manufacture of a novel anti-CD19 CAR-T therapy for B-cell acute lymphoblastic leukemia

Authors: Yang J et al.

Summary: These researchers developed, and evaluated in a first-in-human study, a next-day manufacturing platform for CD19 CAR T-cells (FasT CAR-T). In a preclinical study, these FasT CAR-T cells exhibited excellent proliferation with a younger cellular phenotype, less exhaustion and more effective tumour elimination compared with conventional CAR T-cells. In a phase 1 study of 25 paediatric and adult patients with B-cell ALL, FasT CAR-T cells were successfully manufactured and infused, with a resultant safety profile that was manageable; the grade 3 CRS rate was 24% and the grade 3–4 neurotoxicity rate was 28%, predominantly affecting the paediatric participants. All but two participants had achieved MRD-negative complete remission by day 14, with 20 progressing to allogeneic SCT within 3 months of their FasT CAR T-cell therapy; of these participants, 15 remained disease-free with a median remission duration of 734 days, one relapsed, and the remaining four died from transplant-related mortality. Two of the three patients who did not undergo allogeneic SCT remained in complete remission until 10 months after receiving FasT CAR-T therapy.

Comment: Current CAR T-cell manufacturing processes typically take 10–12 days. Lymphoblastic leukaemia is a rapidly progressive malignancy, sometimes with a doubling time as short as a few days, so time is of the essence for relapsed/refractory patients. Rapid CAR T-cell manufacture allows faster treatment, and potentially a lower manufacturing cost. Moreover, there may be advantages for the CAR T-cell product itself; this group found that 'fast' CAR T-cells were less exhausted and capable of more proliferation than conventionally produced CAR T-cells. Novartis is running trials of its own fast CAR T-cell product, so it is likely we'll see more products exploiting this concept.

Reference: Blood Cancer J 2022;12:104
Abstract

Long-term follow-up of combination of B-cell maturation antigen and CD19 chimeric antigen receptor T cells in multiple myeloma

Authors: Wang Y et al.

Summary: After cyclophosphamide and fludarabine conditioning, 62 patients with relapsed or refractory multiple myeloma received combination anti-BCMA CAR T-cells and anti-CD19 CAR T-cells 1×10^6 cells/kg in this phase 2 trial. After a median 21.3 months of follow-up, the ORR was 92% with a complete response or better rate of 60%. Among 56 evaluable participants, 77% achieved MRD negativity. Participants responded for an estimated median 20.3 months. The median PFS duration was 18.3 months and the median OS duration was not reached. Survival was significantly worse for participants with extramedullary disease. CRS occurred in 95% of participants (10% grade ≥3) and neurotoxic events occurred in 11% (3% grade ≥3). With the exceptions of B-cell aplasia, hypogammaglobulinaemia and infections, late adverse events were infrequent.

Comment: Internationally, anti-BCMA CAR T-cell therapies such as cilta-cel (ciltacabtagene autoleucel) are becoming standard of care for relapsed/refractory multiple myeloma. However, most patients eventually relapse after cilta-cel. One way to address relapse risk is to make 'dual specificity' CAR T-cells, directed against two tumour-related antigens rather than one. Myeloma-like stem cells lack BCMA but express CD19, so the hope is that by targeting both antigens, myeloma relapse risk will be reduced. The median follow-up duration of 21 months is not very 'long-term' in the context of myeloma, but the PFS curve was beginning to suggest a plateau after 2 years. Only time will tell whether CAR T-cell therapies can be curative for myeloma.

Reference: J Clin Oncol 2022;40:2246–56
Abstract

Disparities in representation of women, older adults, and racial/ethnic minorities in immune checkpoint inhibitor trials

Authors: Riaz IB et al.

Summary: These researchers analysed trial-level data from 107 phase 2–3 immune checkpoint inhibitor trials to assess enrolment disparities among the 48,095 participants. Participation of Black, White, Asian, Native American, Pacific Islander and Hispanic participants was reported by 61%, 72%, 64%, 37% and 22% of the trials, respectively, while subgroup analyses of clinical outcomes by race, age and sex were reported by 22%, 78% and 57%, respectively. There was evidence of under-representation of women, patients aged ≥65 years, Black participants and Hispanic participants (respective trial proportions, 32%, 42%, 1.9% and 5.9%; respective enrolment-incidence ratios, 0.90 [95% CI 0.84, 0.96], 0.78 [0.72, 0.84], 0.17 [0.13, 0.22] and 0.67 [0.53, 0.82]). A significant decline in the representation of Black patients was seen from 2009 to 2020 (average annual percentage change, –23.13), and they were also significantly under-represented in phase 3 trials ($p<0.001$).

Comment: A lack of diversity and representation among trial participants has been heavily criticised, particularly where groups that are disproportionately affected by a disease are under-represented in trials for that condition. Several initiatives seek to address this. For example, the 'DRIVE' scheme proposed by oncologist Dr Ruemu Birihay recommends scoring of clinical trials based on representativeness of study participants. As of early 2022, the N Engl J Med requires a supplementary table outlining disease epidemiology, and describing the gender, ethnicity and geographical representativeness of clinical trial participants. Given the well-documented differences in cancer-related mortality between Māori and non-Māori, there will surely be greater scrutiny of trial inclusivity in Aotearoa New Zealand.

Reference: Am J Med 2022;135:984–92.e6
Abstract

Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma

Authors: Budde LE et al.

Summary: This phase 2 study evaluated intravenous mosunetuzumab in 90 patients with relapsed or refractory follicular lymphoma after ≥2 prior treatment lines (including an anti-CD20 therapy and an alkylating agent); the mosunetuzumab regimen consisted of 21-day cycles of 1mg on day 1, 2mg on day 8 and 60mg on day 15 of the first cycle, 60mg on day 1 of the second cycle, and 30mg on day 1 of each cycle thereafter. Participants with a complete response completed treatment after the eighth cycle, whereas those with a partial response or stable disease continued treatment for ≤17 cycles. After a median follow-up of 18.3 months, 60% of patients achieved the primary endpoint of complete response, which was significantly greater when compared with a historical control cohort of copanlisib recipients (p<0.0001). The most common adverse event was CRS (44%; mostly grade 1–2), which was seen mostly during the first cycle. The most common grade 3–4 adverse events were neutropenia or decreased neutrophil count (27%), hypophosphataemia (17%), hyperglycaemia (8%) and anaemia (8%), and the serious adverse event rate was 47%; there were no treatment-related grade 5 adverse events reported.

Comment: Bispecific antibodies, which engage both T-cells and tumour cells, are shaking up the treatment of B-cell lymphomas and myeloma. Response rates are not (yet) as impressive as for gene-redirected CAR T-cell therapies, and the durability of responses is still to be confirmed. However, bispecific antibodies do not require personalised manufacturing, resulting in significant logistical benefits compared with CAR T-cells. Mosunetuzumab is one of two anti-CD20 bispecific antibodies developed by Roche. Results of the NP30179 trial of glofitamab, Roche's other bispecific for lymphoma, have been presented at various conferences during 2022, and should be published soon. It will be interesting to see which agent is progressed.

Reference: Lancet Oncol 2022;23:1055–65
Abstract

Teclistamab in relapsed or refractory multiple myeloma

Authors: Moreau P et al.

Summary: Results were reported for a phase 1–2 trial of subcutaneous teclistamab 1.5 mg/kg each week in 165 heavily pretreated adults with relapsed/refractory multiple myeloma; 77.5% of the participants were triple-refractory (proteasome inhibitor, an immunomodulatory drug and anti-CD38 monoclonal antibody). The ORR at a median follow-up of 14 months was 63%, two-thirds of which were complete responses or better. The rate of MRD-negativity was 26.7% overall, and was 46% in patients achieving a complete response or better. The median duration of response exceeded 18 months and the median PFS duration was 11.3 months. CRS was common (72.1%) but was predominantly of mild or moderate severity (0.6% grade 3; no grade 4). Other frequent adverse events included haematological events (neutropenia, anaemia and thrombocytopenia) and infections.

Comment: While the efficacy of teclistamab did not quite reach that reported for Janssen's own competing anti-BCMA CAR T-cell therapy cilta-cel, the logistics of the bispecific antibody are more straightforward. The adverse effect profile of teclistamab resembles that of cilta-cel – including CRS, neurotoxicity and cytopenias – although severe CRS and severe neurotoxicity were rare. The practical advantages of teclistamab over cilta-cel are somewhat eroded by the need for a hospitalisation for the first teclistamab doses, and for indefinite administration. Patients, clinicians and funders will need to assess the trade-offs between a logistically simpler but ongoing therapy (teclistamab) and a logistically complex one-off therapy (cilta-cel).

Reference: N Engl J Med 2022;387:495–505
Abstract

Overall survival with brentuximab vedotin in stage III or IV Hodgkin's lymphoma

Authors: Ansell SM et al., for the ECHELON-1 Study Group

Summary: This 6-year follow-up of the ECHELON-1 trial evaluated OS in patients with previously untreated advanced stage III–IV Hodgkin lymphoma who were randomised to receive ≤6 cycles of brentuximab vedotin plus AVD (n=664) or ABVD (n=670) as first-line therapy. After a median 73.0 months of follow-up, 39 and 64 participants in the respective brentuximab vedotin plus AVD and ABVD groups had died (hazard ratio 0.59 [95% CI 0.40, 0.88]; the 6-year OS estimates were 93.9% and 89.4%), and PFS was longer with brentuximab vedotin plus AVD (0.68 [0.53, 0.86]). Brentuximab vedotin plus AVD recipients were also less likely to receive subsequent therapy (including transplantation), and only 23 developed second cancers compared with 32 ABVD recipients. An increased incidence of febrile neutropenia among brentuximab vedotin plus AVD recipients prompted primary prophylaxis with granulocyte colony-stimulating factor. Also, there was more peripheral neuropathy seen in the brentuximab vedotin plus AVD versus ABVD recipients, but resolution or amelioration had occurred in most patients at latest follow-up.

Comment: Brentuximab vedotin, an antibody-drug conjugate, will soon be PHARMAC funded for relapsed/refractory Hodgkin lymphoma, so NZ haematologists/oncologists will become familiar with its use. The randomised ECHELON-1 trial brought brentuximab vedotin into front-line therapy for advanced stage Hodgkin lymphoma, by substituting brentuximab vedotin for bleomycin in the 'ABVD' regimen. This long-term follow-up confirms superiority of the new brentuximab vedotin-containing regimen, although the absolute PFS benefit is small. The survival benefit of brentuximab vedotin was greatest for younger patients and for those with high-risk Hodgkin lymphoma (IPS score 4 or higher), while more pregnancies occurred in the brentuximab vedotin arm than in the standard of care arm. This suggests that the brentuximab vedotin regimen may be particularly beneficial as a replacement for BEACOPP, an intensive and fertility-impairing chemotherapy, which is used for fitter patients with high-risk Hodgkin lymphoma.

Reference: N Engl J Med 2022;387:310–20
Abstract