Immuno-Oncology RESEARCH REVIEW™

Making Education Easy

Issue 5 – 2022

In this issue:

Abbreviations used in this issue

axi-cel = axicabtagene ciloleucel
B-ALL = B-cell acute lymphoblastic leukaemia
CAR = chimeric antigen receptor
CNS = central nervous system
CR = complete response
CRS = cytokine-release syndrome
DLBCL = diffuse large B-cell lymphoma
EFS = event-free survival
HR = hazard ratio
LFS = leukaemia-free survival
MM = multiple myeloma
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
PTCL = peripheral T-cell lymphoma
SCT = stem-cell transplantation

Welcome to issue 5 of Immuno-Oncology Research Review, with a focus on haematological cancers.

This issue includes two papers from the N Engl J Med investigating CAR T-cell therapies, namely axicabtagene ciloleucel (axi-cel) and tisagenlecleucel, as second-line therapies in B-cell lymphoma. There is also a paper reporting on a score developed to predict CAR T-cell-related haematological toxicities in relapsed or refractory large B-cell lymphoma. Axi-cel emerges later on in the issue, this time in a report of ZUMA-5 trial outcomes, a phase 2 trial for patients with relapse/refractory advanced-stage indolent non-Hodgkin lymphoma. Given the absence of control arms in trials investigating ciltacabtagene autoleucel for MM, the researchers for the final paper in this issue have compared outcomes between well-matched cohorts of patients from the CARTITUDE-1 trial and real-world patients who had received their physician's choice of treatment.

If you have any comments or feedback to offer on this issue, please don't hesitate to send it to us.

Kind regards,

Dr Ahmed Kolkeila
ahmed@researchreviewmena.com

Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma

Authors: Tilly H et al.

Summary: In this phase 3 trial, patients with previously untreated intermediate- or high-risk DLBCL were randomised to receive six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; n=439) or polatuzumab vedotin plus R-CHP (n=440) plus two cycles of rituximab alone. After median follow-up of 28.2 months, the 2-year PFS rate was significantly greater in the polatuzumab vedotin plus R-CHP group versus the R-CHOP group (76.7% vs 70.2%; stratified HR for progression, relapse or death, 0.73 [95% CI 0.57, 0.95]) but 2-year OS was similar (88.7% vs. 88.6%; HR for death, 0.94 [95% CI 0.65, 1.37]). The two treatments had similar safety findings.

Comment: This is an important trial that shows a clear benefit to the incorporation of polatuzumab vedotin, an anti-CD79 monoclonal antibody-drug conjugate. Polatuzumab vedotin was substituted for vincristine in the polatuzumab vedotin plus R-CHP arm, resulting in similar rates of neuropathy (grade ≥2 in 13% in the polatuzumab vedotin arm and 16% in the R-CHOP arm). The trial population recruited those with IPI 2–5 regardless of cell of origin and included double-hit DLBCL. The study population was predictably enriched for ABC type DLBCL. Subgroups that did not show a clear benefit were patients 60 years of age or younger, those who had lower IPI scores, those who had bulky disease, and those who had the germinal-centre B-cell-like subtype of DLBCL. The numbers for double-hit DLBCL were too small for meaningful analysis. Polatuzumab vedotin plus R-CHP benefits the older patient with ABC subtype and high IPI, but further studies will be needed to determine if younger patients with ABC subtype will have a meaningful improvement over R-CHOP.

Reference: N Engl J Med 2022;386:351–63
Abstract

Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma

Authors: Locke FL et al., for All ZUMA-7 Investigators and Contributing Kite Members

Summary: Patients with refractory or relapsed large B-cell lymphoma were randomised to receive axi-cel (an autologous anti-CD19 CAR T-cell therapy; n=180) or standard 2–3 cycles of investigator-selected, protocol-defined chemoimmunotherapy, followed by high-dose chemotherapy with autologous SCT in responders (n=179) in this phase 3 trial. Compared with standard therapy, axi-cel recipients had a longer median EFS duration after a median 24.9 months of follow-up (8.3 vs. 2.0 months; HR for event or death, 0.40 [95% CI 0.31, 0.51]), a higher response rate (83% vs. 50%) including CRs (65% vs. 32%), and a higher 2-year OS rate at interim analysis (61% vs. 52%). Grade ≥3 adverse events were recorded for 91% and 83% of the axi-cel and standard care recipients, respectively. The proportions of axi-cel recipients who experienced grade ≥3 CRS and neurological events were 6% and 21%, respectively; there were no associated deaths.

Reference: N Engl J Med 2022;386:640–54
Abstract

Second-line tisagenlecleucel or standard care in aggressive B-cell lymphoma

Authors: Bishop MR et al.

Summary: Patients with progressive or refractory aggressive lymphoma (n=322) were randomised to receive tisagenlecleucel with optional bridging therapy (median time from leukapheresis to tisagenlecleucel infusion, 52 days) or standard care with salvage chemotherapy and autologous SCT in this phase 3 trial. In the tisagenlecleucel arm, 95.7% received the agent and the proportion of high-grade lymphomas was higher than in the standard care arm (24.1% vs. 16.9%), as was the proportion with an IPI score ≥2 (65.4% vs. 57.5%). In the standard care arm, 32.5% underwent autologous SCT. Compared with the standard care arm, a higher proportion of the tisagenlecleucel arm had progressed at week 6 (25.9% vs. 13.8%), with no between group difference for median EFS duration (3.0 months in both arms [p=0.61]) or response rate (46.3% vs. 42.5%). There were ten adverse event-related deaths in the tisagenlecleucel arm and 13 in the standard-care arm.

Reference: N Engl J Med 2022;386:629–39
Abstract

Comment: These two randomised trials of CAR T-cell therapy in patients with DLBCL who relapsed within 12 months of first-line therapy were published simultaneously. They show differing results with the axi-cel, ZUMA-7, products showing an advantage to standard chemotherapy salvage, and tisagenlecleucel trial, BELINDA, failing to do so. Rather than assume that axi-cel is the superior product, the conflicting conclusions from these important trials lies in the design of each trial. As highlighted in the accompanying editorials, the axi-cel trial did not allow for bridging therapy other than steroids whereas the tisagenlecleucel trial allowed 1–2 lines of bridging therapy enabling patients with bulky and more aggressive DLBCL therapy access to the CAR T-cell product. In addition, although 83% of the patients received bridging therapy, 42 (26%) had progressive disease before CAR T-cell infusion, but were not excluded from CAR T-cell infusion and were included in the final analysis. These patients are likely more common in real life than those that can be bridged to CAR T-cell with prednisone alone. Hence both trials are valid in demonstrating that patients with less aggressive kinetics will more often benefit from CAR T-cells over conventional autologous SCT.

CAR-HEMATOTOX: a model for CAR T-cell–related hematologic toxicity in relapsed/refractory large B-cell lymphoma

Authors: Rejeski K et al.

Summary: Patterns of haematopoietic reconstitution and potential predictive markers were investigated in 258 patients with relapsed/refractory large B-cell lymphoma treated with axi-cel or tisagenlecleucel. Profound neutropenia was seen in 72% of patients, and in 64%, neutropenia lasted ≥21 days; the median duration of severe neutropenia was 9 days. Predictive biomarkers of haematotoxicity were identified in a training cohort (n=58) using duration of severe neutropenia until day 60 as the primary endpoint, with significant correlations with baseline thrombocytopenia and hyperferritinaemia detected on univariate and multivariate analyses; CRS incidence and severity, immune effector cell-associated neurotoxicity syndrome, and peak cytokine levels were not associated. The CAR-HEMATOTOX model was created, which included markers associated with haematopoietic reserve (e.g., platelet count, haemoglobin level and absolute neutrophil count) and baseline inflammation (e.g., C-reactive protein and ferritin levels), and was validated in independent cohorts from Europe (n=91) and the US (n=109). Pooled validation revealed that CAR-HEMATOTOX discriminated severe neutropenia ≥14 days with an AUC value of 0.89 and respective sensitivity and specificity values of 89% and 68%. A high CAR-HEMATOTOX score indicated a longer duration of neutropenia and higher incidences of severe thrombocytopenia and anaemia.

Comment: This retrospective publication reflects real-life experience of CAR T-cell therapy in USA and European cohorts, with specific focus on associated haematological toxicity. It is noted that in the registration trials for CAR T-cells in B-cell lymphomas, patients had to have a neutrophil count of greater than 1000 and platelet counts greater than 50 or 75 depending on the trial. This real-world study applied such criteria, and showed that two out of three patients (64%) developed prolonged neutropenia, which persisted long after the resolution of lymphodepletion and acute CRS. The median duration of severe neutropenia (absolute neutrophil count 500 cells/mL) was 9 days (95% CI 8, 10) and did not differ significantly by CAR T-cell product. Baseline cytopenia, particularly thrombocytopenia, was significantly linked to an increased duration of neutropenia. Of note, the number of previous lines of treatment and age (a surrogate marker of clonal haematopoiesis) were not associated with a longer duration of neutropenia, whereas elevated baseline levels of C-reactive protein and ferritin exhibited positive correlations with primary prolonged neutropenia. A raised lactate dehydrogenase level, however, was not correlated. This information could be used in the future to define a lower-risk patient population more suitable for an outpatient-based programme. It is not yet clear how patients with a high-risk HEMATOTOX score might have their risk of prolonged count recovery mitigated.

Reference: Blood 2021;138:2499–513
Abstract

The ECHELON-2 trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma

Authors: Horwitz S et al.

Summary: Five-year outcomes (median 47.6 months of follow-up) were reported in this exploratory update of the phase 3 ECHELON-2 study, in which patients with PTCL were randomised to six or eight cycles of brentuximab vedotin plus CHP (n=226) or CHOP (n=226). Compared with CHOP, the brentuximab vedotin plus CHP arm had higher 5-year PFS and OS rates (51.4% vs. 43.0%; HR 0.70 [95% CI 0.53, 0.91] and 70.1% vs. 61.0%; 0.72 [0.53, 0.99], respectively); findings for these outcomes were generally consistent across key subgroups. Peripheral neuropathy was resolved or improved in 72% and 78% of the brentuximab vedotin plus CHP and CHOP groups, respectively. Among relapsers, the objective response rate was 59% in the brentuximab vedotin plus CHP arm after brentuximab vedotin retreatment, and 50% in the CHOP arm after switching to brentuximab vedotin.

Comment: Treatment with brentuximab vedotin plus CHP maintained its survival benefit over CHOP, with a 5-year OS rate of 70.1% vs. 61.0%, demonstrating a 28% reduction in the risk of death, making ECHELON-2 the only frontline PTCL trial to demonstrate an OS benefit. The safety profile remained manageable and very similar to CHOP, including no increase in secondary malignancies. Peripheral neuropathy events continue to either resolve or improve, and the proportion of patients with ongoing peripheral neuropathy was similar between the arms. As we often find, the most improvement was in the better prognosis group, systemic anaplastic large cell lymphoma compared with the other PTCL. Disappointingly, 54 patients with angioimmunoblastic T-cell lymphoma were studied and there was no difference in outcome between either arm. However, patients over 65 years of age had better EFS and OS in the brentuximab vedotin plus CHOP arm. Future studies are planned to explore brentuximab vedotin coupled with CHOEP and brentuximab vedotin maintenance to improve the outcome for non-anaplastic large cell lymphoma groups such as angioimmunoblastic T-cell lymphoma.

Reference: Ann Oncol 2022;33:288–98
Abstract

Independent commentary by Dr Leanne Berkahn

Leanne Berkahn is a consultant haematologist at Auckland City Hospital and senior lecturer in the Department of Molecular Medicine and Pathology at the University of Auckland School of Medicine. Her current research interests are new therapeutic approaches in the management of leukaemia and lymphoma.

Safety and activity of pembrolizumab in combination with rituximab in relapsed or refractory follicular lymphoma

Authors: Nastoupil LJ et al.

Summary: Thirty patients with relapsed rituximab-sensitive follicular lymphoma received ≤16 cycles of intravenous pembrolizumab 200mg every 3 weeks along with intravenous rituximab 375 mg/m^2 each week for 4 weeks during the first cycle in this phase 2 study. The most frequent grade 3–4 adverse events were liver enzyme level abnormalities (3%), diarrhoea (3%), nausea (3%), aseptic meningitis (3%) and pancreatitis (3%), and 80% of participants experienced low-grade immune-related adverse events, including diarrhoea (43%), liver enzyme level abnormalities (33%), thyroid dysfunction (27%) and rash (23%). Grade 3–4 immune-related adverse events were recorded for 13% of the participants, and 20% experienced treatment-related adverse events that led to discontinuation. The ORR (primary endpoint) was 67% (including a CR rate of 50%), median PFS duration was 12.6 months, the 3-year OS rate was 97%, and the remission rate after a median 35 months of follow-up was 23%. Induction of CR and better PFS were predicted by a high CD8+ T-effector score at baseline in the tumour.

Comment: This single-centre phase 2 trial tested the combination of two therapies well known to us individually but not in combination. Exactly why this combination might be effective in relapsed follicular lymphoma remains to be elucidated. The combination has a reasonable safety profile, with diarrhoea being one of the most prominent adverse events. The CR rate was 50% with 12/15 such patients achieving CR by the initial 3-month assessment, which is superior to rituximab alone in this setting, but the PFS was like rituximab alone and only 12.5 months. Patients who had progressed less than a year from their most recent treatment had reduced PFS compared with those who had relapsed greater than 1 year. Correlative studies showed a high CD 8+ effector score in the baseline tumour increased the likelihood of CR and improved PFS. The combination of rituximab and pembrolizumab is safe and can produce early CR, but further improvement is needed in trial design to improve the duration of response. Other immune modulators such as lenalidomide are likely to make up triplet therapy in future trials.

Reference: Blood Adv 2022;6:1143–51
Abstract

Tisagenlecleucel outcomes in relapsed/refractory extramedullary ALL

Authors: Fabrizio VA et al.

Summary: These researchers reported on patients from the Pediatric Real World CAR Consortium with extramedullary B-ALL, stratified by CNS disease (40 with CNS3 and 15 without CNS extramedullary disease), referred to one of 15 US institutions for tisagenlecleucel therapy. Compared with patients without CNS extramedullary disease, those with CNS disease had a greater CR rate (88% vs. 66%) without increased toxicity (p=0.3). There was no significant difference for 24-month OS (p=0.41) or 12-month relapse-free survival (p=0.92) for patients with CNS disease (with or without bone marrow involvement) compared with those without CNS extramedullary disease or with only bone marrow involvement. Outcomes were not influenced by active CNS disease at the time of tisagenlecleucel infusion. OS tended to be better in patients with isolated CNS disease compared with those with combined CNS and bone marrow disease (p=0.12).

Comment: Patients with CNS-relapse ALL have largely been excluded from the clinical trials of CAR T-cell therapy although CAR T-cells have been shown to traffic to sites of extramedullary disease. There have been reports of increased neurotoxicity with CAR T-cell use in patients with concurrent CNS relapse. This paper reports the results of patients who received tisagenlecleucel for relapsed/refractory extramedullary B-ALL disease as part of the multi-institutional Pediatric Real World CAR Consortium. They found no increase in toxicity and similar rates of efficacy to patients receiving CAR T-cells for marrow relapse alone. Patients with CNS disease had 12- and 24-month OS rates of 75.7% (CI 62.1, 92.2) and 69.3% respectively. Most deaths were due to relapse disease rather than toxicity. The 12-month relapse-free survival probabilities for the isolated CNS and CNS plus bone marrow cohorts were 66.1% and 49.5%, respectively. The median time from infusion to relapse was 101 days (range 30–577). Sites of relapse included isolated CNS (n=5), combined CNS plus bone marrow (n=2) and bone marrow only (n=8). Although CRs were seen in 10 of 15 patients with non-CNS extramedullary relapse, only four remained alive without relapse, some of which may be explained by the bulk of relapsed tissue. The authors conclude that a prospective study is therefore needed to determine if CAR T-cell therapy should be the standard of care for patients with relapsed/refractory extramedullary disease to further reduce long-term side effects of salvage radiation and SCT.

Reference: Blood Adv 2022;6:600–10
Abstract

Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5)

Authors: Jacobson CA et al.

Summary: This phase 2 trial enrolled patients with relapsed or refractory indolent non-Hodgkin lymphoma (follicular lymphoma or marginal zone lymphoma) who had received ≥2 previous lines of therapy (including an anti-CD20 monoclonal antibody with an alkylating agent). The participants underwent leukapheresis and received conditioning chemotherapy followed by axi-cel on day 0. After median follow-up of 17.5 months, the ORR was 92% with a CR rate of 74% among 104 participants eligible for analysis. The most frequent grade ≥3 adverse events were cytopenias (70%) and infections (18%). Serious adverse events occurred in 50% of participants, and four (3%) died due to adverse events, one of which was treatment-related (multisystem organ failure).

Comment: ZUMA-5 is a multicentre, single-arm, registrational, phase 2 trial at 15 medical cancer centres in the USA and two in France. Patients were treated in third line and beyond, and those with autologous SCT within 6 weeks or previous allogeneic SCT were excluded. The majority had relapsed follicular lymphoma (n=124) or marginal zone lymphoma (n=24). Of 104 patients who had sufficient follow up for analysis, the ORR was 92%, with a CR rate of 76% and a partial response rate of 16%, with similar responses in follicular and marginal zone. The median follow-up was >2 years and more than half (59%) remained in CR at data cutoff. This compares favourably to the median survival following standard of care third-line therapy with novel agents such as PI3K inhibitors and tazemetostat that have a median duration of response (10.0–13.0 months) and PFS (9.5–13.8 months). Patients with POD24 status or previous autologous SCT also had an excellent ORR. Grade 3 or 4 CRS occurred in 7% and was treated with tocilizumab. Neurological toxicity grade 3–4 was seen in 19% of patients. Detectable CAR T-cell gene marked cells were seen in 69% at 2 years in the 26 evaluable patients. This CAR T-cell product, axi-cel, was prepared rapidly, and far fewer patients received bridging therapy than in trials of aggressive B-cell lymphoma. This is a promising therapy for multiply relapsed follicular and marginal zone lymphoma patients that will hopefully become available locally in the near future.

Reference: Lancet Oncol 2022;23:91–103
Abstract

Hematopoietic cell transplantation after CD19 chimeric antigen receptor t cell-induced acute lymphoblastic leukemia remission confers a leukemia-free survival advantage

Authors: Summers C et al.

Summary: These researchers reported LFS after consolidative HCT for 50 paediatric and young adult participants with refractory/relapsed B-ALL who had achieved remission with 41BB-CD19 CAR T-cell therapy in a phase 1–2 trial. LFS was better after consolidative SCT compared with watchful waiting (p=0.01), including a trend toward significance in those without a history of SCT, compared with those who had previously undergone SCT (respective p values 0.09 and 0.45). LFS was significantly better after consolidative SCT for patients who had CAR T-cell functional persistence ≤63 days (p=0.01), including those who had previously undergone SCT.

Comment: With the advent of CD19-directed CAR T-cell therapy, 70–90% of B-ALL patients with multiply relapsed or refractory disease can now achieve a CR. Unfortunately, 50% will relapse in the first-year after CAR T-cell therapy with few salvage options, hence the question of useful consolidation/maintenance strategies. CAR T-cell therapy can be used to obtain a remission in refractory ALL and bridge to allogeneic SCT without compromise of SCT outcome; in fact, a recent meta-analysis of 758 patients receiving CD19 CAR T-cells found that after CAR T-cell therapy, consolidative SCT was associated with a lower relapse rate and improved long-term survival in B-ALL patients. This study included 138 paediatric or young adult patients receiving CAR T-cells then SCT. With a median follow-up of 4.2 years, the transplant-naïve cohort had a median post-SCT OS of 72.2 months and EFS of 36.9 months, comparing favourably with low- to intermediate-risk patients undergoing a first SCT. Risk factors for a poor outcome were heavy pretreatment, high disease burden at the time of CAR T-cell infusion and SCT in CR1 or greater remission. Prior blinatumomab or inotuzumab also had adverse impacts on PFS and OS, but the numbers were small. Can we predict which patients will best benefit from consolidative SCT after CAR T-cell therapy? Rather than rely on retrospective analyses, a randomised trial of the role of consolidative SCT for patients in CR after CAR T-cells is needed to definitively address this issue.

Reference: Transplant Cell Ther 2022;28:21–9
Abstract

Comparative effectiveness of ciltacabtagene autoleucel in CARTITUDE-1 versus physician's choice of therapy in the Flatiron Health multiple myeloma cohort registry for the treatment of patients with relapsed or refractory multiple myeloma

Authors: Martin T et al.

Summary: The effectiveness of ciltacabtagene autoleucel in participants from the CARTITUDE-1 trial was compared with physician's choice of treatment in an external real-world registrant cohort of patients with MM, with adjustments for unbalanced baseline covariates of prognostic significance between the two groups (baseline characteristics were similar after propensity score weighting). Compared with physician's choice, treatment with ciltacabtagene autoleucel was associated with improved PFS (HR 0.18 [95% CI 0.12, 0.27]), time to next treatment (0.15 [0.09, 0.22]) and OS (0.25 [0.13, 0.46]), with these benefits robust and consistent across sensitivity analyses.

Comment: Ciltacabtagene autoleucel is a novel CAR T-cell therapy that is being evaluated in the CARTITUDE-1 trial (NCT03548207) in patients with relapsed or refractory MM; ciltacabtagene autoleucel has two BCMA (B-cell maturation antigen)-targeting single-domain antibodies. CAR T-cell therapy trials do not have a control arm. This study looked at the efficacy of the ciltacabtagene autoleucel over standard of care (physician's choice of treatment) for patients with advanced myeloma who would have fulfilled criteria for CARTITUDE. The FLATIRON database has longitudinal data from US community-based oncology clinics and academic centres, and includes an MM cohort registry of approximately 10,000 patients from over 280 clinics, representing mainly community-based oncology practices. The trial design details are well beyond the scope of this review, but appeared rigorous with every attempt made to compare patients with the same baseline demographics. The results of the ciltacabtagene autoleucel therapy is very impressive with improved PFS (HR 0.18 after adjustment [p<0.0001]), time to next treatment (HR 0.15 [p<0.0001]), and OS (HR 0.25 [p<0.0001]) versus physician's choice of treatment. This is a very impressive paper that certainly highlights the potential value of CAR T-cell therapy in advanced myeloma.

Reference: eJHaem 2022;3:97–108
Abstract