Immuno-Oncology RESEARCH REVIEW™

Making Education Easy

Issue 11 – 2020

In this issue:

Abbreviations used in this issue

ALL = acute lymphoblastic leukaemia
CAR = chimeric antigen receptor
CLL = chronic lymphocytic leukaemia
CR = complete response
CRS = cytokine-release syndrome
HCC = hepatocellular carcinoma
HLA = human leucocyte antigen
HR = hazard ratio
ICI = immune checkpoint inhibitor
MSI/MSS = microsatellite instability/stability
NK = natural killer
OR = odds ratio
ORR = overall response rate
OS = overall survival
PD-1/PD-L1 = programmed cell death (ligand)-1
PFS = progression-free survival

Covid-19 Response: Our heartfelt thanks

All of us at Research Review want to thank you for the part you are playing in the Covid-19 crisis. Our hats go off to you, and we are proud to be associated with you. Our role in all of this is to support you by keeping you informed and up to date as much as we possibly can.

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Welcome to the eleventh issue of Immuno-Oncology Research Review.

We begin this issue with encouraging results from a small phase 1–2 trial investigating the use of NK (natural killer) cells modified to express an anti-CD19 CAR (chimeric antigen receptor). The findings of a systematic review and meta-analysis suggest that while immunotherapeutic agents are associated with important adverse effects, they do appear to be safer than chemotherapy. Other included research identified distinct response patterns for metastases affecting different anatomical locations, which were also associated with overall response and survival with combination immunotherapy. The issue concludes with a review of CAR T-cell therapies for B-cell lymphomas, including the two that have been approved by the US FDA (axicabtagene ciloleucel and tisagenlecleucel) and others currently under investigation in clinical trials.

We hope you enjoy this issue, and we encourage you to send us your feedback and suggestions.

Kind regards,

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Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors

Authors: Liu E et al.

Summary: Eleven patients with relapsed or refractory CD19-positive non-Hodgkin's lymphoma or CLL (chronic lymphocytic leukaemia) received single infusions of cord blood-derived HLA-mismatched anti-CD19 CAR-NK cells at doses of 1×10^5, 1×10^6 or 1×10^7 cells/kg in this phase 1–2 trial. There was no evidence of CRS (cytokine-release syndrome), neurotoxicity, graft-versus-host disease or increased levels of inflammatory cytokines, including IL-6, after anti-CD19 CAR-NK cell administration. The maximum tolerated dose was not achieved. Four patients with lymphoma and three with CLL experienced complete remission, and one with CLL had remission of the Richter's transformation component but persistent leukaemia. The responses occurred within 30 days of infusion for all doses. Expansion of the infused CAR-NK cells was evident, with persistence at low levels for ≥12 months.

Comment: NK cells have significant cytotoxic ability. The cytotoxicity is controlled by the net balance of signals between activating and inhibitory receptors on the cells. Ligation of an activating receptor by binding to its ligand on a tumour cell leads to target cell death unless an inhibitory receptor binds to a matched HLA molecule on the target. Allogenic NK cells have therefore been effective in cancer therapy because the inhibitory receptors cannot bind to matched HLA, therefore tumours are killed. A limitation to date for the use of NK cell therapy is the lack of long-term survival of the cells post-transfer. The authors in this study created CAR-NK cells and engineered the cytokine IL-15 into the construct. IL-15 is required for NK cell survival and proliferation. The study showed long-term persistence of transferred cells and responses in patients without high levels of toxicity. Patients were immunodepleted, so IL-15 may also be effective in enhancing the number and activity of endogenous T-cells as they replenish in a lymphopenic environment.

Reference: N Engl J Med 2020;382:545–53
Abstract

Influence of age on the efficacy of immune checkpoint inhibitors in advanced cancers

Authors: Ninomiya K et al.

Summary: This was a systematic review with meta-analysis of 24 randomised trials of ICIs in 8157 younger and 6104 older patients with cancer. The respective pooled HRs for ICI efficacy in the younger and older participants were 0.76 (95% CI 0.69, 0.84) and 0.80 (0.71, 0.86) with no significant difference (p=0.82). This finding was consistent for PD-1 and PD-L1 inhibitors with similar survival benefit in both age groups (p=0.96), but survival tended to be worse in the older group compared with the younger group for CTLA (cytotoxic T-lymphocyte protein)-4 inhibitors (HR 0.90 vs. 0.77 [p=0.26]).

Comment: Most clinical trials of ICIs have been performed in young people, but the immune system of the elderly is known to be quite different. Specifically, elderly people have proportionately more memory T-cells at the expense of naïve T-cells, meaning that they may be less able to generate an immune response to new tumour antigens. Ageing studies, however, are difficult to interpret since they usually compare two cohorts of people and are not longitudinal across one cohort. They can also be easily confounded by cytomegalovirus positivity, which can induce memory T-cell inflation and lead to a skewing in the overall T-cell frequency. This study showed no age-related difference in response to ICIs across age groups, although there was a possible defect in the response to anti-CTLA-4 in the older groups, potentially indicating a defect in native T-cell priming. Other studies have shown that older women have more T- and B-cell activity, and older men, more inflammatory cell activity – it would be interesting to analyse these data in the context of the baseline immune response (prior to ICI) in older subgroups of patients.

Reference: Acta Oncol 2020;59:249–56
Abstract

Adverse event profile for immunotherapy agents compared with chemotherapy in solid organ tumors

Authors: Magee DE et al.

Summary: This was a systematic review and meta-analysis of 22 randomised controlled trials comparing immunotherapies with standard chemotherapies in advanced solid organ tumours and reporting adverse events as an outcome (n=12,727). Compared with standard care, immunotherapy recipients had significantly lower rates of grade ≥3 adverse events (16.5% vs. 41.09%; OR 0.26 [95% CI 0.19, 0.35]), any adverse event (OR 0.35 [0.28, 0.44]), adverse event-related discontinuations (0.55 [0.39, 0.78]) and adverse event-related deaths (0.67 [0.46, 0.98]). When analysed by adverse event type, standard chemotherapy was associated with greater rates of fatigue (25.10% vs. 15.83%), diarrhoea (14.97% vs. 11.13%) and acute kidney injury (1.79% vs. 1.31%), whereas immunotherapy was associated with more colitis (1.02% vs. 0.26%), pneumonitis (3.36% vs. 0.36%) and hypothyroidism (6.82% vs. 0.37%).

Comment: A major concern for immunotherapy is the potential for adverse effects. This study reviewed a large number of studies comparing such events from patients treated with ICIs versus traditional chemotherapy. Fewer adverse events were observed with immune-based therapies across multiple tumours, although immune-related adverse events were higher in patients treated with immune-based therapies. However, other studies have shown better quality of life for patients on immune-based therapies compared with chemotherapy. The study highlights that while adverse events can be expected from immune-based therapies, these may not need to be presented as a higher risk than for other more traditional therapies.

Reference: Ann Oncol 2020;31:50–60
Abstract

Efficacy and safety of CAR19/22 T-cell cocktail therapy in patients with refractory/relapsed B-cell malignancies

Authors: Wang N et al.

Summary: Patients with refractory/relapsed ALL (acute lymphoblastic leukaemia; n=51) or non-Hodgkin's lymphoma (n=38) received sequential infusions of anti-CD19 and anti-CD22 third-generation CAR T-cells in this pilot study. In patients with ALL, the minimal residual disease-negative response rate was 96.0%, and over median follow-up of 16.7 months, their median PFS and OS durations were 13.6 months and 31.0 months, respectively. In the non-Hodgkin's lymphoma group, the ORR was 72.2%, with a CR rate of 50.0%, and over median follow-up of 14.4 months, the respective median PFS and OS durations were 9.9 months and 18.0 months. One participant experienced antigen-loss relapse during follow-up. The respective high-grade CRS and neurotoxicity rates were 22.4% and 1.12%; these effects were reversible in all cases except one.

Comment: Anti-tumour immune responses can become ineffective as the selection pressure results in mutations in tumours, often leading to loss of target antigen expression. Despite the success of CAR T-cell therapy in B-cell malignancies, downregulation or selection of antigen-negative tumours can limit efficacy. CAR T-cells target CD19, CD20 or CD22, all molecules involved in signal pathways for B-cell activation. CD19-targeting therapies have been effective and CD22-targeting therapies have previously been used as a 'rescue' for CD19-relapsed patients. This study tested dual delivery of CD19 and CD22 CAR T-cells by sequential administration and showed that it was a safe and potentially effective approach. Double antigen expressing CAR T-cells are in development and could prove even more effective. Targeting of multiple antigens by the immune system protects against both tumour mutations and takes advantages of functional redundancies in the immune system.

Reference: Blood 2020;135:17–27
Abstract

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Site-specific response patterns, pseudoprogression, and acquired resistance in patients with melanoma treated with ipilimumab combined with anti-PD-1 therapy

Authors: da Silva IP et al.

Summary: These investigators examined patterns of response with combination ipilimumab and anti-PD-1 therapy in 140 patients with melanoma who had 833 metastases. They found that the ORR and overall CR rate decreased as tumour burden or the number of metastases increased. Compared with metastases without a CR, those with a CR were of smaller median size (13 vs. 17mm [p<0.0001]). The highest lesional response rates were seen for soft-tissue and lung metastases (79% and 77%, respectively), and the lowest was seen for liver metastases (46%). Furthermore, patients with lung metastases had superior ORR (OR 2.75 [p=0.02]) and PFS (HR 0.46 [p=0.02]), whereas those with liver metastases had inferior ORR (OR 0.33 [p=0.02]), PFS (HR 4.03 [p<0.01]) and OS (HR 3.17 [p=0.01]).

Comment: While combination immunotherapy can be effective, there is considerable heterogeneity in the response to metastatic melanoma across patients. This study looked at the response to immunotherapy in patients with metastases in different organs and found differences in response rate for each site. The immune response is not homogeneously distributed across the body, and therefore there will be a different effect of immunotherapy depending on the cells of the local tumour microenvironment. This should be taken into account when treating metastases, alongside the molecular changes in the primary and metastatic tumours. Collection of immune infiltrate data at all metastatic sites will provide information on how best to target those immune cells.

Reference: Cancer 2020;126:86–97
Abstract

Immune checkpoint inhibitors combined with chemotherapy for the treatment of advanced pancreatic cancer patients

Authors: Ma J et al.

Summary: Patients with advanced pancreatic cancer were retrospectively recruited and treated with chemotherapy either with (n=22) or without (n=36) ICIs. Compared with the chemotherapy only group, the combination group had longer median OS (primary outcome; 18.1 vs. 6.1 months; HR 0.46 [CI 0.23, 0.90]) and PFS (3.2 vs. 2.0 months; 0.57 [0.32, 0.99]), but similar ORRs (18.2% vs. 19.4% [p=0.906]). All participants who achieved a partial response received a doublet chemotherapy regimen regardless of ICI cotreatment. The respective grade ≥3 adverse event rates in the combination and chemotherapy only groups were 31.8% and 16.9%; the serious treatment-related adverse event rate was nonsignificantly higher in the combination group (p=0.183).

Comment: The tumours of people with pancreatic cancer are known to have an immunosuppressive phenotype. However, the nature of this immunosuppression is varied, but is associated with a low number of infiltrating T-cells. There is evidence that damage caused by chemotherapy can induce an inflammatory milieu, which supports immune cell activation and reduces the immune suppression in the tumour. This study supports this concept – a combination of chemotherapy and ICIs was tested and results were promising. Given the potential heterogeneity of the immune suppressive mechanisms, an analysis of the infiltrating immune cells in pancreatic cancer patients could lead to more precise treatment decisions for the immune therapy components of this combination approach.

Reference: Cancer Immunol Immunother 2020;69:365–72
Abstract

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Independent commentary by Associate Professor Roslyn Kemp

Associate Professor Roslyn Kemp (BSc Hons, Otago [1997], PhD, Otago, Malaghan Institute [2001]) is a researcher who has a particular interest in colorectal cancer and gut-specific immune responses in health and disease. Her current research focus involves T-cell and myeloid cell subsets in people with colorectal cancer and inflammatory bowel disease, and aims to improve diagnosis, prognosis and treatment. In particular she is interested in the tumour immune microenvironment and the interactions between immune cells and tumour associated cells. Roslyn is a member of the Gut Health Network and the Ako Aotearoa Academy for Tertiary Teaching Excellence and is Secretary- General of the International Union of Immunological Societies.

Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/ mismatch repair-deficient cancer

Authors: Marabelle A et al.

Summary: In the phase 2 KEYNOTE-158 study, 233 patients with advanced non-colorectal high-MSI (microsatellite instability)/DNA mismatch repair cancer who had failed prior therapy received pembrolizumab 200mg once every 3 weeks for 2 years or until disease progression, unacceptable toxicity or withdrawal; the patients had 27 different tumour types, the most common being endometrial, gastric, cholangiocarcinoma and pancreatic. After a median follow-up period of 13.4 months, the objective response rate was 34.3%, and the respective median PFS and OS durations were 4.1 months and 23.5 months. The treatment-related adverse event rate was 64.8% with a grade 3–5 rate of 14.6%. There was one treatment-related fatality, due to grade 5 pneumonia.

Comment: MSS (microsatellite stability) refers to mutations in the tumour genome, and high-MSI tumours are presumed to therefore be immunogenic. There is a higher response rate to immune therapies in patients with high-MSI colorectal cancer than MSS colorectal cancer. This study tested the response to pembrolizumab in a variety of high-MSI cancers and confirmed the finding from colorectal cancer patients – anti-PD-1 therapy is more effective in high-MSI than MSS tumours. The presumption is that there are more activated T-cells in high-MSI than MSS tumours, and anti-PD-1 therapy supports their antitumour function. Monitoring the T-cell phenotype in these patients could provide insight into the mechanistic link between MSI status and the local and systemic immune response. Previous studies in colorectal cancer have shown that the infiltrating immune response is a better predictor of outcome than MSI status. New studies analysing both MSI and tumour immune infiltrates could be a more powerful biomarker of response to immune therapies than either alone.

Reference: J Clin Oncol 2020;38:1–10
Abstract

Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240

Authors: Finn RS et al., on behalf of the KEYNOTE-240 investigators

Summary: Patients with advanced HCC (hepatocellular carcinoma) who had been previously treated with sorafenib (n=413) were randomised 2:1 to receive best supportive care with either pembrolizumab or placebo in this phase 3 trial; the median follow-up periods for the respective arms were 13.8 months and 10.6 months. Compared with the placebo arm, the pembrolizumab arm had longer median OS duration (13.9 vs. 10.6 months; HR 0.781 [95% CI 0.611, 0.998]) and PFS duration at both the first interim and final analyses (3.0 vs. 2.8 months; 0.775 [0.609, 0.987] and 3.0 vs. 2.8 months; 0.718 [0.570, 0.904], respectively). These differences did not meet the predefined criteria for statistical significance. The respective grade ≥3 adverse event rates in the pembrolizumab and placebo arms were 52.7% and 46.3%, with treatment-related event rates of 18.6% and 7.5%. There was no evidence of hepatitis C or B flare.

Comment: This study showed some efficacy of anti-PD1 therapy as a second-line treatment for HCC patients, although this did not reach statistical significance according to prespecified criteria. The liver is a unique immunological site, with a high number of cells and molecules that create an immune-tolerant environment. It is possible that ICIs may not be sufficient to overcome the immunosuppressive environment of the liver. Confusingly, HCC often arises initially via chronic local inflammation. The inflammation may be driven by any of the multitude of immune components present in the liver. There is evidence of both pro- and anti-inflammatory cytokines in HCC tumours. Collectively, the immune environment is so complex in the liver and liver tumours that it may be difficult to predict a response to immune therapies in all patients.

Reference: J Clin Oncol 2020;38:193–202
Abstract

CD22 CAR T-cell therapy in refractory or relapsed B acute lymphoblastic leukemia

Authors: Pan J et al.

Summary: Thirty-four paediatric and adult patients with relapsed or refractory B-ALL who had failed prior CD19 CAR T-cell therapy received CD22 CAR T-cell therapy in this research. Among evaluable participants on postinfusion day 30 (n=30), the complete remission (with or without incomplete count recovery) rate was 80%. Only mild CRS and neurotoxicity was seen for most participants. Seven participants who achieved complete remission required no additional treatment, with three remaining in remission beyond 6 months. Eleven participants who achieved complete remission were bridged to transplantation, eight of whom were still in remission at 4.6–13.3 months post-transplantation; their 1-year leukaemia-free survival rate was 71.6%. There was no evidence of CD22 antigen loss or mutation among relapsed patients.

Comment: CD19 and CD22 are common targets for CAR T-cell therapy of B-cell lymphoma. In this study, the authors used CD22 CAR T-cells to treat relapsed patients previously treated with CD19 CAR T-cells – both antigens are expressed on B-cells. The second therapy was effective, in line with other similar studies. Interestingly, four patients again relapsed after CD22 CAR T-cell therapy, and no CD22 antigen loss or mutation occurred in these patients. Although this is a small number of patients, it raises discussion about the kinetics and selection pressure of antigen loss on tumour cells during CAR T-cell therapy. Modelling the changes in antigen expression, both CD19 and CD22, during the course of these therapies could be a useful tool to inform treatment decisions.

Reference: Leukemia 2019;33:2854–66
Abstract

CAR T-cell therapy for B-cell lymphomas

Authors: Chavez JC et al.

Summary: These authors reviewed the biology, structure, clinical trial results and toxicity of two CAR T-cell products commercially approved in the US and others currently being investigated in multicentre clinical trials in B-cell non-Hodgkin's lymphomas. They concluded that CAR T-cells targeting CD19 are the new standard of care in diffuse large B-cell lymphoma that is refractory to ≥2 prior lines of therapy, with the caveat that around half of these patients will continue to succumb to their disease. They note that as such, future research needs to focus on the successful identification of disease-, treatment- and patient-related factors that will help successfully predict treatment outcomes. They also note that ongoing and future clinical trials will also need to address why there are some patients treated early with immune modulators, ICIs and other immunotherapies who fail to achieve a CR within 90 days.

Comment: CAR T-cell therapy is increasingly used for B-cell lymphomas. This article reviews the use of commercially approved or currently tested CAR T-cell products for B-cell non-Hodgkin's lymphoma patients. The discussion highlights multiple issues with persistence, survival and toxicity. These highlight the fact that the immune response and the tumour have a dynamic and kinetic relationship. The heterogeneity and complexity of immune cell networks and their interaction with heterogenous and changing tumour cells lead to differences in cell survival and persistence between patients. The addition of lymphoproliferative and/or survival cytokines, either by administration or engineered into the CAR T-cell product, may help with cell persistence, but cytokines are pleiotropic and are likely to have effects on other immune cells too.

Reference: Ther Adv Hematol 2019;10:2040620719841581
Abstract