Immuno-Oncology RESEARCH REVIEW™

Making Education Easy

Issue 9 – 2023

In this issue:

Abbreviations used in this issue

CAR = chimeric antigen receptor
CR = complete response
CTLA = cytotoxic T-lymphocyte antigen
EBV = Epstein-Barr virus
HR = hazard ratio
ICI = immune checkpoint inhibitor
ILD = interstitial lung disease
NSCLC = non-small-cell lung cancer
OS = overall survival
PD-1/-L1/-L2 = programmed cell death (ligand)-1/2
PFS = progression-free survival
PR = partial response
PTSD = post-traumatic stress disorder
QOL = quality of life

Welcome to issue 9 of Immuno-Oncology Research Review.

We begin this issue with research reporting the impacts that poverty and neighbourhood opportunity have on outcomes for young recipients of CD19-directed CAR T-cell therapies. There is also research reporting that patients receiving CAR T-cells often have an overly optimistic perception regarding their prognosis, as well as high rates of psychological distress. We also report the results of a phase 2 trial of pucotenlimab, a novel recombinant humanised anti-PD-1 monoclonal antibody that selectively blocks the binding of PD-1 with its ligands PD-L1 and PD-L2, in patients with locally advanced or metastatic melanoma who have failed conventional treatment. This issue concludes with research reporting on the longest follow-up to date of a bivalent vaccine plus bevacizumab combination in patients with ovarian cancer.

We hope you enjoy this update in immuno-oncology research. Your comments and feedback are always welcome.

Kind regards,

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Impact of poverty and neighborhood opportunity on outcomes for children treated with CD19-directed CAR T-cell therapy

Authors: Newman H et al.

Summary: These US-based researchers investigated the impact of household poverty and neighbourhood social determinants on CAR T-cell therapy outcomes for 206 patients aged 1–29 years with relapsed or refractory CD19+ acute lymphoblastic leukaemia or lymphoblastic lymphoma. Household poverty (Medicaid-only insurance) was recognised in 35.9% of the patients, and 24.9% were assessed to have low-neighbourhood opportunity (based on the Childhood Opportunity Index). Compared with less advantaged patients, those without household poverty and those from low-opportunity neighbourhoods were more likely to receive CAR T-cell therapy with a high disease burden (38% vs. 30% and 37% vs. 26%, respectively). There was no significant difference according to household poverty or neighbourhood opportunity for CR rate, which was 93% overall. Patients from low-opportunity neighbourhoods were more likely to relapse than those who weren't (adjusted HR 2.3 [95% CI 1.3, 4.1]), but their mortality rate was not significantly different (1.2 [0.6, 2.4]).

Comment: In this study, children from households with poverty or from low-opportunity households were assessed for response to CD19-directed CAR T-cell therapy; the authors determined no difference in CR or OS in these groups. The authors used health insurance status to proxy household poverty, but this is not straightforward in a USA setting, where insurance cover varies widely even within existing families and policies. Amongst the other potential variables identified by the authors, it would be important to include past exposure and disease from infection. Children from more resource-limited homes have higher rates of childhood infectious diseases, all of which imprint the immune response for future exposures. It would be interesting to determine whether the effects of early childhood infections are associated with any response to immunotherapies in cancer.

Reference: Blood 2023;141:609–19
Abstract

Independent commentary by Professor Roslyn Kemp

(BSc Hons, Otago [1997], PhD, Otago, Malaghan Institute [2001])

Roslyn 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 a Council Member of the International Union of Immunological Societies.

Leveraging big data of immune checkpoint blockade response identifies novel potential targets

Authors: Bareche Y et al.

Summary: A comparative meta-analysis was undertaken of genomic and transcriptomic biomarkers of response to anti-PD-1/PD-L1 or anti-CTLA-4 agents or their combination in >3600 patients across 12 tumour types, with an open-source web application (predictIO.ca) employed for exploration. It was found that ICI response could be predicted across tumour types by tumour mutational burden and by 21 of 37 gene signatures. The authors then used their pan-cancer analysis to develop a *de novo* gene expression signature called PredictIO, which they showed to have superior predictive value over other biomarkers. A T-cell dysfunction score for each gene within PredictIO was computed to identify novel targets by their ability to predict dual PD-1/CTLA-4 blockade in mice. They found that the *F2RL1* and *RBFOX2* genes (which encode protease-activated receptor-2 and RNA-binding motif protein-9, respectively) were concurrently associated with worse clinical outcomes to ICI therapy, T-cell dysfunction in ICI-naïve patients and resistance to dual PD-1/CTLA-4 blockade in preclinical models.

Comment: New technologies such as single-cell sequencing have created enormous amounts of data. How to use these data in a clinically relevant way is now a major challenge for researchers and clinicians. These authors combined gene expression datasets across multiple cancers to study signatures that predict response to ICIs. They also created a potentially valuable tool, PredictIO, as the 'master' signature. Similar tools have been created with both gene and protein data by others, and one of the challenges for the research community is to accept one or a few tools to ensure standardised assessment. A recent article highlighted new analysis tools for big data and showed that almost all of them were only ever used, and cited by, the group that invented them. There are also limitations in using gene expression signatures to predict effects of therapies on complex immune cells, which do not fit nicely into the GEO pathways; integration of both gene and protein data has been shown to be superior at determining immune responses in patients, but this approach is particularly challenging at a real-world level.

Reference: Ann Oncol 2022;33:1340–17
Abstract

Perception of prognosis, quality of life, and distress in patients receiving chimeric antigen receptor T-cell therapy

Authors: Dhawale TM et al.

Summary: One hundred and two patients scheduled for CAR T-cell therapies completed pretreatment assessments of QOL and anxiety, depression and PTSD symptoms, as well as assessments of cognitive understanding of prognosis, emotional coping with prognosis and adaptive response. Just over a third of the patients (34%) reported that their oncologist had told them that their cancer was curable, and 64% reported being told they had a >50% chance of achieving cure. Clinically significant depression, anxiety and PTSD symptoms were found to be present in 26%, 30% and 21% of the patients, respectively. There was no association detected of cognitive understanding of prognosis with QOL or mood, but both better emotional coping with prognosis and a greater adaptive response were significantly associated with better QOL and reduced depression, anxiety and PTSD symptoms.

Comment: Diagnosis of cancer and discussions of treatment are obviously highly stressful for the patient. The study looked at perceptions of prognosis and linked these to QOL assessments for patients receiving CAR T-cell therapy. The finding that patients were overly optimistic about results is concerning and highlights a need for researchers to balance the need to publicise exciting new findings with the practical implementation. CAR T-cell therapy, and its promise for cancer treatment, features in the public media as a wonder drug – this has led to patient-led fundraising campaigns for therapies that are not appropriate, and potentially to some of the perceptions in this study. Immunology research is complicated, and immunotherapies are highly specific to an individual. The authors recommend interventions to help patients to cope with the treatment; part of this could be via explanation of the complex nature of immune responses.

Reference: Cancer 2023;129:441–9
Abstract

Risk of pneumonitis in non-small cell lung cancer patients with preexisting interstitial lung diseases treated with immune checkpoint inhibitors

Authors: Sawa K et al.

Summary: The association of ICI therapy with pneumonitis was explored in a retrospective cohort of inpatients aged ≥20 years with NSCLC treated with ICIs (n=328) or conventional chemotherapy (n=849) and a new diagnosis of ILD (interstitial lung disease). The cumulative incidence of pneumonitis (primary endpoint) did not differ significantly between the ICI and conventional chemotherapy groups (p=0.868), with the only significant predictors of pneumonitis being age ≥65 years and smoking history (respective HRs 1.86 [95% CI 1.11, 3.10] and 2.04 [1.02, 4.11]).

Comment: ILD is characterised by an inflammatory infiltrate and progressive fibrosis. Pneumonitis can occur following chemotherapy in lung cancer patients with ILD. ICIs can induce inflammatory immune responses because they disrupt the normal regulatory processes of immune responses. The authors showed that treatment with ICIs did not increase the risk of pneumonitis in NSLCL patients with ILD. ILD represents a range of inflammatory states and mechanisms. It would be interesting to study these patients based on their inflammatory cell infiltrate, and the mechanisms of inflammation – the authors acknowledge a limitation of classifying ILD diagnosis in the study. Infiltrating inflammatory cells, such as those in ILD and pneumonitis, in many tissues have diverse functions, and some can be regulated by existing drugs. A contribution of the lung microbiome has also been suggested in the development of ILD. An analysis of these conditions in lung cancer patients could potentially provide ways to predict occurrence of disease.

Reference: Cancer Immunol Immunother 2023;72:591–8
Abstract

Effectiveness of immune checkpoint inhibitors in patients with advanced esophageal squamous cell carcinoma

Authors: Yap DWT et al.

Summary: A meta-analysis was performed on survival data from randomised controlled trials of anti-PD-1-based regimens versus chemotherapy in oesophageal squamous cell carcinoma (CheckMate-648, ESCORT-1st, KEYNOTE-590, ORIENT-15, KEYNOTE-181, ESCORT, RATIONALE-302, ATTRACTION-3 and ORIENT-2) for participants with low PD-L1 expression. Data from first-line trials evaluating a tumour proportion score showed that for participants with a score <1%, immunochemotherapy did not confer a significant OS benefit compared with chemotherapy (HR 0.91 [95% CI 0.74, 1.12]), whereas data from first-line trials that evaluated a combined positive score showed that for participants with a score of <10, immunochemotherapy was associated with a modest OS benefit over chemotherapy (0.77 [0.62, 0.94]).

Comment: Anti-PD-1 therapies work by disrupting the signals between PD-1 on T-cells and PD-L1/2 on other cells, including tumour cells. For effective treatment, both the receptor and the ligand need to be expressed, or there is nothing to inhibit. The authors studied oesophageal squamous cell carcinoma, with a special focus on low PD-L1 expressing tumour cells. Combining populations of individuals with disparate PDL-1 expression means that differences between those with high PD-L1 expression (likely to respond to anti-PD-1 therapy) and low PD-L1 expression (possibly less likely to respond) can be lost. The authors showed that the test and limits used to measure PD-L1 expression (tumour proportion score versus combined positive score) can influence the outcome of an intervention study using anti-PD-1 therapies. These results highlight the need to determine an individual's immune response in the context of a tumour to predict which therapy can best be used. Immune cells and molecules fluctuate during the course of tumour growth, and targeting pathways that are not being used by the tumour or the immune response is not always effective treatment.

Reference: JAMA Oncol 2023;9:215–24
Abstract

Durability of response to immune checkpoint inhibitors in metastatic Merkel cell carcinoma after treatment cessation

Authors: Weppler AM et al.

Summary: These researchers reported on 40 patients with metastatic Merkel cell carcinoma who had discontinued ICI therapy for reasons other than disease progression after a median 13.5 months of treatment. Elective ICI cessation was reported for 77.5% of these patients, while the rest discontinued due to treatment-related toxicity. Over a median 12.3 months from ICI cessation, 35% of patients experienced disease progression, with respective rates of 26%, 57% and 100% among participants who discontinued following CR (n=31), PR (n=7) and stable disease (n=2), respectively. Following treatment cessation, median PFS duration was 21 months, with a third of patients progressing during their first year without treatment. Compared with patients who discontinued ICI therapy due to toxicity, those who stopped electively had longer median PFS duration (29 vs. 11 months). Among the 14 patients with progressive disease, eight restarted ICI therapy, with four achieving CRs and two achieving PRs, while one had stable disease and the other progressed.

Comment: ICIs have been successful in treating melanoma, including metastatic Merkel cell carcinoma. These responses have been durable after treatment cessation in many cancers, including metastatic melanoma, but were not durable in metastatic Merkel cell carcinoma. The authors suggest many reasons for this difference, including the age of the cohort – metastatic Merkel cell carcinoma usually occurs in older adults (the cohort median age was 75 years). Immune responses become weaker as we age, particularly the ability of T-cells to respond to infections (and tumours). The impaired response includes a lower ability of T-cells to proliferate and to become activated. As PD-1 expression increases with T-cell activation, those with impaired T-cell function may have reduced numbers of antitumour T-cells. Quantifying immune responses before treatment could be useful in predicting durable responses in metastatic Merkel cell carcinoma patients.

Reference: Eur J Cancer 2023;183:109–18
Abstract

Safety and efficacy of pucotenlimab (HX008) – a humanized immunoglobulin G4 monoclonal antibody in patients with locally advanced or metastatic melanoma

Authors: Cui C et al.

Summary: Patients with locally advanced or metastatic melanoma who had failed conventional treatment (n=119) received pucotenlimab 3 mg/kg every 3 weeks until disease progression, intolerable toxicity or treatment discontinuation for any other reason in this phase 2 trial. After ~16–25 months of follow-up, the overall response rate was 20.17%, and the respective median PFS and OS durations were 2.89 months (assessed by the independent review committee; 2.46 months per investigator assessment) and 16.59 months. The incidence of treatment-related adverse events was 77.3%, with a grade ≥3 rate of 15.1% and no associated mortality. A biomarker analysis revealed that CCL11 (eotaxin-1) and CCL2 (MCP-1) were associated with response to treatment, whereas TNF-α and VEGF were associated with treatment failure.

Comment: Pucotenlimab is a new anti-PD-1 antibody, similar in structure and function to nivolumab, at least *in vitro*. This study showed efficacy and safety in melanoma. The study was carried out in China, where there is a higher rate of acral and mucosal melanoma than in many other countries, which highlights the need to test interventions across multiple populations. As well as tumour and patient endpoints, the study analysed cytokine production in blood during the course of treatment for potential use as biomarkers of response. The cytokine analysis revealed an increase in CCL11 (eotaxin-1; which attracts eosinophils) and CCL2 (MCP-1; which recruits monocytes and T-cells to sites of inflammation) when patients were at PR compared with disease progression status; in contrast, TNF and VEGF were lower in these patients. The authors used a cytokine bead array, which analyses multiple cytokines simultaneously. They did not present analyses of patterns between different cytokines during treatment – often changes in multiple cytokines reflect an ongoing immune response better than study of single cytokines. Thus, such cytokine signatures may be a better option for biomarkers of response.

Reference: BMC Cancer 2023;23:121
Abstract

Pembrolizumab monotherapy versus chemotherapy in platinum-pretreated, recurrent or metastatic nasopharyngeal cancer (KEYNOTE-122)

Authors: Chan ATC et al.

Summary: Patients with platinum-pretreated recurrent and/or metastatic nasopharyngeal carcinoma were randomised to receive pembrolizumab (n=117) or capecitabine-gemcitabine-docetaxel chemotherapy (n=116), mostly as second-line or later therapy, in the open-label phase 3 KEYNOTE-122 trial. Median follow-up after randomisation was 45.1 months. There was no significant difference between the pembrolizumab versus chemotherapy arm for median OS duration (primary endpoint; 17.2 vs. 15.3 months [p=0.2262]). The incidences of grade 3–5 treatment-related adverse events in the respective pembrolizumab and chemotherapy arms were 10.3% and 43.8%, and the treatment-related mortality rates were 0.9% and 1.8%.

Comment: This study is a final report comparing pembrolizumab with chemotherapy in the KEYNOTE-122 trial of nasopharyngeal carcinoma. The clinical results showed that the immunotherapy didn't improve OS but had lower level of adverse events. Interestingly, infection with EBV can play a role in development of nasopharyngeal carcinoma. EBV infection can result in systemic immune suppression, and EBV-infected nasopharyngeal carcinoma cells have been shown to have higher expression of PD-L1 than noninfected nasopharyngeal carcinoma cells. All participants were EBV-positive, and an analysis of EBV-specific immune response, in particular T-cell phenotype, would have been interesting to include over the course of treatment. In fact, future analysis of tumour versus EBV-specific T-cells could reveal mechanisms of suppression of T-cells by the virus and lead to better targeting of immunotherapies. The authors also comment on potential effects of measurements of PD-L1 expression on tumour cells and archived tissues compared with status at time of treatment, raising similar issues as the study from Yap et al. in this issue. A consensus on methodology and limits for PD-L1 expression across cancers could benefit many similar studies.

Reference: Ann Oncol 2023;34:251–61
Abstract

Clinical outcomes by infusion timing of immune checkpoint inhibitors in patients with advanced non-small cell lung cancer

Authors: Rousseau A et al.

Summary: These researchers examined the effect of the time of day that ICI infusion occurs on survival in a retrospective cohort of 180 patients with advanced NSCLC treated in any line (77% second-line or later) with a median of 12 infusions of single-agent anti-PD-1 or anti-PD-L1 therapy. Compared with the patients who had received <20% of their ICI infusions in the evening, median PFS duration was significantly shorter in the 65 patients who had received ≥20% of their infusions after 16:30h (4.9 vs. 9.4 months [p=0.020]); they also had a numerically, nonsignificantly shorter median OS duration (14.0 vs. 26.2 months [p=0.090]). A multivariate analysis revealed that OS significantly correlated with performance status and line of treatment, but not receipt of ≥20% of ICI infusions in the evening. While receipt of ≥20% of ICI administrations after 16:30h was associated with PFS (HR 1.44 [95% CI 1.01, 2.05]), significance was lost when the total number of ICI infusions was included in the model (1.20 [0.83, 1.75]).

Comment: The effect of circadian rhythms and time of day interventions is an exciting new topic for immunologists. Several recent studies have shown differences in responses to vaccines (including to SARS-COV2), metabolic responses to food and exercise, and fluctuations in the frequencies of circulating lymphocytes. It is only logical to assume that immune interventions may be affected by these rhythms. Most medications in trials (and in real life) are given during the day, and only now are studies comparing the effects of medications at different times. This study provides preliminary evidence that infusions later in the day may affect responses, although a direct mechanism via immune cells was not proposed, especially given that antibody binding to receptors on T-cells is not likely to lead to an immediate effect. However, the differences in the number and types of T-cells, and other immune cells, circulating in the blood and moving through tissue, can be affected by circadian rhythms, thus these results warrant further study in immune therapy for cancers. Others have suggested that clinical trials also include randomisation of time of day to avoid bias.

Reference: Eur J Cancer 2023;182:107–14
Abstract

Long-term outcomes of patients with recurrent ovarian cancer treated with a polyvalent vaccine with bevacizumab combination

Authors: Kahn RM et al.

Summary: Safety, immunogenicity and outcome data were reported for 21 patients with high-grade serous ovarian cancer in second or greater remission treated with a polyvalent antigen-KLH plus OPT-821 vaccine construct and bevacizumab at a single centre. One of the patients developed a dose-limiting toxicity of grade 4 fever, and two developed grade 3 hypertension related to bevacizumab. The proportions of 19 evaluable participants with immunogenic responses to ≥3 and ≥2 antigens were 68% and 84%, respectively. Four patients remained alive >5 years after treatment. For responders (immunogenic response to ≥3 antigens) and nonresponders (immunogenic response to ≤2 antigens), the respective median PFS durations were 4.9 months and 5.0 months, and the respective median OS durations were 30.7 months and 34.2 months. A two-timepoint analysis of baseline and week 17 revealed that each 10-unit increase in IL-8 level was associated with improved PFS (HR 0.43 [p=0.04]) and each 10-unit increase in PDGF level was associated with worse OS (1.01 [p=0.02]).

Comment: In ovarian cancer, a T-cell infiltrate has been associated with good patient prognosis, although other studies have shown infiltrate of some T-cell subsets can lead to enhanced tumour growth and metastasis. This study attempts to generate immune responses to the tumour by using a new vaccine, containing five putative tumour antigens, in conjunction with bevacizumab, an anti-VEGF antibody. The authors measured antigen-specific IgM and IgG, and a panel of angiogenesis related cytokines in the serum. They showed antibody responses to >1 antigen in the majority of patients, but no association with either cytokine levels or improved patient survival. The authors highlight the need to study more immune parameters, including antigen specific T-cells, but could also analyse cytokine signatures rather than individual cytokines. The complexity of the immune response means that more parameters that can be measured will lead to a better indication of ongoing immune responses. Analysis of data collectively, rather than separately, will also lead to a better understanding of the cells and molecules involved in ongoing immune responses in the context of a tumour.

Reference: Cancer Immunol Immunother 2023;72:183–91
Abstract