Immuno-Oncology RESEARCH REVIEW™

Making Education Easy

Issue 3 – 2021

In this issue:

Abbreviations used in this issue
CAR = chimeric antigen receptor
CTLA = cytotoxic T-cell lymphocyte
CRS = cytokine-release syndrome
GI = gastrointestinal
ICI = immune checkpoint inhibitor/inhibition
NSCLC/SCLC = (non-)small-cell lung cancer
ORR = objective response rate
OS = overall survival
PD-1/PD-L1 = programmed cell death (ligand)-1
PFS = progression-free survival

Welcome to issue 3 of Immuno-Oncology Research Review.

This issue begins with a retrospective review of patients receiving ICIs for cancer, investigating the association between concomitant GI infections and severity of immune-mediated diarrhoea and colitis. The results of an investigation of corticosteroid use for managing severe toxicities associated with CAR T-cell therapy suggest that the lowest dose should be used for the shortest duration, and they should probably be started as late as is clinically feasible. We have also included what is claimed to be the first prospective study investigating antitumor activity and tolerability of pembrolizumab plus low-dose ipilimumab for melanoma after failure of anti-PD-1/L1 therapy (including non-anti-CTLA-4 antibody combinations). This is followed by another melanoma study comparing ipilimumab plus anti-PD-1 versus ipilimumab monotherapy for anti-PD-(L)1-resistant metastatic disease, to conclude the issue.

We thank you for your comments and feedback, and look forward to receiving more.

Kind regards,

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Outcomes of immune checkpoint inhibitor-related diarrhea or colitis in cancer patients with superimposed gastrointestinal infections

Authors: Ma W et al.

Summary: The records of patients with cancer who developed immune-mediated diarrhoea and colitis while receiving ICIs were retrospectively reviewed for this research to explore the impact of concurrent GI infections; 22 patients with infections (excluding *Clostridioides difficile* and cytomegalovirus as the sole infection) were compared with 50 matched controls without GI infections. Seventeen patients had *Escherichia coli* infections of different pathotypes, and five had viral infections (e.g. adenovirus, norovirus, sapovirus). Compared with controls, a greater proportion of the patients with GI infections had grade 3–4 colitis (43% vs. 18% [p=0.041]), but overall, the presence of a GI infection did not significantly affect the risk of immune-mediated diarrhoea and colitis recurrence or OS. Antibiotic therapy did not affect infliximab or vedolizumab requirement, but was associated with a higher risk of recurrent immune-mediated diarrhoea and colitis (50.0% vs. 0.0% [p=0.015]).

Comment: The study highlights the complexity of the immune response to cancer but also in maintaining intestinal homeostasis. A healthy gut microflora is essential for development of an immune system, and to maintain tolerance over time. ICI increases immune cell activation and can disrupt the balance of the tolerogenic gut environment, leading to colitis and similar inflammatory issues in the gut, including ICI-related diarrhoea. This in turn, creates susceptibility to infection. The study exposes multiple interconnecting immune-mediated roles that need to be considered when using ICI to treat cancer, and when using antibiotics to treat infections. It is also important to understand the role of the local gut immune system in healing tissue damage following inflammation, by the production of cytokines. Careful management of patients requires understanding of these fundamental immune feedback loops.

Reference: Am J Clin Oncol 2021;44:402–8

Abstract

Chimeric antigen receptor T-cells safety

Authors: Dolladille C et al.

Summary: This observational, cross-sectional, pharmacovigilance cohort study analysed case reports from the WHO VigiBase and meta-analysed data from CAR T-cell trials and cohorts to evaluate adverse drug reactions associated with axicabtagene-ciloleucel and tisagenlecleucel use. There were nine classes of adverse drug reactions associated with these CAR T-cell therapeutics, namely CRS (n=1378), neurological disorders (n=963), haematological disorders (n=532), infections (n=287), CV disorders (n=256), pulmonary disorders (n=186), renometabolic disorders (n=123), haemophagocytic-lymphohistiocytosis (n=36) and hepatic disorders (n=32). A fatal outcome due to the adverse drug reaction was reported in 5.5% of cases, and all-cause mortality was 14.7%; the deaths related to the adverse drug reactions were associated with haemophagocytic-lymphohistiocytosis, cerebral vascular disorders, infections and respiratory failure. Meta-analyses revealed that the most frequent any-grade adverse drug reactions were CRS, haematological disorders and neurological disorders, with fatal outcomes seen mostly with neurological disorders, CRS and infections.

Comment: CAR T-cells are proving to be effective in treating haematological cancers. The majority of CAR T-cells target the B-cell antigen CD19. This study collected safety data from a large cohort to determine the frequencies and types of adverse drug reactions. CRS was the most commonly recorded adverse drug reaction, and this stems from the fact that the transferred T-cells become activated in response to the specific ligand, CD19, which is ideal for destroying the tumour cells, but also leads to production of antitumour cytokines. Because cytokines are pleiotropic, these proteins have effects on other body systems, and can lead to multiple organ failure. A useful area of research is to develop predictive biomarkers of CRS, including serum levels of C-reactive protein or of the cytokines themselves, in a rapid manner to prevent the development of CRS effects. Interestingly, infections with fungal and other pathogens were also reported as adverse drug reactions. This has been reported before, and appears counterintuitive – an activated immune response could help to prevent infections. However, the targeting of all B-cells via CD19 can lead to depletion of healthy B-cells and a reduction in the body's ability to produce an antibody response to pathogens. More importantly, most patients are pretreated with chemotherapy, reducing the body's ability to respond to infection. Balancing the number and types of immune cells required to fight infections but also to fight cancer will be an ongoing challenge.

Reference: Am J Hematol 2021;96:1101–11
Abstract

Prognostic impact of corticosteroids on efficacy of chimeric antigen receptor T-cell therapy in large B-cell lymphoma

Authors: Strati P et al.

Summary: These researchers reported clinical outcomes for 100 recipients of standard anti-CD19 CAR T-cell therapy for relapsed or refractory large B-cell lymphoma, 60 of whom had received corticosteroids to manage treatment-associated toxicities. Corticosteroids were given at a median cumulative dexamethasone-equivalent dose of 186mg for a median of 9 days, starting on days 0–7 in 45 of the patients and day >7 in 15 patients. After a median 10 months of follow-up, use of higher cumulative corticosteroid doses had a significantly negative impact on PFS. Moreover, OS was significantly shorter with high cumulative corticosteroid doses in the setting of prolonged and early use following CAR T-cell infusion.

Comment: CAR T-cell therapy aims to increase the frequency and function of tumour-specific T-cells. Because the cells become activated when recognising tumour antigens, there are numerous potential toxicities associated with an active immune response, including CRS. One means to reduce these adverse events is to try to limit the extent of the immune activation, by using corticosteroids. This is clearly a difficult balancing act to retain effective antitumour immunity but to avoid immune-mediated pathology. The study shows that corticosteroid use did not significantly impact survival, unless used at high cumulative doses. The researchers propose a low dose and short duration in order to maintain the delicate balance of immune function. To better understand the effects of corticosteroids in this context, the impact on T-cell number, activation and function needs to be measured. T-cell functions, especially cytotoxicity and cytokine production, are impacted differently by steroids. Dissecting the mechanism of corticosteroids on the CAR T-cell therapy for patients will allow better management decisions.

Reference: Blood 2021;137:3272–6
Abstract

Prospective correlation between the patient microbiome with response to and development of immune-mediated adverse effects to immunotherapy in lung cancer

Authors: Chau J et al.

Summary: How the microbiome in various body sites correlates with treatment response and the development of immune-related adverse events in 34 evaluable patients treated with ICIs for lung cancer was explored in this prospective study. Compared with 32 healthy controls, patients with lung cancer exhibited significantly lower α-diversity of the gut microbiota. There was significant relative enrichment of the gut microbiome with *Bifidobacterium* and *Desulfovibrio* spp. in patients who did not experience immune-related adverse events. Responders to combined chemoimmunotherapy had a significant increase in *Clostridiales* and decrease in *Rikenellaceae* spp. of the gut microbiome, enrichment of *Finegoldia* spp. in nasal microbiome, and increased *Megasphaera* and reduced *Actinobacillus* spp. in buccal samples. Longitudinal analyses of samples revealed a trend for α-diversity and certain microbial changes associated with the development and resolution of immune-related adverse events.

Comment: There is a well-documented and important relationship between the gut microbiota and the immune system. Without a commensal gut microflora, the immune system does not develop properly and immune responses are often regulated poorly. To study the effect of ICIs, research into the effects on the gut microbiota needs to be included. Recent studies have shown that the gut microbiota composition can affect patient responses to ICIs in melanoma. The current study also looks at the microbiota in the nasal and buccal areas. There are lymphoid structures in these sites, and it is feasible to assume there is some interaction between local immune cells and the local microbiota. Collectively, this pilot study highlights some differences in gut microbiota between healthy people and people with lung cancer, and therefore justifies further study into the relationship between cancer and the gut microbiome. There are several limitations, including the low and heterogeneous patient number and lack of essential controls, and the effect of chemotherapy may override any effect of ICIs on microbial communities. However, the study does highlight the necessity to include factors that are likely to affect an immune response during ICI therapy, including the microbiota. Future studies to determine or predict ICI efficacy could include collection of microbiome data from patients to create the large datasets needed to determine the effect of this important component of the body.

Reference: BMC Cancer 2021;21:808
Abstract

The landscape of immune checkpoint inhibitor therapy in advanced lung cancer

Authors: Wang C et al.

Summary: This was a systematic review of 38 trials (n=20,173) assessing immunotherapy for lung cancer with the predefined endpoints of OS, PFS, ORR and treatment-related adverse events. Compared with chemotherapy, ICI therapy was associated with significantly prolonged survival in patients with NSCLC and also those with SCLC (respective hazard ratios 0.74 [95% CI 0.70, 0.79] and 0.82 [0.75, 0.90]). When compared with standard of care alone, the addition of ICIs appeared to provide superior disease control and survival benefits. In patients with SCLC, the OS and PFS benefits with immunotherapy were only seen when limited to first-line treatment.

Comment: The efficacy of ICIs is not well studied in SCLC compared with NSCLC, or indeed, other solid tumours. The study assessed efficacy of ICIs in SCLC and NSCLC in combination with standard of care and as mono- or combination therapies. The strength of this research is in the subgroup analyses performed, which necessarily take into account the heterogeneity of types of cancer, but also individual patients. What is also important is the heterogeneity of the immune response in general, and following ICIs. This is in terms of types and frequencies of cells, recruitment to the tumour and function once they are there. Given that both tumour heterogeneity and patient variability are hugely affected by types of immune response, it is interesting to see the variability in responses. Accepting heterogeneity in ICI treatment decisions, and studying subsets of patients, will be essential for better targeting of existing ICIs. These findings also argue for collection of detailed immune response data, at baseline and during treatment, to determine the contribution of immune cells in the heterogeneity of the responses.

Reference: BMC Cancer 2021;21:968
Abstract

Immune-related adverse events: promising predictors for efficacy of immune checkpoint inhibitors

Authors: Zhong L et al.

Summary: These researchers analysed data from 40 studies (n=8641) reporting data on the association of immune-related adverse events of ICIs with corresponding efficacy. The reported incidences of immune-related adverse events were 15.34–85.23%, and the major sites included the skin, endocrine, organ, GI tract, liver and lung. Compared with the group of participants without immune-related adverse events, the group who experienced immune-related adverse events had significantly better OS, PFS and ORR in pooled and stratification analyses. Moreover, within the immune-related adverse event group, OS was significantly better with skin, endocrine organ or GI tract involvement compared with liver or lung involvement.

Comment: Prediction of efficacy of ICIs is still challenging. The amount of PD-L1 expression on tumour cells is straightforward to obtain and has shown some predictive power; tumour mutational burden and microsatellite stability have also been tested and shown to be useful in some situations. This study analysed immune-related adverse events as a predictor of patient response. The rationale is that ICI aims to improve activation and function of T-cells, and immune-related adverse events are usually the result of an activated immune response. The predictive ability of immune-related adverse events for anti-CTLA-4 therapy was better than for anti-PD-(L)1 therapy, suggesting that initial activation of T-cells may be more indicative of a good response. The authors suggest a low-grade immune-related adverse event may be acceptable to retain antitumour effects. However, an antitumour immune response is actually a network of interconnected immune cells, mediated by T-cells, and these interconnected immune cells can also influence immune-related adverse events. Considerations around balancing the multiple positive and negative effects of cells and immune mediators will be key for managing patients, and inclusion of detailed immune data in clinical trials could help with treatment decision making.

Reference: Cancer Immunol Immunother 2021;70:2559–76
Abstract

Preexisting autoimmune disease and immune-related adverse events associated with anti-PD-1 cancer immunotherapy

Authors: Hoa S et al.

Summary: The safety and efficacy of ICIs was assessed for a retrospective series of 27 patients with pre-existing autoimmune diseases from the Canadian Research Group of Rheumatology in Immuno-Oncology. Pre-existing autoimmune diseases were rheumatoid arthritis (30%), psoriasis/psoriatic arthritis (30%), inflammatory bowel disease (15%) and axial spondyloarthritis (11%), and lung cancer and melanoma were the most frequent cancers. All patients received anti-PD-1 therapies, with two also receiving sequential anti-CTLA-4 therapy. During a median 11.0 months of follow-up, 52% of the patients experienced exacerbation of their autoimmune disease; 14% were severe, 57% required corticosteroids, 50% required immunosuppression and 14% required ICI discontinuation. Patients who had previously required more intensive immunosuppression (i.e., biologics) tended to have more frequent or severe exacerbations of their autoimmune disease. Background immunosuppression at the time ICI therapy was started did not preclude autoimmune disease flares. Rheumatic immune-related adverse events, mostly polyarthritis and tenosynovitis, were frequent in patients with pre-existing psoriasis, inflammatory bowel disease or axial spondyloarthritis. Tumour progression was not associated with immunosuppressive drug use before or after ICI initiation, and was numerically less frequent in patients who experienced immune-related adverse events.

Comment: ICI therapy has been used successfully in many patients, but because it relies on activation of an existing immune response, most patients with pre-existing autoimmune diseases were excluded from early trials. Patients with pre-existing autoimmune diseases are now being treated with ICIs, and this study assessed the adverse events from patients with a broad range of pre-existing autoimmune diseases receiving ICIs. These are essential data to collect, although multiple pre-existing autoimmune diseases are included, despite different immune mechanisms involved in each, limiting the applicability of some of the findings. Not only does each disease have multiple mechanisms leading to pathology and symptoms, immune-based treatments also differ in action and target cells or molecules. The researchers note that the heterogeneity in patients makes it difficult to generalise, but it is important to collect these data. The study highlights the complicated balance between generating an antitumour immune response and avoiding an autoimmune or autoinflammatory response. Collection of associated immune cell data alongside response and adverse event data for patients with pre-existing autoimmune disease undergoing ICI treatment would allow better management of individuals.

Reference: Cancer Immunol Immunother 2021;70:2197–207
Abstract

Pembrolizumab in patients with metastatic breast cancer with high tumor mutational burden

Authors: Alva AS et al.

Summary: This paper reported results from the phase 2 TAPUR study for the subgroup of 28 participants with metastatic breast cancer with high tumour mutational burden (9–37 mutations per megabase) treated with pembrolizumab 2 mg/kg or 200mg infusions every 3 weeks. The disease control rate was 37%, the ORR was 21%, median PFS duration was 10.6 weeks and median OS duration was 30.6 weeks. PFS was not associated with tumour mutational burden. Five participants experienced ≥1 serious adverse event or grade 3 adverse event that was at least possibly treatment-related.

Comment: The ability to predict responses to ICIs would allow for more targeted administration and ideally better prognoses. Tumour mutational burden reflects the number of mutations in the tumour genome – more mutations in a tumour means that there may be an increased immune response in the tumour, although this is not always the case. For example, microsatellite instability can be predictive of ICI response in many tumours, and this has also been associated with a more activated immune response in some studies. Another common biomarker is the expression level of PD-L1 on tumours. Together, mutational burden and PD-L1 expression can predict ICI response; however, all of these studies are hampered by inconsistencies in methodology, the inclusion of appropriate patient controls, heterogeneity in mutations and many other technical issues. Almost none of the studies actually look for an association between mutation and immune response. For biomarkers to be effective predictors of response, a coherent effort needs to be made to standardise approaches to measure the biomarkers, to take into account the biology of the biomarker used, and to link both of these with the baseline and ongoing number and type of T-cells in each patient.

Reference: J Clin Oncol 2021;39:2443–51
Abstract

Pembrolizumab plus ipilimumab following anti-PD-1/L1 failure in melanoma

Authors: Olson DJ et al.

Summary: Patients with advanced melanoma who had progressed on anti-PD-1 monotherapy (n=60) or anti-PD-1/L1 combined with non-anti-CTLA-4 therapy (n=10) received four administrations of pembrolizumab 200mg plus ipilimumab 1 mg/kg once every 3 weeks followed by pembrolizumab monotherapy in this trial; 13 participants had progressed in the adjuvant setting. The response rate according to irRECIST criteria (primary endpoint) was 29%, including five complete responses and 15 partial responses. The respective median PFS and OS durations were 5.0 months and 24.7 months, and the median response duration was 16.6 months. No significant difference was seen between responders versus nonresponders for median time on prior anti-PD1/L1 therapy or time to anti-PD1 plus CTLA-4 therapy. Responses were seen in PD-L1-negative, non-T-cell-inflammatory and intermediate tumour phenotypes. The incidence of grade 3–4 drug-related adverse events was 27%.

Comment: This study demonstrated antitumour function of low-dose anti-CTLA-4 in combination with anti-PD1 in anti-PD-(L)1-resistant melanoma, confirming other similar studies. Interestingly, this study had exploratory outcomes associating tumour gene expression patterns with clinical outcomes, a 'T-cell inflamed gene expression signature'. The researchers showed that responses to the combination ICI were better in those patients with a lower expression of this signature, i.e. non-T-cell inflamed. This seems paradoxical given that ICI efficacy relies on a T-cell response, with data showing that the first response to ICI is better in patients with a T-cell inflamed signature. Predicting which patients will respond to which ICI combination would lead to much more efficient and effective targeting of therapies. It may be useful to study infiltrating T-cell number, activation and function to determine the mechanism(s) behind these findings.

Reference: J Clin Oncol 2021;39:2647–55
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 Secretary- General of the International Union of Immunological Societies.

Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy

Authors: da Silva IP et al.

Summary: This retrospective cohort study included patients with metastatic melanoma (unresectable stage III and IV), resistant to anti-PD-(L)1 therapy, who had been treated with ipilimumab monotherapy (n=162) or ipilimumab plus anti-PD-1 therapy (pembrolizumab or nivolumab; n=193). Compared with ipilimumab monotherapy, ipilimumab plus anti-PD-1 therapy was associated with a higher ORR at median follow-up of 22.1 months (31% vs. 13% [p<0.0001]), longer median OS duration (20.4 vs. 8.8 months; hazard ratio 0.50 [95% CI 0.38, 0.66]) and longer median PFS (3.0 vs. 2.6 months; 0.69 [0.55, 0.87]). Grade 3–5 adverse events were similar (31% and 33% in the ipilimumab plus anti-PD-1 and ipilimumab monotherapy groups, respectively), with the most common being diarrhoea/colitis (12% and 20%) and raised aminotransferase levels (12% and 9%).

Comment: In anti-PD(L)-1-resistant metastatic melanoma patients, a combination of anti-CTLA-4 and anti-PD1 had a higher efficacy than anti-CTLA-4 alone. Because anti-CTLA-4 and anti-PD-1 have different roles in T-cell biology, a combination is more likely to keep more cells activated and for longer. While CTLA-4 acts primarily to reduce activation of T-cells upon first exposure to antigen, PD-1 is expressed on T-cells upon activation. Interestingly, PD-1 expression on T-cells has been associated with improved effector function, including cytokine production and cytotoxicity. It is also expressed on populations of regulatory T-cells. It is important, then, not to simplify mechanisms of action for ICIs, or to assume an easy predictor of outcome based on expression of one molecule. It is possible that variability in responses, and therefore resistance of some patients, may be due to unintended effects on different T-cell populations.

Reference: Lancet Oncol 2021;22:836–47
Abstract