Renal Cancer Research Review™

Making Education Easy

Issue 21 - 2022

In this issue:

Abbreviations used in this issue:

ALP = alkaline phosphatase; **ALT** = alanine transaminase; **ccRCC** = clear cell renal cell carcinoma; **CI** = confidence interval; **CT** = computed tomography; **Gy** = Gray; **HR** = hazard ratio; **MERTK** = MER proto-oncogene, tyrosine kinase; **mRCC**= metastatic renal cell carcinoma; **OR** = odds ratio; **ORR** = overall response rate; **OS** = overall survival; **PBRM1** = protein polybromo-1; **PDGFR** = platelet-derived growth factor receptor; **PD-1** = programmed death receptor-1; **PD-L1** = programmed death ligand-1; **PFS** = progression-free survival; **RCC** = renal cell carcinoma; **SABR** = stereotactic ablative body radiotherapy; **SEER** = Surveillance, Epidemiology and End Results; ***SETD2*** = SET (Suppressor of Variegation, Enhancer of zeste and Trithorax) domain containing 2 gene; **VEGF** = vascular endothelial growth factor; ***VHL*** = Von Hippel-Lindau tumour suppressor gene.

Welcome to issue 21 of Renal Cancer Research Review.

In a US study we discover that a bifidogenic live bacterial product (CBM588) enhances clinical outcome in patients with metastatic renal cell carcinoma treated with nivolumab plus ipilimumab. A multinational study informs us that approximately 20% of renal cancer patients receiving immune checkpoint inhibitor therapy who undergo stereotactic radiosurgery experience radiation necrosis. Other topics covered in this issue include patterns of first-line targeted therapy in older adults with metastatic renal cell carcinoma, stereotactic radiotherapy plus pembrolizumab for oligometastatic renal cell carcinoma, and proteogenomic analysis of clear cell renal cell carcinoma.

We hope you find the selected studies interesting and we welcome your feedback.

Kind Regards,

Associate Professor Alexander Guminski

alex.guminski@researchreview.com.au

Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma: A randomized phase 1 trial

Authors: Dizman N et al.

Summary: This single-centre, open-label study, examined the use of a bifidogenic live bacterial product (CBM588) in 30 metastatic RCC patients (clear cell and/or sarcomatoid histology) receiving nivolumab and ipilimumab. Relative abundance of *Bifidobacterium* species did not differ before versus after treatment nor was there a difference in Shannon's diversity index. Progression-free survival (PFS) was longer in patients receiving live bacterial supplementation (12.7 vs 2.5 months; HR 0.15; 95% CI 0.05-0.47; p = 0.001).

Comment: Data from pre-clinical and observational studies suggested an impact of the gut microbiome on response to immunotherapy for advanced cancer. The mechanism is thought to involve modulation of the immune system by contact with the particular predominant organisms residing in the gut. Alterations in the composition of gut flora, which is a dynamic ecosystem, can thus reset immune effector and regulatory cells throughout the body in a way that favours a better systemic response of their cancer to checkpoint inhibitor therapy. Stool metagenomic sequencing is a standard technique for showing the relative abundance of different bacterial species in the microbiome. Bifidobacterium species have been identified previously as being associated with better responses to immunotherapy. This is a small prospective trial of patients starting combination immunotherapy with 20 patients receiving a supplement and 10 patients as controls. Results showed that the supplement itself did not alter the microbiome composition, which was the primary endpoint, however, a significant and marked clinical benefit was seen and with no change in typical side effects. Larger studies will be required to better understand the complexity of microbiome manipulation on immunotherapy response, and strongest evidence will be to show that a change in a patient's microbiome composition improves clinical outcomes compared with no change. This is an exciting area as gut microbiome modulation is potentially an easily modifiable target to significantly improve patient outcomes.

Reference: Nature Medicine 2022;28:704-712

Abstract

Radiation necrosis in renal cell carcinoma brain metastases treated with checkpoint inhibitors and radiosurgery: An international multicenter study

Authors: Lehrer EJ et al.

Summary: This multinational study examined the development of radiation necrosis in 50 patients with 395 mRCC brain metastases receiving immune checkpoint inhibitors and stereotactic radiosurgery (median margin dose 20 Gy; 4% received prior whole-brain radiation therapy; median treated tumour volume 3.32 cm^3). The median volume of normal brain tissue receiving a dose of 12 Gy or higher was 8.42 cm^3, and the rate of any-grade radiation necrosis did not differ between patients receiving concurrent immune checkpoint inhibitors and stereotactic radiosurgery and nonconcurrent treatment recipients (17.4% vs 22.2%). Symptomatic radiation necrosis also did not differ between concurrent and nonconcurrent treatment recipients (4.3% vs 14.8%). Increased tumour volume during stereotactic radiosurgery was associated with developing radiation necrosis (OR 1.08; 95% CI 1.01-1.19; p = 0.04).

Comment: A concern for the treatment of brain metastases with radiotherapy, particularly with high-dose, targeted stereotactic radiosurgery, in patients also exposed to checkpoint inhibitor immunotherapy is the risk of developing radionecrosis. This is a pathological exaggerated immune response at the site of former metastasis that in itself causes an inflammatory mass that may be associated with oedema and symptoms due to the effect of the mass on adjacent brain. In some cases this can lead to surgery to relieve symptoms or because of uncertainty as to whether the mass is inflammatory or recurrent tumour. This survey of 50 renal cancer patients reported a radiation necrosis diagnosis in 17.4% of patients treated concurrently with immune checkpoint inhibitor therapy and radiotherapy and 22.2% in patients treated sequentially, and this was symptomatic in 4.3% and 14.8%, respectively. Only two patients received prior whole brain radiotherapy. There were 395 brain metastases analysed. Larger tumour volume treated was a modest risk factor; however, the size of this study was probably too small to give robust estimates of risk factors. Fortunately, most patients had relatively mild symptoms that could be controlled with medical therapy.

Reference: Cancer 2022;128(7):1429-1438

Abstract

Association between sarcopenia and survival of patients with organ-confined renal cell carcinoma after radical nephrectomy

Authors: Lee J et al.

Summary: This retrospective study (2004-14) assessed the influence of preoperative sarcopenia on oncologic outcomes of organ-confined RCC after radical nephrectomy in 632 patients with pT1-2 RCC. Overall, 268 (42.4%) were classified as sarcopenic (preoperative CT skeletal muscle index with gender-specific cut off at third lumbar vertebra of 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women). Sarcopenic patients were older (57 vs 53 years) and more likely to be male (71.3% vs 59.9%) with lower body mass index (BMI; 23.0 vs 25.9 kg/m^2). Sarcopenia was associated with worse OS (94.0% vs 82.1%; $p < 0.001$) and poorer cancer-specific survival (97.5% vs 91.8%; $p < 0.001$). Multivariate analysis suggested that sarcopenia was an independent risk factor for all-cause (HR 2.58; 95% CI 1.02-6.54) and cancer-specific (HR 3.07; 95% CI 1.38-6.83) mortality.

Comment: This relatively large study of Korean patients undergoing nephrectomy for early RCC looked at the role of sarcopenia, or muscle loss, as a risk factor for tumour relapse, overall and cancer-specific survival. A significant degree of sarcopenia can be present and not readily obvious on visual examination, but can be detected and quantified using CT images and appropriate software for analysis. Patients with sarcopenia had similar tumour characteristics; however, their long-term outcomes were worse for both renal cancer and all-cause survival. An important question is whether this is due to systemic effects of the malignancy or to compromised general physical condition. If the latter then a focus on nutritional and physical pre-surgical optimisation (so called "pre-hab") and attention to postoperative recovery (conventional rehabilitation) may help to improve patient outcomes. Studies looking at circulating factors may identify biomarkers and better clarify the pathology driving sarcopenia in some patients with early renal cancers. This can hopefully lead to interventions to improve the outcomes of these patients otherwise suitable for curative intent surgery.

Reference: Ann Surg Oncol. 2022;29(4):2473-2479
Abstract

Patterns of first-line targeted therapy utilization and adherence among older adults diagnosed with metastatic renal cell carcinoma

Authors: Hicks BM et al.

Summary: This US retrospective (2007-15) analysis of cancer registry and administrative claims data assessed patterns of first-line targeted therapy use and adherence in 2093 older adults (aged ≥66 years) with mRCC. Overall, 28.8% of patients received first-line targeted therapy within 4 months of diagnosis, with the number increasing over time. Targeted therapy initiation was associated with older age (1-year increment OR 0.95; 95% CI 0.93-0.97), high comorbidity burden (OR 0.65; 95% CI 0.46-0.93) and clear cell histology (OR 1.54; 95% CI 1.19-2.00). At 120 days after diagnosis, 48.2% of patients had a high proportion of days receiving oral targeted therapy, which was attenuated by inclusion of patients who died (34.2%) during this period.

Comment: This registry and insurance claims database study is useful for describing the reality of treatment administration to older patients with advanced renal cancer. Inclusion cut-off was age of ≥66 years which is consistent with clinical society guidelines; however, there is a significant range in patient health status and suitability for treatment from that age and above. During the period examined, anti-VEGF tyrosine kinase inhibitors were the predominant therapeutic modality but these are associated with significant potential side effects. The study showed a high proportion of patients (71.2%) did not start treatment within 4 months of diagnosis, likely influenced by prioritising quality of life and avoidance of treatment toxicity over survival gain and possibly delaying treatment until significant cancer-related symptoms developed. Significant comorbidities resulted in lower likelihood of receiving cancer treatment. Clinicians may have greater preference for treatment of older patients with single-agent anti-PD1 or anti-PD-L1 antibodies given their relatively lower side effect profile. Treatment initiation likely also depends on the clinical and social support available to help manage side effects and maintain compliance. Optimising patient support and comorbid health are important to allow older patients to access the benefits of active treatment, as is development of therapies with lower overall toxicity.

Reference: J Geriatr Oncol. 2022;13(3):325-333
Abstract

Independent commentary by Associate Professor Alexander Guminski
Associate Professor Alexander Guminski is a medical oncologist working in head and neck cancer, genito-urinary and non-melanoma skin cancers. He has interests in novel biological agents and immunotherapy for treatment of advanced cancers. Specific interests include treatment sequencing, combinations of immunotherapy with radiotherapy, peptide receptor radionuclide therapy and conventional chemotherapy, and use of targeted agents in selected patients. Clinical appointments are at Royal North Shore Hospital, North Shore Private and Mater Hospitals in Sydney. He is a Clinical Associate Professor in Medicine at the University of Sydney Northern Campus, adjunct research fellow at the Kolling Institute in Sydney and clinical lead for trials in the Northern Sydney Health District.

Immune inactivation by CD47 expression predicts clinical outcomes and therapeutic responses in clear cell renal cell carcinoma patients

Authors: Jiang W et al.

Summary: This lab-based study used tumour tissue microarrays to assess the clinical significance of CD47 and its relationship to immune infiltration and molecular features in 1491 patients with clear cell RCC (ccRCC). Overall, patients with high CD47 expression had poorer OS and inferior recurrence-free survival and CD47 expression was associated with a heavily immune infiltrated but immunosuppressed microenvironment. $CD8^+$ T-cell infiltration had a discordant prognostic value with varying CD47 expression, with high $CD8^+$ T-cell infiltration in high CD47 patients being associated with worse clinical outcome while in low CD47 patients it was associated with favourable prognosis. Mutated *PBRM1* and *SETD2* genes were correlated with decreased mRNA expression of CD47. Patients with high CD47 expression had an improved PFS when receiving immune checkpoint inhibitor plus VEGF receptor/tyrosine kinase inhibitor combination therapy

Comment: Identification of important modulators of response to checkpoint inhibitor immunotherapy is a key goal of cancer research. The components to this study included a large single institution cohort from China, a large publicly available database and also data from a high recruiting clinical trial with well curated patient follow-up. CD47 is expressed on many cells and acts as an inhibitor of cell phagocytosis (ingestion and destruction) by certain immune cells (macrophages and dendritic cells). Abundant expression of CD47 is seen in many tumours and is associated with worse prognosis. Overall, this study found that expression of the marker CD47 conferred worse PFS and OS for renal cancer patients. This study also elucidates one mechanism by which effector immune cell ($CD8^+$ T cells) infiltration into tumour may not always lead to an anti-tumour immune response. High $CD8^+$ expression has been frequently associated with improved outcomes and response to immunotherapy; however, this study highlights that in renal cancer it is conditional on CD47 expression. Patients with high $CD8^+$ expression and low CD47 expression did better; however, high $CD8^+$ with high CD47 saw poorer outcomes. This is important as CD47 can potentially be targeted and so may be a clinically useful way to overcome innate tumour resistance to immunotherapy in selected patients, provided its normal protective effect on host cells can be sufficiently preserved.

Reference: Urol Oncol. 2022;40(4):166.e15-166.e25
Abstract

Stereotactic radiotherapy and short-course pembrolizumab for oligometastatic renal cell carcinoma – The RAPPORT Trial

Authors: Siva S et al.

Summary: The multicentre, single-arm phase I/II RAPPORT trial assessed 20 Gy stereotactic ablative body radiotherapy (SABR) followed by pembrolizumab in 30 patients with oligometastatic ccRCC. Over a median follow-up of 28 months, 83 oligometastases were irradiated. Grade 3 treatment-related adverse events occurred in 4 (13%) patients; pneumonitis (n = 2), dyspnoea, and elevated ALP/ALT. At 2 years, freedom from local progression was 92%, objective response rate (ORR) was 63% and disease control rate was 83%. Estimated 1-year OS was 90%, 2-year OS was 74%, 1-year PFS was 60% and 2-year PFS was 45%.

Comment: Combining radiotherapy with immunotherapy has potential synergies due to effects of radiation on the tumour and tumour microenvironment; however, the interaction may be complex. Direct destruction of tumour can lead to release of neo-antigens and may eradicate response suppressive immune cells within the tumour surrounds, both of which can help stimulate an effective anti-cancer action in a checkpoint inhibitor-primed patient. However, some documented preclinical effects of radiotherapy may lead to a lessening of the immunotherapy anti-tumour effect, suggesting that sequencing and interval of radiotherapy with checkpoint inhibitor treatment are important. This Australian study recruited 30 patients having had ≥2 previous lines of systemic therapy and with ≤5 RCC metastases all suitable for ablative radiotherapy. Following radiotherapy, patients received standard dose pembrolizumab immunotherapy with treatment completed after 24 weeks. The majority of lesions treated were lung metastases. Overall control of the treated sites was high at 92% at 2 years; however, most of the patients had progressed elsewhere by this timepoint. Toxicity appears acceptable, and of interest, three of the four higher-grade toxicities involved pulmonary complications, which may relate to the frequent combination of lung radiotherapy with immunotherapy. This successful phase I/II trial establishes a combination that can be tested in a randomised trial against systemic therapy alone.

Reference: Eur Urol. 2022;81(4):364-372
Abstract

Nivolumab in combination with stereotactic body radiotherapy in pretreated patients with metastatic renal cell carcinoma. Results of the phase II NIVES study

Authors: Masini C et al.

Summary: The multicentre, single-arm, phase II NIVES trial assessed the use of SABR (10 Gy in three fractions for 7 days) plus nivolumab (240 mg every 14 days for 6 months and then 480 mg every 4 weeks) in 69 mRCC patients. Over 1.5 years of follow-up, 23 patients died, ORR was 17% and disease control rate was 55% with a median PFS of 5.6 months (95% CI 2.9-7.1) and median OS 20 months (95% CI 17-not reached). Median time to treatment response was 2.8 months and median duration of response was 14 months.

Comment: This study also looked at the use of radiotherapy in combination with immunotherapy in patients with renal cancer; however, with some differences compared to the Australian study above led by Dr Siva. The patients had metastatic disease after 2 or 3 previous lines of systemic therapy, with only one metastatic site selected for radiotherapy. The immunotherapy agent used was nivolumab, which is an anti-PD1 antibody as is pembrolizumab. Radiotherapy was commenced at the same time as the first immunotherapy infusion. The study aimed to improve the historic nivolumab response rate of around 25% in the second-line setting to 40% due to mechanisms as discussed above. However, the cohort of 69 patients showed a response rate of 17% although the disease control rate was 55%. The median PFS was 5.6 months and median OS 20 months, and overall, the authors did not see a signal for benefit of radiotherapy to only part of the metastatic burden in advanced patients commencing late line nivolumab immunotherapy. These data are nonetheless important in helping to design further studies targeting patients with oligometastatic or oligoprogressive disease and consideration of timing when combining radiotherapy and immunotherapy.

Reference: Eur Urol. 2022;81(3):274-282
Abstract

Incidence and distribution of new renal cell carcinoma cases: 27-year trends from a statewide cancer registry

Authors: Alzubaidi AN et al.

Summary: This retrospective (1990-2017) analysis of the Pennsylvania Cancer Registry assessed the incidence, distribution, and trends of new RCC cases over 27 years. Overall, 59,628 RCC cases were recorded, 86% were >50 years of age, 61% were males, and 89% were Caucasian. SEER staging included 64% local, 17% regional, and 16% distant disease. Over the study interval, age-adjusted rates (AAR) of all RCC cases increased from 9.9 to 18.0 patients per 100,000 population with an average annual percent change (APC) of 2.3% ($p < 0.01$). AAR for local disease increased from 5.4 to 12.7 patients per 100,000 population (APC 3.2%; $p < 0.01$) while regional disease increased from 1.9 to 2.9 patients per 100,000 population (APC 1.0%; $p = 0.01$). Younger patients (<50 years) experienced a greater rate of increase than older patients (APC 3.8% vs 2.0%; $p < 0.05$).

Comment: The longer-term trends in cancer incidence, prevalence and survival are influenced by changes in diagnostic testing and therapeutics as well as potential changes in patient risk factors for developing specific cancers (such as obesity, changes in exercise or smoking and other health behaviours, as well as migration and changes in ethnic mix). This study has looked over a 27-year period from 1990 to 2017 in the US state of Pennsylvania with almost 60,000 renal cancer cases recorded. The overwhelming number of patients were over 50 years old and Caucasian, with 61% being male. Approximately two-thirds of cases had localised tumours. The data showed a near doubling of age-adjusted incidence over the time of the study data with an annual increase of 2.3% per year. Although inadvertent detection due to imaging for other presentations likely contributed to some of the increase, one-third of patients presented with either locally advanced or frankly metastatic disease. Behavioural changes such as obesity may also have contributed to some of the increase. Data on changes in incidence are important for planning services, investments in therapies and providing public health advice on modifiable risk factors.

Reference: J Kidney Cancer VHL. 2022;9(2):7-12
Abstract

A phase 1-2 trial of sitravatinib and nivolumab in clear cell renal cell carcinoma following progression on antiangiogenic therapy

Authors: Msaouel P et al.

Summary: This phase I/II trial assessed the optimal dosage for the tyrosine kinase inhibitor sitravatinib plus a fixed dose of nivolumab in 42 immunotherapy-naive patients with ccRCC refractory to previous antiangiogenic therapies. Combination therapy had no unexpected toxicities, and the ORR was 35.7% with a median PFS of 11.7 months. Overall, 80.1% of patients were alive after a median follow-up of 18.7 months. Response to sitravatinib plus nivolumab was correlated with baseline peripheral blood neutrophil-to-lymphocyte ratio. Patients with liver metastases had durable responses like those in patients without liver metastases. Correlative studies suggested that a reduction in immune-suppressive myeloid cells in the periphery and in the tumour microenvironment occurred with sitravatinib.

Comment: Overcoming resistance to immunotherapy is a key goal of renal cancer research. The tumour microenvironment contains a dynamic mix of immune cells with complex functional interactions. Immune cells from the myeloid lineage have been identified to confer a suppressive effect reducing the activity of anti-cancer effector immune cells that have been stimulated by checkpoint inhibitor therapy. An ability to down-regulate myeloid derived cells has therefore been proposed as a logical mechanism to augment the effect of immunotherapy. Sitravatinib is a tyrosine kinase inhibitor with targets including AXL, MERTK and PDGFR, all of which have been proposed to mediate the immune suppressive effects of myeloid-derived cells. Pre-clinical evidence also suggest sitravatinib can increase the number of exhausted effector $CD8^+$ T cells in tumours supporting combination with checkpoint inhibitor immunotherapy. This early phase trial has established a clinically feasible combination of sitravatinib and nivolumab in previously untreated renal cancer patients. No unexpected toxicities were seen, and a reasonable response rate was observed. Further studies will be required to see if there is advantage to the combination compared with other available treatments and whether tests can be identified to select patients more likely to respond to the combination.

Reference: Sci Transl Med. 2022;14(641):eabm6420
Abstract

A proteogenomic analysis of clear cell renal cell carcinoma in a Chinese population

Authors: Qu Y et al.

Summary: This Chinese study examined the proteogenomics of 232 tumour and adjacent non-tumour tissue samples from ccRCC patients. CcRCC tumour tissue had extensive metabolic dysregulation and enhanced immune response. Molecular subtyping identified three subtypes (GP1-3), with GP1 the most aggressive exhibiting the strongest immune phenotype, increased metastasis, and metabolic imbalance. Nicotinamide N-methyltransferase (NNMT) was identified as a potential marker of ccRCC and a drug target for GP1. NNMT induced DNA-dependent protein kinase catalytic subunit homocysteinylation, increased DNA repair, and promoted ccRCC tumour growth.

Comment: This study in a high-profile journal explored combined genome and protein expression profiling of ccRCC from an East Asian population with a focus on metabolic re-programming as this has been identified previously in studies on renal carcinomas from Western populations. Samples of tumour and adjacent normal renal tissue from 232 patients with median follow-up of 85 months were analysed. Important findings were the association of chromosome 12q gain and 3p loss with worse disease-free survival and OS and dysregulated metabolic and immune function with corresponding aberrant changes in gene transcripts. A total of 10,475 non-silent mutations in 6875 genes were identified with the most frequent including *VHL*, *PBRM1* and *SETD2*. Interestingly *VHL* appears less frequently mutated in East Asian populations compared with a European cohort. At the protein level, 2756 proteins were differentially detected between tumour and adjacent tissue. Three subtypes of tumour could be assigned based on complete molecular subtyping, with an aggressive subtype that could be characterised by proteomic sequencing. This study reports a large number of potential therapeutic targets including NNMT which causes homocysteine metabolism dysregulation which in turn directly affects DNA repair, establishing a link with the aggressive malignant phenotype. Further research to translate the insights from this and similar studies into therapies will be keenly awaited.

Reference: Nat Commun. 2022;13(1):2052
Abstract

