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Welcome to the 8th issue of Renal Cancer Research Review.

Something old, something new; in this issue we have reports of new agents, new versions of old agents, new ways of taking old agents, confirmation that old agents don’t work, suggestions that new ways of delivering old agents might help, and what to do with old treatments when new agents work well. The first paper in this issue reports promising results from a phase I/II study of a first-in-class hypoxia-inducible factor (HIF)-2α inhibitor, MK-6482. MK-6482 was well tolerated with a favourable safety profile in heavily pretreated patients with clear cell RCC. A phase III trial is planned.

The findings of two vaccine studies in patients with metastatic RCC are reviewed. The first paper concluded rocapudencel-T (a vaccine prepared from dendritic cells, co-electroporated with tumor and CD40L RNA) did not improve overall survival in combination with sunitinib as first-line therapy. The second, α1,3Gal-expressing allogeneic immunotherapy, was well tolerated and demonstrated antitumor activity in pretreated metastatic RCC.

Also included are two articles exploring interleukin-2 therapy. Bempegaldesleukin, an engineered IL-2 cytokine prodrug and with a slow-release formulation, mitigated toxicity and had beneficial effects on anti-tumour immune responses. Results of a phase I/II study found administration of IL-2 as a continuous infusion over 8 hours mitigated toxicity while clinical benefits was equivalent to high-dose bolus administration.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,

Dr Craig Gedye
craig.gedye@researchreview.com.au

Phase I/II study of the oral HIF-2 α inhibitor MK-6482 in patients with advanced clear cell renal cell carcinoma (RCC)

Authors: Choueiri TK, et al

Summary: Fifty-five patients with advanced clear cell renal cell carcinoma (RCC) who had received at least 1 prior therapy were enrolled. Patients were administered 120 mg of MK-6482, a hypoxia-inducible factor (HIF)-2α inhibitor, orally once daily, with a median follow-up of 13 months. The authors reported the most common adverse events (AEs) were anaemia (75%), fatigue (67%), dyspnoea (47%), nausea (33%), and cough (31%). They noted anaemia (26%) and hypoxia (15%) were the most common grade 3 AEs, and there were no grade 4/5 drug-related AEs. Overall response rate (ORR) was 24% with 13 confirmed partial responses (PRs). Thirty-one patients (56%) had stable disease (SD), with a disease control rate of 80%. Thirty-five of 52 (67%) patients with baseline and post-baseline assessments had tumour shrinkage. Median progression-free survival (PFS) was 11.0 months and the 12 month PFS rate was 49%. As of May 15, 2019, 30 patients (55%) discontinued treatment appeared reasonable with only two patients discontinuing the treatment due to side effects. This is promising early data; in fact so promising that the current randomised phase II trial using everolimus as the comparator is arguably unethical without cross-over. Combination of HIF-2α inhibition with checkpoint immunotherapy is an obvious next step if monotherapy activity is confirmed.

Reference: J Clin Oncol 2020 Feb;38(6): 611-611

Abstract

Comment: Advanced kidney cancer is best treated today with combinations of immunotherapeutic and/or anti-angiogenic drugs. Unfortunately these drugs still fail most people, and their disease will progress. A plethora of me-too options are available but are of limited efficacy. Most clear cell kidney cancers are driven by VHL gene loss, which signals through HIF-2α to stimulate the vascular endothelial growth factor and promote cancer invasion, growth and proliferation. A new oral agent called MK-6482 inhibits HIF-2α and was studied in 55 patients who have been failed by a median of three prior therapies. A total of 24% patients had significant tumour shrinkage and almost 80% experienced some kind of disease control. The patient’s experience of treatment appeared reasonable with only two patients discontinuing the treatment due to side effects. This is promising early data; in fact so promising that the current randomised phase II trial using everolimus as the comparator is arguably unethical without cross-over. Combination of HIF-2α inhibition with checkpoint immunotherapy is an obvious next step if monotherapy activity is confirmed.

Independent commentary by Dr Craig Gedye
BSc(Hons) MBChB FRACP PhD

Dr Gedye is a physician/scientist, dual trained as a medical oncologist, clinical trialist and basic science researcher. He works for patients with melanoma, brain, kidney, prostate, testis, and bladder cancer at the Calvary Mater Newcastle, and is the Clinical Research Director at the NSW Statewide Biobank. He chairs the Renal Cancer Subcommittee for ANZUP Cancer Trials Group, and is the coordinating principal investigator for the KeyPAP and UNISON trials. He undertakes translational and basic cancer research at the Hunter Medical Research Institute, University of Newcastle. Dr Gedye’s research focus is on cancer heterogeneity; why treatments work for some patients but not others. This challenging research spans the translational spectrum from patient experience to basic science.
Results of a multicenter phase II study of atezolizumab and bevacizumab for patients with metastatic renal cell carcinoma with variant histology and/or sarcomatoid features

Authors: McGregor BA, et al

Summary: The study cohort consisted of patients with variant histology RCC or RCC with ≥ 20% sarcomatoid differentiation. Patients (n=60) received atezolizumab 1,200 mg and bevacizumab 15 mg/kg intravenously every 3 weeks; the majority (65%) were treatment naive. The ORR for the overall population was 33% and 50% in patients with clear cell RCC with sarcomatoid differentiation and 26% in patients with variant histology RCC. Median PFS was 8.3 months (95% CI, 5.7 to 10.9 months). Programmed death-ligand 1 (PD-L1) status was available for 36 patients; 15 (42%) had ≥ 1% expression on tumour cells. ORR in PD-L1-positive patients was 60% (n = 9), compared to 19% (n = 4) in PD-L1-negative patients. Eight patients (13%) had treatment-related grade 3 toxicities, and there were no treatment-related grade 4-5 toxicities.

Comment: In the absence of head-to-head comparisons (which will never occur), RCC and urothelial carcinoma clinical trials have given the strongest hints that PD1 antibodies are inferior to PD1 antibodies in the clinic. The combination of atezolizumab and bevacizumab is no longer being developed in RCC for example. But data from existing trials are still illustrative. This abstract concurs with other reports of reasonable activity (50% response rate) of checkpoint inhibitors for people with sarcomatoid differentiation in their cancers, much greater than the very poor outcomes experienced when treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs).

Reference: J Clin Oncol 2020 Jan;38(1): 63-70

Abstract

Pathologic response and surgical outcomes in patients undergoing nephrectomy following receipt of immune checkpoint inhibitors for renal cell carcinoma

Authors: Singla N, et al

Summary: Eleven nephrectomies (10 radical, 1 partial) were performed for RCC in 10 patients after nivolumab monotherapy or combination ipilimumab/nivolumab. All surgical margins were negative and median postoperative follow-up was 180 days. One patient had complete response to immunotherapy and 3/4 patients who underwent metastasectomy for hepatic, pulmonary, or adrenal lesions had no detectable malignancy in any of the metastases resected. Four patients experienced a complication. One patient died of progressive disease ≥ 3 months after surgery, and 1 patient died of pulmonary embolism complicated by sepsis.

Comment: Who could have imagined this dilemma 5 years ago: “the immunotherapy has controlled the cancer everywhere else in my body… doctor, should I have the cancer in my kidney removed?” With the failures of CARMENA and SURTIME trials to show benefit for cytoreductive nephrectomy in people taking VEGFR TKI, it is almost surreal to now be reconsidering this issue again for the checkpoint inhibitors. This small report indicates that surgery might be considered in some patients taking ICI, but that patients remain vulnerable to periprostatic complications and to progression of their disease. Whether surgery helps or hinders immunotherapy should be the question of prospective clinical trials.

Reference: Urol Oncol. 2019 Dec;37(12):924-931

Abstract

Cost-neutral optimization of pazopanib exposure by splitting intake moments: A prospective pharmacokinetic study in cancer patients

Authors: Greenwood SL, et al

Summary: This cross-over trial compared the pharmacokinetics of pazopanib 800 mg once daily with pazopanib 400 mg twice daily in nine patients. With 800 mg once daily dosing, median minimum plasma concentration, area under the concentration-time curve from 0 to 24 h, and maximum plasma concentration were 22.3 mg/L (interquartile range 18.5-27.6), 773 mg h/L (557-1009), and 40.6 mg/L (36.4-56.4) compared with 41.6 mg/L (30.5-55.8, p = 0.004), 942 mg h/L (885-1419, p = 0.027), and 40.6 mg/L (36.4-56.4) compared with 41.6 mg/L (30.5-55.8, p = 0.074) with 400 mg twice daily.

Comment: Some days I feel more stupid than usual… This tiny study uncovers once again the seemingly bottomless reservoir of ignorance that we carry into each clinic room, when we see each patient. One of the points of difference claimed for pazopanib compared to sunitinib is that it is ‘less toxic’: which might be explained by the observation in many studies that pazopanib is effectively under-dosed, and that many people can’t experience higher dose exposure due to GI absorption limitations. This study shows that a cost-neutral strategy of BD dosing can dramatically - 80% - increase steady-state plasma concentrations of the drug. Imagine making a drug more effective just by dosing it differently? Given the major pivot to first-line immunotherapy for metastatic RCC, this is more of historical interest, but it once again challenges us to continue to optimise therapy throughout the life-cycle of a drug. The registrational trial is just the beginning.


Abstract

Results of the ADAPT phase 3 study of Rocapudencel-T in combination with sunitinib as first-line therapy in patients with metastatic renal cell carcinoma

Authors: Figlin RA, et al

Summary: Patients with metastatic RCC were randomised to Rocapudencel-T plus standard of care (SOC, n=307) and SOC alone (n=155). The investigators reported median overall survival (OS) in the combination and SOC groups was 27.7 months and 32.4 months respectively. PFS was 6.0 months and 7.8 months for the combination and SOC groups respectively. The ORR was 42.7% for the combination group and 39.4% for the SOC group. Immune responses were detected in 70% of patients treated with Rocapudencel-T and correlated with OS. Furthermore, the vaccine produced IL-12 and higher numbers of T regulatory cells present in the peripheral blood of mRCC patients.

Comment: Cancer vaccines don’t work… This large phase III clinical trial in renal cell carcinoma used a variation of the sipuleucel-T recipe – leukopheresis of peripheral blood mononuclear cells, culture of these cells ex vivo to create in vitro dendritic cells, load these cells up with potential tumour targets (in this form, RNA) and add some spice with an immune stimulator (CD40L RNA). Mix carefully, immunise patients already taking a standard therapy (that is somewhat immuno suppressed in itself) and then… watch as nothing happens. Well, almost nothing. Biomarkers of immune stimulation and suppression associated with survival, again indicating that RCC is an immunogenic cancer. Cancer vaccines don’t work.

Reference: Clin Cancer Res. 2020 Feb 7. [Epub ahead of print]

Abstract

A phase I study of alpha-1,3-galactosyltransferase-expressing allogeneic renal cell carcinoma immunotherapy in patients with refractory metastatic renal cell carcinoma

Authors: Hahn AW, et al

Summary: HyperAcute Renal (HAR) immunotherapy consists of two allogeneic renal cancer cell lines genetically modified to express α1,3Gal. A total of 18 patients with refractory metastatic RCC were enrolled. HAR was injected intradermally weekly for 4 weeks then biweekly for 20 weeks. Concomitant treatment was permitted after the initial 2 months of HAR therapy. The investigators observed two grade 3 AEs attributed to HAR, lymphopenia and injection site reaction. There were no grade 4/5 AEs. One patient had a PR and eight patients had SD, for a disease control rate of 50% (9/18). Median OS with low-dose HAR was 14.2 months and was 25.3 months with high-dose HAR.

Comment: Cancer vaccines might work… In this very small study, an interesting and novel way of creating a cancer vaccine was tested. Genetically modifying cultured kidney cancer cell lines to express bacterial cell surface markers, the authors were able to deliver a vaccine to patients who had been failed by many other lines of therapy, and remarkably generated evidence of clinical benefit, with even one patient responding to therapy. The vaccine works by encoding human kidney cancer cells with the GATA1 gene, which coats cells with α1,3 Gal, a carbohydrate found in most mammalian cell membranes, but not found in primates, including humans, who have lost the gene. While this is a barrier to xenotransplantation of organs… it is exploited in this strategy as a way of aggressively activating the immune system, and indeed there are some toxicities of the vaccine. Cancer vaccines might work…

Reference: Oncologist. 2020 Feb;25(2):121-e213

Abstract

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Please CLICK HERE to download CPD Information

Reference: Oncologist. 2020 Feb;25(2):121-e213

Abstract
Please refer to the Approved Product Information before prescribing. The Product Information is available upon request from BMS Medical Information Department: 1800 067 567 or can be accessed at http://www.medicines.org.au/files/bqpopdiv.pdf

PBS INFORMATION: OPDIVO monotherapy – Authority required (STREAMLINED) for the treatment of patients with advanced (Stage IV) clear cell variant renal cell carcinoma. OPDIVO in combination with YERVOY – Authority required (STREAMLINED) for the treatment of patients with intermediate/poor-risk, previously untreated advanced clear cell variant renal cell carcinoma. Refer to PBS Schedule for full authority information.

WARNING: IMMUNE-RELATED ADVERSE REACTIONS WITH OPDIVO AND YERVOY (IPILIMUMAB) COMBINATION THERAPY. Immune-related adverse reactions are seen more frequently, and are more severe, with OPDIVO and YERVOY combination therapy than with OPDIVO or YERVOY monotherapy. Immune-related adverse reactions can involve any organ system. The majority of these initially manifest during treatment; however, a minority can occur weeks to months after discontinuation. Some immune-related adverse reactions can be permanent (such as thyroid dysfunction and diabetes mellitus). Life-threatening or fatal immune-related adverse reactions have occurred include colitis, intestinal perforation, hepatitis, pneumonitis, hypophysitis, adrenal insufficiency, toxic epidermal necrolysis, myocarditis, encephalitis and myasthenia gravis (see Sections 4.4 Special warnings and precautions for use and 4.8 Adverse Effects). Early diagnosis and appropriate management are essential to minimise life-threatening complications (see Section 4.2 Dose and method of administration). Monitoring at least prior to each dose is recommended. Advise patients of the importance of immediately reporting possible symptoms. Physicians should consult the YERVOY product information prior to initiation of OPDIVO in combination with YERVOY. The combination of OPDIVO and YERVOY should be administered and monitored under the supervision of physicians experienced with the use of immunotherapy in the treatment of cancer.

Bempegaldesleukin selectively depletes intratumoral Tregs and potentiates T cell-mediated cancer therapy

Authors: Sharma M, et al

Summary: Bempegaldesleukin (NKTR-214) is an interleukin-2 (IL-2) cytokine prodrug that provides sustained activation of the IL-2 pathway. This group assessed NKTR-214 in combination with anti-PD-1 and anti-CTLA-4 inhibition therapy or peptide-based vaccination in mice. They found NKTR-214 had superior anti-tumour activity over native IL-2 and systemically expands anti-tumour CD8+ T cells while inducing Treg depletion in tumour tissue but not in the periphery. In addition, similar trends of intratumoral Treg dynamics were observed in a small cohort of patients treated with NKTR-214.

Comment: What’s old is new again? Part 1: After it became clear in the 1970 and 1980s that RCC is the chemo-resistant cancer par excellence, the treatment paradigm in advanced kidney cancer relied on immune hormones, cytokines such as interferon and IL-2. Given at high-dose to young patients with excellent performance status, people needed to be admitted to ICU for isotropic support whilst the systemic inflammatory response syndrome unleashed by the bolus of cytokine washed through their body. Perhaps only 10% of patients were eligible for treatment, and in 10% of these, durable complete responses were experienced; 1-in-100 chance of a cure. And 10% mortality during the ICU admission. Eek. With the surge of interest in checkpoint immunotherapy, discarded immune strategies like vaccines and cytokines are coming back into play. Several new formulations of these cytokine agents are being tested, often delivering in a slow-release format to mitigate toxicity. One agent, called NKTR-214 for now, is a pegylated formulation of IL-2, and is in late-stage trials in several cancers. In this pre-clinical manuscript, the authors show that not only does the “slow-release” formulation mitigate toxicity, but that it also has a beneficial effect on anti-tumour immune responses. One of the theoretical weaknesses of IL-2 given in large bolus doses was that it promoted the growth of immunosuppressive regulatory T-cells as much as effector CD8 T-cells. NKTR-214 appears to skew this more favourably towards an anticancer response, at least in preclinical models. Watch this space.


Abstract

Interleukin-2 chronotherapy for metastatic renal cell carcinoma: Results of a phase I-II study.

Authors: Re GL, et al

Summary: This study explored IL-2 therapy administered according to the circadian rhythm’s influence on the immune and hormonal systems. Two patients were treated at 5:00-13:00, 15 at 13:00-21:00, and 13 at 21:00-5:00. Follow-up was for a median of 16 months. The team observed 9 cases of grade 3 toxicity in 7 patients at the highest dose (16.8 MlU/m2); no grade 4 toxicity occurred. One patient was lost to follow-up; 3 patients were alive at last contact; and 29 patients died. There were 4 cases of grade 3 toxicity at 13:00-21:00, and 13 at 21:00-5:00. Follow-up was for a median of 16 months. The team

Comment: What’s old is new again? Part 2: A report from long-term follow-up of a small study suggests that IL-2 delivered by infusion over 8 hours is more tolerable than bolus delivery. The study occurred in the cytokine and TKI era, and though it was designed to test the idea of giving treatment at a certain time of day, so-called chronotherapy, the secondary analysis is more revealing. By giving IL-2 as a continuous infusion over 8 hours, the toxicity is much more muted, and clinical benefit was at least as frequent as the high-dose bolus delivery schedule that mandated patients be admitted to ICU. In the era of a number of “slow-release” IL-2 formulations being tested in early phase clinical trials, it suggests that there may be a path to reintroduce cytokine therapy as an adjunct to immune checkpoint inhibitors.

Reference: Cytokine. 2020 Apr;128:154984

Abstract

Safety and efficacy of restarting immune checkpoint inhibitors after clinically significant immune-related adverse events in metastatic renal cell carcinoma

Authors: Abou Aalawi S, et al

Summary: This retrospective study included patients with metastatic RCC treated with ICI who had >1 week treatment interruption for immune-related adverse events (irAEs). Of 409 patients treated with ICIs, 80 developed irAEs resulting in treatment interruption; 45% of whom were restarted on an ICI and 55% who permanently discontinued. After re-treatment, 50% experienced subsequent irAEs (12 new, 6 recurrent) with 19% grade 3 events and 13 drug interruptions. Median time to irAE recurrence after re-treatment was 2.8 months. Retreatment resulted in 6 (23.1%) additional responses in 26 patients whose disease had not previously responded. From first ICI initiation, median time to next therapy was 14.2 months and 9.0 months, and 2-year OS was 76% and 66% in the retreatment and discontinuation groups, respectively.

Comment: Sailing between Scylla and Charybdis; what do you do when a patient has experienced a severe irAE on checkpoint immunotherapy, and then they experience further disease progression? Do you re-expose them to immunotherapy… or not? This report in RCC mirrors existing retrospective real word data in the melanoma field; consider retreatment, but prepare the patient and yourself for a bumpy ride. The rate of further irAE was considerable, and many of these were again severe, grade 3 or above, but overall these could be managed, and patients appeared to live as long, if not longer than those who chose not to rechallenge with the ICIs. Tie yourself to the mast and hope for a safe journey.

Reference: J Immunother Cancer. 2020 Feb;8(1)

Abstract

Nivolumab in patients with metastatic renal cell carcinoma and chronic hepatitis C virus infection

Authors: Taimafeyo I, et al

Summary: This retrospective study included data from patients with clear-cell metastatic RCC, chronic HCV infection (case study group), and had received nivolumab until disease progression or unacceptable toxicity. A total of 44 matched patients were included. The researchers concluded HCV-infected patients had significantly longer OS and PFS. Median OS was 27.5 and 21.7 months in study and control groups, respectively (P = 0.005); median PFS was 7.5 and 4.9 months, respectively (P = 0.013). Despite no differences in ORR between groups (27% vs. 23%, P = 0.7), patients with HCV had significantly more durable responses (P = 0.01). Furthermore, nivolumab was well tolerated in all HCV-positive patients and did not significantly impact HCV concentration in the absence of antiviral therapy.

Comment: Finally, this report brings us full-circle in the immune checkpoint inhibitor story. When the CTLA4 and PD1 immune checkpoints were first appreciated and studied, the immediate therapeutic impact was imagined to be in chronic viral infections; HIV, HBV and HCV. Targeting immune checkpoints for cancer treatment was a secondary, but now burgeoning indication. As is usual, clinical trials of novel medications have excluded people suffering comorbid conditions, such as chronic HCV infection. The authors report that, not only was single-agent anti-PD1 immunotherapy safe and tolerable in this population of patients, they appeared to benefit more than people without viral infection. No appreciable impact on HCV viral load was noted, so the mechanism for why these people might benefit more remains speculative.

Reference: Cancer Immunol Immunother. 2020 Feb 20 [Epub ahead of print]

Abstract

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