Bladder Cancer Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

AE = adverse event; **BCG** = bacillus Calmette–Guérin; **ctDNA** = circulating tumour DNA; **HR** = hazard ratio; **MMC** = mitomycin C; **MVAC** = methotrexate, vinblastine, doxorubicin, cisplatin; **(N)MIBC** = (non-) muscle-invasive bladder cancer; **OS** = overall survival; **PFS** = progression-free survival; **5FU** = fluorouracil.

Welcome to the latest issue of Bladder Cancer Research Review

We begin with a phase 2 study which indicates that a complete response following gemcitabine, cisplatin and nivolumab may facilitate bladder sparing in patients with MIBC. This is followed by a single-arm trial which showed that patients administered neoadjuvant durvalumab alongside chemotherapy followed by cystectomy demonstrated high event-free and overall survival rates at 2 years. The next paper reports on the encouraging feasibility of genomic profiling via plasma ctDNA as an option to facilitate timely genotype-matched therapies in metastatic urothelial cancer. We conclude with an intriguing study which demonstrated equivalent outcomes among urothelial cancer patients treated with either the new gold standard enfortumab vedotin or a pembrolizumab platinum rechallenge – this suggests that a platinum rechallenge may be a feasible option for those ineligible for enfortumab vedotin.

We hope you find these and the other selections in this review interesting and informative, and we welcome your thoughts and comments.

Warm regards,

Associate Professor Andrew Weickhardt
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Gemcitabine and cisplatin plus nivolumab as organ-sparing treatment for muscle-invasive bladder cancer

Authors: Galsky MD et al.

Summary: This phase 2 trial evaluated the outcomes following four cycles of gemcitabine, cisplatin and nivolumab as a bladder-sparing treatment among 76 patients with MIBC. Those who achieved a clinical complete response were able to continue without cystectomy. A total of 33 patients (43%) achieved a clinical complete response, 32 of whom chose to not undergo cystectomy. The response rate had a positive predictive value of 0.97 for the composite outcome (<ypT1N0 among those who chose immediate cystectomy or 2-year metastasis-free survival among those who did not undergo immediate cystectomy).

Comment: Do patients with MIBC need a cystectomy or radiation? This fascinating but small trial shows that some patients treated with chemotherapy and nivolumab develop a complete response to therapy that is durable, and may not need treatment with surgery or radiation to their bladder for many years. 43% of patients developed a complete response, and of these, only 8 of 32 developed local recurrence needing cystectomy over the median follow-up period of 30 months. Only one patient developed metastatic recurrence. Immune biomarkers were promising but not definitive in predicting outcomes. These data suggest further trials are warranted of bladder preservation in patients treated neoadjuvantly with immunotherapy. Note that a concurrent alternative trial with chemotherapy only using dose-dense MVAC was closed prematurely due to an excess of metastatic recurrences in the patients who chose subsequent bladder preservation alone.

Reference: Nat Med. 2023;29(11):2825-34
Abstract

Perioperative chemoimmunotherapy with durvalumab for muscle-invasive urothelial carcinoma

Authors: Cathomas R et al.

Summary: In this primary analysis of the single-arm, phase 2 SAKK 06/17 trial, researchers explored the value of adding neoadjuvant durvalumab alongside gemcitabine/cisplatin chemotherapy in 52 evaluable patients with stage cT2-T4a cN0-1 MIBC, followed by radical surgery and adjuvant durvalumab. At 2 and 3 years, event-free survival rates were 76% and 73%, respectively, while OS rates were 85% and 81%. Following resection, 17 patients (33%) achieved a complete pathologic response and 31 (60%) a pathologic response <ypT2 ypN0. During neoadjuvant treatment, 42% and 25% of patients experienced grade 3 and 4 treatment-related AEs.

Comment: Neoadjuvant chemotherapy and immunotherapy in the earlier-discussed HCRN trial from Galsky et al. showed promise in terms of long durable complete responses. This European study used durvalumab with chemotherapy in contrast, with a not-dissimilar response rate of 33%, but all patients proceeded to cystectomy. Side effects were manageable. Larger trials of chemotherapy, chemotherapy with immunotherapy or immunotherapy alone are pending to better define the optimal neoadjuvant strategy in MIBC.

Reference: J Clin Oncol. 2023;41(33):5131-9
Abstract

Clinical utility of plasma ctDNA sequencing in metastatic urothelial cancer

Authors: Helal C et al.

Summary: These researchers investigated the feasibility of plasma circulating tumour DNA (ctDNA) to facilitate timely genomic profiling in patients with metastatic urothelial cancer. A total of 140 patients enrolled in the STING trial were included in the analysis. Assay results were available after a median of 20 days. Overall, ctDNA analyses revealed a similar genomic landscape to what was seen in tissue samples, with high concordance (r=0.843; p<0.001). A total of 63 patients (45%) had at least one actionable target; 39 patients (21.1%) showed a high tumour mutational burden, 20 (10.8%) harboured *FGFR3* alterations and 14 (7.6%) homologous recombination deficiency alterations. Among 63 patients who were advised to undergo matched therapy, eight underwent treatment, with a median PFS of 5.2 months and overall response rate of 50%. Patients with *FGFR3* alterations showed shorter PFS with immunotherapy than other patients.

Comment: Molecular profiling of urothelial cancer patients has become important due to the activity, albeit still modest, of *FGFR* inhibitors. Patients with metastatic disease have an approximate 10-30% chance of an *FGFR* mutation or fusion in their tumours, and the FDA approval of erdafitinib and trials of newer *FGFR* inhibitors point to the utility of the testing pathway. The ctDNA detection of mutations is encouraging in this paper, given the difficulties in some patients with metastatic disease in obtaining tissue, or time from original tissue collection. The paper is enhanced by comparison of mutation profiling with tissue-based testing pathways, showing high concordance.

Reference: Eur J Cancer. 2023:195:113368
Abstract

Genomic tumor correlates of clinical outcomes following organ-sparing chemoradiation therapy for bladder cancer

Authors: Kamran SC et al.

Summary: In an effort to identify molecular features associated with favourable long-term responses to bladder-sparing trimodality therapy, these researchers conducted whole-exome sequencing and transcriptome profiling on pretreatment tumours of 76 patients with MIBC. At a median follow-up of 74.6 months, 39 patients showed an unfavourable long-term response while 37 showed a favourable response. Outcomes following trimodality therapy were not predicted by tumour mutational burden. Improved locoregional control and modified bladder-intact event-free survival were associated with DNA damage response gene alterations. In particular, *ERCC2* alterations were associated with significantly improved modified bladder-intact event-free survival (HR 0.15; p=0.030) and bladder-intact event-free survival, which incorporated all-cause mortality (HR 0.33; p=0.044). Patients with *ERCC2* alterations showed high sensitivity to concurrent cisplatin-based chemotherapy.

Comment: The Boston-based group have many years of experience using chemoradiotherapy for bladder preservation in patients with muscle-invasive urothelial cancer. Just under 80 patients with tumour mutational and transcriptomic data were analysed here to try to identify biomarkers of longer-term response, as determined by bladder-intact event-free survival. Notably, patients with tumours harbouring DNA damage response gene alterations had a much better outcome in this cohort. The Boston group used cisplatin as a radiosensitiser, and it would be interesting to note if there were similar findings in UK cohorts that use 5FU/MMC. Speaking to the relationship of the biomarker to the chemotherapy rather than predicting radiation outcomes, the small proportion of patients with *ERCC2* mutations (necessary for platinum metabolism, approx. 10%), had extremely good outcomes. Further work needs to separate radiation biomarkers from chemotherapy and implement risk-based treatment algorithms.

Reference: Clin Cancer Res. 2023;29(24):5116-27
Abstract

Clinical and genomic landscape of *FGFR3*-altered urothelial carcinoma and treatment outcomes with erdafitinib

Authors: Guercio BJ et al.

Summary: This paper outlined the genetic landscape of *FGFR*-altered metastatic urothelial cancer based on prospectively clinical data, as well as the real-world clinical outcomes following erdafitinib. Erdafitinib sensitivity was predicted by *FGFR3* alterations in 43% of patients (81/187) with localised upper tract specimens, 39% (199/504) of those with non-muscle-invasive disease, 14% (75/526) of those with muscle-invasive disease and 26% (59/228) of those with metastatic disease. A potentially sensitising *FGFR2* fusion was detected in one patient. Discordant *FGFR3* mutational status between primary and metastatic tumours was recorded in 26% (7/27) of patients with *FGFR3*-altered metastatic disease. The response rate with erdafitinib was 40%, although median PFS and OS reached 2.8 and 6.6 months, respectively. Dose-reductions took place in 38% of patients, and interruptions in 50%. Prospective cell-free DNA analysis indicated that *FGFR3*, *AKT1* and *TP53* alterations were mechanisms of resistance to erdafitinib.

Comment: Here, the promise of targeted therapy enhancing patient outcomes seems greater than reality. As discussed earlier, patients with urothelial cancer may have tumours with *FGFR3* alterations, but outcomes with treatment in this American series highlight the limited durability of treatment and high rates of toxicity. Perhaps erdafitinib will be viewed as the gefitinib of bladder cancer, rapidly replaced by more potent second- and third-generation targeted inhibitors, which has occurred in *EGFR*-mutant lung cancer. Clinicians will note the higher rates of *FGFR* mutations and fusions detected in non-muscle-invasive disease, consistent with prior data. Future trials of *FGFR*-targeted therapy are focused on this sub-group, with particular focus on the intravesical delivery of therapy.

Reference: Clin Cancer Res. 2023;29(22):4586-95
Abstract

EV-301 long-term outcomes: 24-month findings from the phase III trial of enfortumab vedotin versus chemotherapy in patients with previously treated advanced urothelial carcinoma

Authors: Rosenberg JE et al.

Summary: The 2-year safety and efficacy data from the EV-301 trial were reported in this exploratory analysis. A total of 608 patients with previously treated, metastatic urothelial cancer were randomised to receive either enfortumab vedotin (n=301) or chemotherapy (n=307). At a median follow-up of 23.75 months, there were 207 and 237 deaths in the enfortumab vedotin and chemotherapy arms, respectively. Those administered enfortumab vedotin showed significantly improved PFS (HR 0.63; p<0.00001) and OS (HR 0.70; p=0.00015) versus chemotherapy. Investigators noted that no novel safety concerns were identified and that AEs were manageable; those in the enfortumab vedotin arm experienced higher rates of grade ≥3 decreased neutrophil count (14.1% vs. 6.1%), decreased white blood cell count (7.2% vs. 1.4%), anaemia (7.9% vs. 2.7%), skin reactions (47.3% vs. 15.8%), peripheral neuropathy (48.0% vs. 31.6%) and hyperglycaemia (6.8% vs. 0.3).

Comment: Longer-term follow-up of the EV-301 trial highlights the ongoing superiority over third-line chemotherapy in metastatic urothelial cancer, but also the toxicity. The introduction in October 2023 of enfortumab vedotin to Australia via the PBS will have given clinicians time to witness the wide array of potential toxicities that occur with this agent. The EV-301 data in particular highlight the high rate of neuropathy in almost 50% of patients, and remind clinicians that expert advice is required for managing some patients with severe skin toxicity.

Reference: Ann Oncol. 2023;34(11):1047-54
Abstract

Sequential intravesical gemcitabine/docetaxel provides a durable remission in recurrent high-risk NMIBC following BCG therapy

Authors: Yim K et al.

Summary: The safety and efficacy of sequential intravesical gemcitabine/docetaxel for BCG-unresponsive NMIBC were examined in this multicentre, retrospective analysis. Among a total of 102 patients with BCG-unresponsive disease who received ≥5/6 induction instillations of gemcitabine/docetaxel, the recurrence-free survival rates at 6, 12 and 24 months were 78%, 65% and 49%, respectively. Radical cystectomy was undertaken by 20 patients at a median of 15.5 months following induction, and six patients had developed muscle-invasive disease at a median follow-up of 18 months. Compared to BCG-relapsing disease, those with BCG-refractory disease were more likely to develop high-grade recurrence (HR 2.14; 95% CI 1.02—4.49). Sequential intravesical gemcitabine/docetaxel was well-tolerated; AEs most commonly included urinary urgency/frequency (41%) and dysuria (21%) and 6.9% of patients experienced a delay in treatment schedule due to AEs.

Comment: There has been an explosion in interest in patients with BCG-refractory/resistant disease recently, with a slew of different expensive, and in Australia, unavailable or expensive therapies such as pembrolizumab or intravesical nadofarogene. Is there a low-cost solution? This series is consistent with other series of intravesical gemcitabine/docetaxel, highlighting the modest but reasonable outcomes achieved using this combination (78% 6-month recurrence-free survival). There are side effects such as urinary frequency in some patients, but in the absence of financial access or trial access, most patients in Australia should either be considering a cystectomy, or alternatively this combination if they want to preserve their bladder.

Reference: Urol Oncol. 2023;41(11):458.e1-7
Abstract

Field cancerization is associated with tumor development, T-cell exhaustion, and clinical outcomes in bladder cancer

Authors: Strandgaard T et al.

Summary: These investigators carried out genomic and proteomic analyses of bladder biopsies and urine samples from 136 patients with high-risk, BCG-treated NMIBC to explore the prognostic role of field cancerisation. High field cancerisation was associated with poorer short-term outcomes (p=0.029) as well as high tumour mutational burden (p=0.007), high tumour neoantigen load (p=0.029) and high tumour-associated CD8 T-cell exhaustion (p=0.017). *KDM6A*, *ARID1A* and *TP53* alterations in normal-appearing bladder biopsies were early drivers of disease. Bladder tumour burden was reflected by urinary tumour DNA levels; high urinary tumour DNA following BCG was associated with disease progression (p=0.003) and poorer clinical outcomes (p=0.027). High levels of proteins associated with proliferation and angiogenesis were detected alongside high field cancerisation.

Comment: This interesting basic science paper explores the correlation of field cancerisation characteristics with clinical outcomes and immune responses. The research is well-conducted, and the correlates between enhanced immune response but higher tumour development in patients with increased clonal mutant changes in surrounding normal urothelial cells are not too surprising. This is likely due to higher neo-antigen exposure and CD8 infiltration. Future work is required to investigate the non-invasive assessment of cancer field development using urinary biomarkers.

Reference: Eur Urol. 2024;85(1):82-92
Abstract

Improving compliance with guidelines may lead to favorable clinical outcomes for patients with non-muscle-invasive bladder cancer

Authors: Sato T et al.

Summary: This retrospective, multicentre study from Japan evaluated the adherence to guideline recommendations and subsequent outcomes among 1204 patients with NMIBC. Maintenance BCG was not administered to 91.0% and 74.0% of patients with intermediate- and high-risk tumours, respectively, with significantly poorer recurrence-free survival for both patient groups. For those with T1 NMIBC, guidelines recommend a second transurethral resection and maintenance BCG, however this was only carried out in 16.7% of this patient group. Propensity-matching revealed that patients who underwent guideline-recommended therapies had significantly improved recurrence-free survival than those who did not.

Comment: Repeated intravesical instillation of BCG cannot be fun, and patients are often asking their urologists whether further multiple instillations are necessary when they develop bladder irritation. These symptoms and time demands often limit the duration of BCG instillation. Given the higher rates of recurrence in those failing to proceed with guideline-directed therapy, clinicians would be best to discuss these sorts of data to encourage adherence.

Reference: Int J Urol. 2023;30(12):1155-63
Abstract

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Independent commentary by Associate Professor Andrew Weickhardt

Andrew is a medical oncologist at the Olivia Newton-John Cancer and Wellness Centre in Melbourne. He has an interest in using immunotherapy and personalised treatments for patients with genitourinary cancer. He is actively involved in translational research investigating biomarkers of response and resistance to these treatments and is involved in several phase 1 trials of new drugs in development.

Enfortumab vedotin versus platinum rechallenge in post-platinum, post-pembrolizumab advanced urothelial carcinoma

Authors: Taguchi S et al.

Summary: In this multicentre, propensity score-matched study, enfortumab vedotin was compared with a platinum-based chemotherapy rechallenge in the treatment of advanced urothelial cancer. Between 2018-23, pembrolizumab was administered to 283 patients following platinum-based chemotherapy. Following this, 41 patients received enfortumab vedotin and 25 a platinum rechallenge. Patients in the enfortumab vedotin and platinum rechallenge groups showed similar PFS (5 vs. 8 months, respectively) and OS (11 vs. 12 months). Following propensity-score matching, oncological outcomes remained equivalent (PFS not reached vs. 8 months; OS not reached vs. 11 months). The authors concluded that both treatment options should be effective for patients with advanced urothelial cancer following platinum and pembrolizumab.

Comment: The Japanese have for some time published small, single-arm series of post-pembrolizumab platinum rechallenge in patients with urothelial cancer. Here, they provocatively compare the outcomes to the new gold standard enfortumab vedotin, and report equivalent outcomes. The baseline characteristics are unbalanced however, and likely skew the outcomes towards patients treated with platinum-based chemotherapy, given a lower tumour load and better responses to first-line therapy. The study does raise this treatment as an option for patients who cannot have enfortumab vedotin for medical reasons, and suggests that Australian clinicians be mindful of this combination as compared to single-agent docetaxel or other treatments.

Reference: Int J Urol. 2023;30(12):1180-6
Abstract

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