Bladder Cancer Research Review™

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Issue 4 - 2023

In this issue:

Abbreviations used in this issue:

BCG = bacillus Calmette-Guérin; **Chemo** = chemotherapy; **CSS** = cancer-specific survival; **ddMVACx6** = 6 cycles of neoadjuvant dose-dense MVAC; **DOR** = duration of response; **GCx4** = 4 cycles of gemcitabine & cisplatin; **HR** = hazard ratio; ***HRR*** = homologous recombination repair gene; **ICER** = incremental cost-effectiveness ratio; **ICI** = immune checkpoint inhibitor; **IO** = immunotherapy; **MVAC** = methotrexate, vinblastine sulphate, doxorubicin hydrochloride (Adriamycin), cisplatin; **ORR** = overall response rate; **OS** = overall survival; **PARP** = poly adenosine diphosphate-ribose polymerase; **PD-L1** = anti-programmed cell death ligand-1; **PFS** = progression-free survival; **RFS** = recurrence-free survival; **TRAE** = treatment-related adverse event; **QALY** = quality adjusted life years.

Welcome to the latest issue of Bladder Cancer Research Review

We begin our first issue of the year with an ongoing clinical trial which assessed the safety and efficacy of enfortumab vedotin plus pembrolizumab for locally advanced or metastatic urothelial cancer. This is followed by the double-blind, randomised phase 2 BAYOU trial which compared durvalumab plus olaparib vs. durvalumab alone in patients with untreated metastatic urothelial carcinoma ineligible for platinum therapy. The next paper reports on another randomised, double-blind, phase 2 trial which examined the efficacy of rucaparib in extending PFS for metastatic urothelial carcinoma following chemo, in patients with DNA repair deficiency biomarker-positive disease. We conclude this issue with a single-arm phase 2 trial which investigated the combination of pembrolizumab and nab-paclitaxel in platinum-refractory or cisplatin-ineligible advanced urothelial cancer.

We hope you find this update in Bladder Cancer research informative for clinical practice, and we always welcome your comments and feedback.

Kind Regards,

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Enfortumab vedotin plus pembrolizumab in previously untreated advanced urothelial cancer

Authors: Hoimes CJ et al.

Summary: The safety and efficacy of enfortumab vedotin plus pembrolizumab for locally advanced or metastatic urothelial cancer was examined in this ongoing open-label, multicentre phase 1B/2 trial. Evaluable patients ineligible for first-line cisplatin treatment (n=45) were administered 3-weekly cycles of enfortumab vedotin (1.25mg/kg on days 1 and 8) and pembrolizumab (200mg on day 1). The authors noted that the safety profile (primary endpoint) was manageable: the most frequent TRAEs included peripheral sensory neuropathy (55.6%), fatigue (51.1%) and alopecia (48.9%). Grade ≥3 TRAEs were experienced by 64.4% of patients, most commonly increased lipase (17.8%), maculopapular rash and fatigue (both 11.1%), and one patient died. After a median of 9 treatment cycles, the majority of patients experienced a reduction in tumour size. The ORR and complete response rates were 73.3% and 15.6%, respectively, while the median OS and median DOR were 26.1 and 25.6 months.

Comment: Patients with metastatic urothelial cancer who were ineligible to receive cisplatin-based first-line therapy received the novel combination of enfortumab and pembrolizumab in this expansion cohort of EV-108. The impressive rate of response and durability have led to some conjecture over this regimen being the future of treatment in bladder cancer. Certainly, compared to relative recent cohorts of carboplatin-based first-line chemo (median OS ≈14-18 months), the median OS of 26.1 months looks very impressive. The key issue now is whether the same results can be replicated outside the US centres where this study was conducted and how this compares to 'induction' carboplatin/gemcitabine then maintenance avelumab. Enfortumab can lead to neurotoxicity as well as issues with skin rash, decreasing dose intensity. We eagerly await the data from the randomised trial of the different approaches in the EV-302 trial and note that the proportion of patients in this study in the control chemo arm that receive avelumab maintenance will likely significantly affect the result.

Reference: J Clin Oncol. 2023;41(1):22-31

Abstract

Durvalumab plus olaparib in previously untreated, platinum-ineligible patients with metastatic urothelial carcinoma

Authors: Rosenberg JE et al.

Summary: The BAYOU trial was a multicentre, double-blind, randomised phase 2 trial which compared the efficacy and safety of durvalumab (anti-PD-L1) plus olaparib (PARP inhibitor), vs. durvalumab alone in patients with untreated metastatic urothelial carcinoma ineligible for platinum therapy. A total of 154 patients (20% with *HRR* mutations) were randomised 1:1 to be administered either durvalumab (1500mg once 4-weekly) plus olaparib (300mg twice a day), or durvalumab plus a placebo. The difference in PFS (primary endpoint) between the durvalumab plus olaparib and durvalumab alone arms was not statistically significant (4.2 vs. 3.5 months; HR 0.94; p=0.789). However, secondary analyses suggested that patients with *HRR* mutations who received durvalumab plus olaparib had superior PFS (5.6 vs. 1.8 months; HR 0.18; 95% CI 0.06—0.47) and OS (8.6 vs. 5.8 months; HR 0.56; 95% CI 0.25—1.23). The safety profile of durvalumab plus olaparib was manageable, with 18% and 9% of patients experiencing grade 3 and 4 TRAEs, respectively.

Comment: Defects in DNA damage repair pathways have been documented in approximately 20-30% of patients with metastatic urothelial cancer. However, the results of using single-agent PARP inhibitors in this population are mixed, with the only exception to the otherwise negative trials being the phase 2 trial ATLANTIS which used rucaparib. This BAYOU trial studies the value of PARP in a broader population (allcomers), adding olaparib to immunotherapy (PD-L1 inhibition with durvalumab) in the first-line setting, and comparing this to olaparib alone. The PFS difference in the overall unselected population was the primary endpoint – an overly ambitious target which olaparib failed to achieve. A preplanned analysis of outcomes in the subgroup with *HRR* mutations showed a 3-month difference in both PFS and OS in this group. Future work should restrict PARP use to this subgroup, focusing on the appropriate combination with immunotherapy and time in the treatment course such as combined in maintenance avelumab at time of progression.

Reference: J Clin Oncol. 2023;41(1):43-53
Abstract

A randomized, double-blind, biomarker-selected, phase II clinical trial of maintenance poly ADP-ribose polymerase inhibition with rucaparib following chemotherapy for metastatic urothelial carcinoma

Authors: Crabb SJ et al.

Summary: These researchers investigated the efficacy of rucaparib (PARP inhibitor) in extending PFS for metastatic urothelial carcinoma following chemo in patients with DNA repair deficiency biomarker-positive disease. Eligible patients (n=40) were randomised 1:1 to receive either rucaparib (600mg twice daily) or placebo until disease progression or unacceptable toxicity. Those in the rucaparib arm experienced significantly longer PFS than those in the placebo arm (35.3 vs. 15.1 weeks; HR 0.53; p=0.07), and rucaparib had a tolerable safety profile, with the most common TRAEs including fatigue (63.2%), raised alanine aminotransferase (57.9%), nausea (36.8%) and rash (21.1%).

Comment: The ATLANTIS trial used a biomarker approach to better define the role of PARP inhibition in urothelial cancer, selecting only patients with DNA damage repair defects to treat with either rucaparib or placebo following first-line chemo for metastatic urothelial cancer. Rucaparib extended PFS in this population, rather than resulting in further tumour shrinkage. Unsurprisingly, the side effects were similar to all PARP inhibitors, such as nausea and fatigue. Combinations of avelumab and PARP inhibitors such as rucaparib should be explored in a biomarker-defined population.

Reference: J Clin Oncol. 2023;41(1):54-64
Abstract

Comparative cost-effectiveness of neoadjuvant chemotherapy regimens for muscle-invasive bladder cancer

Authors: Joyce DD et al.

Summary: This analysis compared the cost-effectiveness of 6 cycles of neoadjuvant dose-dense MVAC (ddMVACx6) vs. four cycles of gemcitabine and cisplatin (GCx4) before radical cystectomy for muscle-invasive bladder cancer. Researchers utilised a decision-analytic Markov model to calculate 5-year, 10-year and lifetime probabilities from VESPER trial data, and measured effectiveness in quality-adjusted life years (QALY) and incremental cost-effectiveness ratio (ICER). ddMVACx6 was found to cost $16,100 more than GCx4, however it also improved QALY by 0.30, giving it an ICER of $53,284/QALY and making it more cost-effective than GCx4 overall. Probabilistic sensitivity analysis also found that ddMVACx6 was cost-effective at both 10-year and lifetime horizons in 79% and 81% of microsimulations, respectively.

Comment: Dose-dense MVAC remains favoured by only a few centres for neoadjuvant chemo in muscle invasive bladder cancer, perhaps due to concerns regarding toxicity and lack of clear efficacy advantage over cisplatin/gemcitabine before the VESPER study. This trial previously reported a PFS advantage, and an updated cost analysis also shows superiority in both QALY and ICER modelling. This type of analysis probably provides too little to convince clinicians who are nervous about toxicity that the regimen should replace cisplatin/gemcitabine, given the use of the latter regimen as a standard of care in all recent neoadjuvant trials.

Reference: Cancer. 2022;128(24):4194-4202
Abstract

TUXEDO: a phase I/II trial of cetuximab with chemoradiotherapy in muscle-invasive bladder cancer

Authors: James ND et al.

Summary: The feasibility and preliminary efficacy of administering cetuximab alongside chemoradiotherapy for muscle-invasive bladder cancer was explored in this open-label, single-arm, prospective phase 1/2 trial carried out across six hospitals in the UK. The primary outcomes were the effect on the completion of radiotherapy treatment at phase 1, and local control at 3 months following treatment at phase 2. A total of seven evaluable patients were enrolled in phase 1, and 23 patients in phase 2 (median age 70.1 years; 27 males; 20 with performance status of 0; 26 had already received neoadjuvant chemo). Eligible patients received an initial loading dose of 400mg/m^2 of cetuximab on Day 1 of Week 1, before 250mg/m^2 weekly for 7 weeks. On Day 1 of Week 1 prior to commencing radiotherapy, patients were administered 12mg/m^2 of mitomycin C, with 500 mg/m^2 intravenous 5FU administered continually on Days 1-5 and 22-26. Between Weeks 1-7, patients received CT-planned radical radiotherapy (64 Gy in 32 fractions to the whole bladder). There were 18 serious adverse events across the trial. Eight patients ceased cetuximab due to adverse effects, however all patients completed the scheduled radiotherapy in phase 1 with no dose reductions or delays. At 3 months after treatment in phase 2, 25/30 patients (77%) had local control.

Comment: Outcomes with bladder preservation could be improved with the addition of novel agents to chemoradiation. While recent studies have examined the addition of PD1/PDL1 inhibitors, TUXEDO examines whether cetuximab offers meaningful benefit. While the addition of cetuximab to radiation is common practice in head and neck cancer, this is not standard in bladder cancer, and limited data exists to support its use in metastatic disease. The response rate in the bladder to this multi-modality therapy in this study at 3 months is pleasingly high (77%), but this is similar to prior studies of chemoradiation alone. Perceptions regarding lack of biological rationale, distraction by the tidal wave of similar IO + chemoradiation studies, and lack of a home run response rate >90% make it hard to see a developmental pathway for cetuximab here.

Reference: BJU Int. 2022;131(1):63-72
Abstract

Non-metastatic muscle-invasive bladder cancer: the role of age in receiving treatment with curative intent

Authors: van Hoogstraten LMC et al.

Summary: The objective of this cohort study conducted in the Netherlands was to identify the characteristics of patients who remained untreated for non-metastatic muscle-invasive bladder cancer, despite being potentially curable. A total of 15,047 patients with cT2–T4aN0/xM0/x urothelial muscle-invasive bladder cancer were identified from a national cancer registry between 2005-2019. Logistic regression analyses revealed that for patients aged ≥75 years, factors associated with remaining untreated included increasing age (1/3 of patients ≥75 years remained untreated), cT4a stage, previous radiotherapy in the pelvic or abdomen area, worse performance status and worse renal function. For patients aged <75 years, 1/10 remained untreated, the factors for which included cT4a stage, performance status and renal function only. Median OS was significantly lower for patients who were untreated compared to those who were treated, regardless of their age (6.4 vs. 16.0 months), and patients aged ≥75 years experienced the widest interhospital variation for remaining untreated (37-69%).

Comment: A major challenge in the treatment of muscle invasive bladder cancer is the comorbidities that prevent delivery of standard curative therapy. Age by itself should not affect delivery of care to patients. Analysis here shows that performance status, renal function and cT4a status (growth into adjacent structures) are important factors that lead to a lack of treatment with curative intent. This real-world study is also noteworthy for a dismal OS rate among patients that in fact received neoadjuvant treatment (16 months), suggesting that there is a need for improvements in outcomes in this supposedly curative population.

Reference: BJU Int. 2022;130(6):764-75
Abstract

Elevated T-cell exhaustion and urinary tumor DNA levels are associated with bacillus Calmette-Guérin failure in patients with non-muscle-invasive bladder cancer

Authors: Strandgaard T et al.

Summary: These researchers attempted to characterise the molecular predictors of recurrence in high-risk non-muscle invasive bladder cancer following bacillus Calmette-Guérin (BCG) failure. A total of 156 patients with BCG -treated non-muscle invasive bladder cancer were included in the analysis. RNA sequencing and whole-exome sequencing was used to evaluate metachronous tumours, while urine was investigated for tumour-derived DNA and immune-oncology-related proteins. Results revealed that the immune system was activated by BCG irrespective of clinical response, however the urine samples of patients with post-BCG high-grade recurrence contained CD70, PD1 and CD5 immunoinhibitory proteins. Post-BCG T-cell exhaustion was significantly associated with post-BCG high-grade recurrence (p=0.002), and for pre-BCG tumours, a high predicted post-BCG exhaustion score was associated with poorer high-grade RFS following BCG (p=0.002). There were high expressions of cell-division and immune function genes in pre-BCG tumours in patients with post-BCG T-cell exhaustion. Patients with pre-BCG class 2a and 2b tumours experienced poorer post-BCG high-grade RFS (p=0.015), and those at a high risk of recurrence included those who did not have post-BCG tumour-derived DNA clearance (p=0.018). A significant proportion of patients with *MUC4* mutations (p=0.002) and high pre-BCG neoantigen load (p=0.017) were found to have post-BCG exhaustion.

Comment: This detailed study shows that progression of non-muscle invasive bladder cancer may be due to exhaustion of CD8 T-cells. Potentially, identification of this CD8 T-cell exhaustion can be done by detecting persistent urinary tumour-derived DNA or tumour protein expression within the superficial bladder cancer. Interestingly, *FGFR3* mutations were associated with better outcomes following BCG treatment. The authors also used a ratio of differentially expressed genes to create a post BCG exhaustion predictor (ExhP) which they likely will want to commercialise. The findings do require validation in a prospective clinical trial as they are probably not good enough to warrant that by themselves.

Reference: Eur Urol. 2022;82(6):646-56
Abstract

Improved survival in real-world patients with advanced urothelial carcinoma

Authors: Taguchi S et al.

Summary: This retrospective, multicentre cohort study calculated the improvements in survival in patients with advanced urothelial carcinoma undergoing salvage chemo in real-world settings following the introduction of pembrolizumab in 2017, and its specific impact in prolonging survival. Propensity score matching was used to compare OS and CSS between patients treated in an earlier period before pembrolizumab (2003-2011; n=200) with data from a more recent 5-year period (2016-2020; n=331). Compared with patients in the earlier cohort, those in the recent period experienced significantly longer CSS (12.0 vs. 21.0 months) and OS (12.0 vs. 19.0 months). Similarly, compared to patients in the earlier cohort, those who underwent treatment with pembrolizumab also had significantly longer CSS (11.0 vs. 25.0 months) and OS (11.0 vs. 24.0 months). There were no significant differences in CSS or OS between patients from the earlier cohort and those from the recent cohort who did not receive pembrolizumab.

Comment: The use of pembrolizumab and other PD1/PD-L1 immunotherapy drugs have led to impressive reported results in clinical trials of these agents in metastatic disease. Notably, there have been durable responses in 15-30% of patients lasting longer than 2 years following platinum therapy, and improvements in OS in patients from the pivotal KEYNOTE 45 trial. However, real-world patient outcomes could conceivably be skewed by comorbidities that were screened out of trial participation. Reassuringly, those trial results appear to translate into real-world outcomes with improvements in this modern era, particularly in those receiving pembrolizumab compared to those who did not.

Reference: Int J Urol. 2022;29(12):1462-9
Abstract

A phase 2 trial of nab-paclitaxel in combination with anti-PD1 therapy in advanced urothelial cancer

Authors: Tsung I et al.

Summary: The safety and efficacy of the combination of pembrolizumab and nab-paclitaxel for platinum-refractory or cisplatin-ineligible advanced urothelial cancer were examined in this single-arm phase 2 trial. Evaluable patients (n=36; 50% platinum-refractory) were administered 125 mg/m^2 nab-paclitaxel on days 1 and 8 and 200mg pembrolizumab on day 1 every 21 days until progression or unacceptable toxicity. After 6 cycles, nab-paclitaxel could be discontinued, and after interim analysis the nab-paclitaxel starting dose decreased to 100mg/m^2. There was a confirmed ORR of 50.0%, with 15 partial and 3 complete responses, and 86.1% of patients experienced a reduction in tumour size. After a median follow-up of 19.7 months, the median OS was 18.2 months (95% CI 10.6—not reached), median PFS 6.8 months (95% CI 4.4—not reached) and median DOR 4.4 months (95% CI 4.0—8.6) A total of 21/36 patients experienced grade ≥3 adverse events including fatigue and anaemia, however no novel or unexpected toxicities occurred after a decrease in the nab-paclitaxel starting dose. Immune-mediated adverse events occurred in ten patients.

Comment: It is difficult to reconcile this study with the failures of the recently conducted large phase 3 trials of immunotherapy combined with platinum-based chemo. The response rate of 50% seems at least additive here, which was not apparent in the larger phase 3 trials. While this may be just related to a smaller trial and wider CIs on the response rate, it remains possible that certain chemo agents combine better with immunotherapy. Previously there has been conjecture that premedications such as dexamethasone may wipe out any benefit from concurrent chemo. This view is challenged here however, given that the requirements for premedication with nab-paclitaxel remain higher for longer compared to cisplatin-based therapy. Certainly, more work needs to be done to investigate this combination further - ideally in a clinical trial.

Reference: J Urol. 2023;209(1):121-30
Abstract

Association of the time to immune checkpoint inhibitor (ICI) initiation and outcomes with second line ICI in patients with advanced urothelial carcinoma

Authors: Talukder R et al.

Summary: The outcomes of patients with advanced urothelial carcinoma treated with first-line platinum-based chemo and administered second-line ICI were investigated in this retrospective, multi-centre cohort study. Researchers excluded patients who were receiving switch maintenance ICI. Time to second-line ICI therapy was defined as the time between the start of first-line platinum-based chemo to the start of second-line ICI, and patients were assigned to 1 of 3 cohorts: <3 months, 3-6 months and >6 months. PFS and OS were calculated from the commencement of second-line ICI, and ORR with second-line ICI, with 215, 219 and 215 patients included in each analysis, respectively. Patients with time to second-line ICI <3 months had shorter PFS (HR 1.64; 95% CI 1.02—2.63) and OS (HR 1.77; 95% CI 1.10—2.84) than those who commenced second-line ICI >6 months. The difference in ORR between patients <3 months vs. 3-6 months vs. >6 months to second-line ICI was not statistically significant.

Comment: This retrospective multi-centre study supports preclinical work that suggests that platinum resistance occurs contemporaneously with 'cold' immune changes, rendering tumours inert to immune stimulation with PD1 inhibition. Indeed, patients who had progressed within 3 months of platinum-based chemo only had a median OS of 4 months compared to 14 months in those progressing over 6 months from the time of chemo cessation. Response rates were numerically less (13% vs. 25%) between these groups, but not statistically significant. Clearly patients with early progression need better options than immunotherapy, and conceivably antibody drug conjugates may fill this role.

Reference: Clin Genitourin Cancer. 2022;20(6):558-67
Abstract

Bladder Cancer Research Review™

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.

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