Bladder Cancer Research Review™

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Issue 12 - 2024

In this issue:

Abbreviations used in this issue:

(a)HR = (adjusted) hazard ratio; **BCG** = bacillus Calmette-Guérin; **ctDNA** = circulating tumour DNA; **DFS** = disease-free survival; **EV** = enfortumab vedotin; **MIUC** = muscle-invasive urothelial carcinoma; **(N)MIBC** = (non-) muscle-invasive bladder cancer; **OS** = overall survival; **PFS** = progression-free survival; **RFS** = recurrence-free survival; **TURBT** = trans urethral resection of bladder tumour; **UTUC** = upper tract urothelial carcinoma; **1L** = first-line.

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Welcome to the latest issue of Bladder Cancer Research Review

We begin with two papers which outline the final OS data from IMvigor130, reporting that atezolizumab + platinum-based chemotherapy was not superior to placebo + platinum-based chemotherapy in untreated, 1L urothelial cancer. An interesting population-based study from The Netherlands finds that bladder-preserving therapy is associated with similar oncological outcomes as radical cystectomy in patients with non-metastatic MIBC, and another real-world study observes that BCG is just as effective for immunomodulated patients with NMIBC as those who are immunocompetent - with no increased rate of BCG dissemination. We conclude with a systematic review and meta-analysis that reveals BCG dose reductions for NMIBC are not associated with poorer oncological outcomes, although further randomised trials are needed before it can be considered an option for patients.

I hope you find these ten selections interesting and of value for your clinical practice, and I look forward to reading your feedback.

Warm regards,

Associate Professor Arun Azad
arun.azad@researchreview.com.au

Atezolizumab plus chemotherapy versus placebo plus chemotherapy in untreated locally advanced or metastatic urothelial carcinoma (IMvigor130)

Authors: Grande E et al.

Summary: In IMvigor130, 1213 patients with locally advanced/metastatic urothelial carcinoma were randomised 1:1:1 to receive first-line (1L) atezolizumab plus platinum-based chemotherapy (group A), atezolizumab monotherapy (group B) or placebo plus platinum-based chemotherapy (group C). The interim analysis of arms A (n=451) and C (n=400) showed no OS benefit with 1L atezolizumab + platinum-based chemotherapy compared to placebo + platinum-based chemotherapy, although there was an improvement in PFS. This paper presents the final OS analysis. At a median follow-up of 13.4 months, patients administered atezolizumab + platinum-based chemotherapy did not show a significant improvement in OS compared to placebo + platinum-based chemotherapy (n=400; 16.1 vs. 13.4 months, respectively; HR 0.85; p=0.023; pre-specified significance boundary p=0.021). There were no novel safety signals.

Comment: These are important results presented from the IMvigor130 trial, showing that atezolizumab + platinum-based chemotherapy is not superior to placebo + platinum-based chemotherapy in untreated 1L urothelial cancer. These data contrast with the OS benefit seen in the EV-302 (enfortumab vedotin + pembrolizumab) and CheckMate-901 (gemcitabine + cisplatin + nivolumab) trials. Is PD-L1 inhibition less effective in the 1L setting for urothelial cancer than PD-1 inhibition? It would appear so. The 1L treatment options for urothelial cancer going forward are going to be EV + pembrolizumab or cisplatin + gemcitabine + nivolumab. The next question is how to pick between these two 1L options.

Reference: Lancet Oncol. 2024;25(1):29-45
Abstract

Atezolizumab monotherapy versus chemotherapy in untreated locally advanced or metastatic urothelial carcinoma (IMvigor130)

Authors: Bamias A et al.

Summary: This exploratory analysis of IMvigor130 compared the final OS data from patients in arm B (n=362) who received atezolizumab monotherapy, versus group C (n=400) who received placebo + platinum-based chemotherapy. At a follow-up of 13.4 months, there was no significant difference in OS between those administered atezolizumab monotherapy versus placebo + platinum-based chemotherapy (13.4 vs. 15.2 months; HR 0.98; 95% CI 0.82—1.16). No unexpected safety signals were reported.

Comment: This further analysis from IMvigor130 showed that atezolizumab monotherapy is not superior to platinum-based chemotherapy in 1L metastatic urothelial cancer. These results are not surprising, based on the data from the same trial showing no benefit from the addition of atezolizumab to platinum-based chemotherapy. Clearly, chemotherapy has a role in 1L metastatic urothelial cancer, whether that's as the payload in an antibody-drug conjugate (enfortumab vedotin) or as 'traditional' cytotoxic treatment (platinum-based chemotherapy). These data are a key reminder that urothelial cancer is a chemotherapy-sensitive disease, but recent results from the EV-302 and CheckMate-901 trials also remind us that combining chemotherapy with immunotherapy is the way forward for 1L metastatic urothelial cancer.

Reference: Lancet Oncol. 2024;25(1):46-61
Abstract

Disease-free survival of patients with muscle-invasive bladder cancer treated with radical cystectomy versus bladder-preserving therapy

Authors: Brück K et al.

Summary: Data from a population-based cancer registry in the Netherlands were used to examine the DFS of patients with non-metastatic muscle-invasive bladder cancer (MIBC) who underwent radical cystectomy compared to those who received bladder-preserving therapy. Among 1432 patients, 1101 were treated with radical cystectomy and 331 with bladder-preserving therapy. At a median follow-up of 39 months, after adjusting for baseline differences between groups, there was no significant difference in 2-year DFS (primary endpoint) between radical cystectomy and bladder-preserving therapy (61.5% vs. 55.3%; aHR 0.84; 95% CI 0.69-1.05); the 2-year OS rates were 74.0% and 66.0%, respectively (aHR 0.80; 95% CI 0.64-0.98). Investigators concluded that this subgroup of patients should be offered both curative treatment regimens.

Comment: Radical cystectomy versus bladder-preserving therapy for MIBC always stirs up healthy debate. While there is a paucity of randomised data directly comparing the two approaches, this population-based study from The Netherlands adds further evidence that bladder-preserving therapy appears to result in similar oncological outcomes as radical cystectomy. This begs the question as to whether all MIBC patients should be seen by both a urologist and a radiation oncologist prior to definitive treatment being undertaken. I don't think this is routine practice across Australia, but it probably should be.

Reference: Int J Radiat Oncol Biol Phys. 2024;118(1):41-9
Abstract

Sequential endoluminal gemcitabine and docetaxel for the treatment of clinically non-invasive high-grade upper tract urothelial carcinoma

Authors: McElree IM et al.

Summary: This retrospective review explored the safety and efficacy of endoluminal gemcitabine + docetaxel as a renal-sparing treatment option among patients with clinically non-invasive, high-grade upper tract urothelial carcinoma (UTUC) and no radiographic or endoscopically visible disease. A total of 31 patients (median age 74 years) were included in the analysis, of whom 51% would have been reliant on dialysis if they had undergone nephroureterectomy. Before initiating treatment, 9.8% of all units showed high-grade biopsy-proven disease, while 90% showed localising high-grade cytology. At a median follow-up of 29 months, 3-year PFS and 3-year OS were both 75%. AEs were reported by 16 patients (52%); one event was grade 5 and five were grade 3. It was concluded that this treatment shows promising safety and efficacy for certain patients with high-grade UTUC.

Comment: An interesting study tackling a very challenging clinical scenario: non-invasive but high-grade UTUC. Obviously, these patients cannot be successfully treated with intravesical therapy and therefore not infrequently, they proceed to nephroureterectomy despite not having muscle-invasive disease. In this study, the authors gave gemcitabine + docetaxel via nephrostomy or retrograde ureteral catheter. Although a retrospective study, the therapeutic approach taken seemed to result in relatively good oncological outcomes, with a PFS of 75% at 3 years. Obviously, prospective and randomised data would be ideal, but this trial provides some guidance for clinicians in this difficult clinical setting.

Reference: Urol Oncol. 2024;42(1):20.e9-15
Abstract

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Royal Australian & New Zealand College of Radiologists (RANZCR) members can claim reading related to their practice as a CPD activity under the category 'journal reading and web based no certificate *reflection required'. More info.

Bacillus Calmette-Guérin (BCG) therapy is safe and effective in non-muscle invasive bladder cancer (NMIBC) patients with immunomodulating conditions

Authors: Durant AM et al.

Summary: Generally, bacillus Calmette-Guérin (BCG) is contraindicated for immunomodulated patients with non-muscle invasive bladder cancer (NMIBC) due to concerns regarding safety and efficacy. This population-level study included patients aged ≥66 years from the SEER-Medicare database who had completed adequate BCG between 1975-2013. Among a total of 4277 patients, 14.2% were immunomodulated. Immunomodulated patients had significantly higher Charlson comorbidity scores, and were more likely to be female, older at diagnosis and female (all p<0.001). There were no differences between immunocompetent and immunomodulated groups in terms of progression to chemotherapy (p=0.17), checkpoint inhibitors (p>0.99), metastasis (p=0.19), partial cystectomy (p=0.93), radical cystectomy (p=0.40), 5-year total bladder cancer progression (p=0.30) or cancer-specific death (p=0.18). With regard to safety, both groups experienced similar rates of disseminated BCG (p=0.51).

Comment: An interesting study showing that BCG is as effective for NMIBC in patients with immunomodulatory conditions (e.g. solid-organ transplantation, HIV and autoimmune conditions) versus those who are classified as immunocompetent. Importantly, there was no excess risk of disseminated BCG for the immunomodulated group, and clinical efficacy outcomes were comparable for patients with and without an immunomodulatory condition. As patients with immunomodulatory conditions are typically excluded from clinical trials, these real-world data provide important guidance supporting the use of BCG in this patient population.

Reference: Urol Oncol. 2024;42(1):21.e21-8
Abstract

Sequential intravesical gemcitabine and docetaxel for treatment-naïve and previously treated intermediate-risk nonmuscle invasive bladder cancer

Authors: McElree IM et al.

Summary: The efficacy and tolerability of intravesical gemcitabine + docetaxel following TURBT in patients with intermediate-risk NMIBC were assessed in this retrospective analysis. Researchers identified 77 eligible patients who were treated between 2012-22, of whom 87% presented with Ta low-grade lesions, 3.9% with Ta high-grade, 6.5% with Ta low-grade + focal Ta high-grade and 2.6% with T1 low-grade. Prior intravesical therapy (BCG, mitomycin, docetaxel monotherapy) had been administered to 43% of patients. At a median follow-up of 26 months, overall RFS was 71%. Median RFS was significantly longer among treatment-naïve versus previously treated patients (p=0.04), and the 2-year estimated RFS rates were 79% and 53%, respectively. Therapy was well-tolerated; most AEs were grade 1-2, and three patients (3.9%) were unable to tolerate a full course of treatment.

Comment: Due to the problem of BCG-resistant or refractory disease, and with the ongoing BCG shortage globally, other effective intravesical options are urgently needed for NMIBC. There has been a lot of interest in gemcitabine + docetaxel as an intravesical treatment for NMIBC. In this study, the authors saw high RFS rates with minimal toxicity from intravesical gemcitabine + docetaxel. This study adds further evidence for a potential role of intravesical gemcitabine + docetaxel in NMIBC, and supports ongoing prospective trials evaluating this combination.

Reference: Urol Oncol. 2023;41(12):485.e1-7
Abstract

Impact of age >70 years on oncological outcomes in patients with non-muscle-invasive bladder cancer treated with Bacillus Calmette–Guérin

Authors: Contieri R et al.

Summary: Retrospective data from a single centre were analysed in order to examine the impacts of age on cancer outcomes among older patients with NMIBC who were treated with BCG. From a total of 632 evaluable patients, 43.8% were aged >70 years while 56.2% were ≤70 years. Those who were >70 years did not show higher rates of high-grade recurrence (p=0.644) or overall progression (p=0.067), and neither of these were independently predicted by age >70 years (p=0.749 and p=0.134, respectively). Similarly, there was no statistically significant difference in cancer-specific mortality between those aged >70 versus ≤70 years (p=0.057).

Comment: Like many cancers, bladder cancer is more common in older patients. This study found that patients >70 years of age treated with BCG for NMIBC had no excess risk of progression or high-grade recurrent disease. In fact, age was not an independent predictor of progression or high-grade recurrent disease. I don't think these data will change clinical practice, as age is not typically a factor when deciding whether to give BCG. Nevertheless, it does provide reassurance that BCG appears equally effective in older patients. Enhancing clinical outcomes in older patients by delivering optimal intravesical therapy is critical, as we all want to avoid having to offer a cystectomy in this patient population.

Reference: BJU Int. 2024;133(1):63-70
Abstract

Updated overall survival by circulating tumor DNA status from the phase 3 IMvigor010 trial

Authors: Powles T et al.

Summary: In the open-label, phase 3 IMvigor010 trial, patients with ctDNA-positive muscle-invasive urothelial carcinoma (MIUC) experienced an OS benefit with adjuvant atezolizumab versus observation. This exploratory, ad-hoc analysis presents the updated OS and safety results from patients with evaluable ctDNA samples. Among a total of 809 ITT patients, 581 were included, of whom 37% were ctDNA-positive. At a follow-up of 46.8 months, patients with ctDNA-positivity had significantly shorter OS than those who were ctDNA-negative (HR 6.3; 95% CI 4.3—9.3), and ctDNA was able to detect patients with an OS benefit with atezolizumab (HR 0.59; 95% CI 0.42—0.83). Patients who showed greater decreases in ctDNA experienced longer OS; those with reductions of 100%, 50-99% and <50% had median OS rates of 60.0, 34.3 and 19.9 months, respectively. Regardless of ctDNA status, AEs occurred more frequently with atezolizumab than with observation. It was noted that further prospective studies are warranted.

Comment: IMvigor010 showed that atezolizumab did not improve OS versus observation in the adjuvant setting for MIUC. Importantly though, there was an OS benefit for atezolizumab in the subgroup of patients who were ctDNA-positive. This is intuitive, as ctDNA-positive patients will almost certainly have metastatic disease and are more likely to benefit accordingly from adjuvant treatment than patients who are ctDNA-negative and more likely to not have metastatic disease. This is a really critical observation that is being further explored in ongoing studies incorporating ctDNA analysis for treatment selection.

Reference: Eur Urol. 2024;85(2):114-22
Abstract

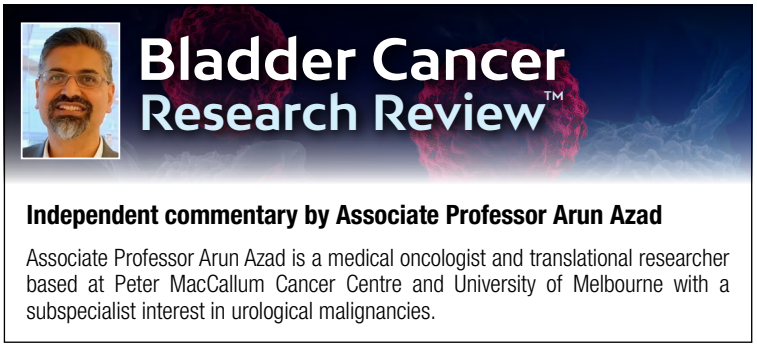
Avelumab first-line maintenance for advanced urothelial carcinoma

Authors: Sridhar SS et al.

Summary: Javelin Bladder 100 demonstrated that OS and PFS were prolonged in patients with advanced urothelial carcinoma randomised to avelumab + best supportive care (BSC) versus BSC alone. This exploratory, post-hoc analysis compared outcomes according to duration of 1L chemotherapy and interval before maintenance. At a median follow-up of >19 months, the HRs for OS for avelumab + BSC versus BSC alone demonstrated similar efficacy regardless of chemotherapy duration (quartile [Q]<1 0.65; Q1–Q2 0.79; Q2–Q3 0.74; >Q3 0.63), number of chemotherapy cycles (four 0.69; five 0.98; six 0.66) and interval between chemotherapy and maintenance (4 to <6 weeks 0.75; 6 to <8 weeks 0.67; 8–10 weeks 0.69). Similar findings were reported for PFS and for safety signals.

Comment: This is a sub-study from JAVELIN100 showing that maintenance avelumab in metastatic urothelial cancer has similar efficacy irrespective of duration of prior chemotherapy and interval between finishing chemotherapy and starting avelumab. This provides reassurance to clinicians that avelumab can be used in a broad population of patients who have a complete or partial response, or stable disease after platinum-based chemotherapy. These are useful data, but with the recent results from EV-302 and CheckMate-901, it is hard to see much of a role for avelumab in the long-term.

Reference: Eur Urol. 2024;85(2):154-63
Abstract



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The impact of dose reduction of Bacillus Calmette–Guérin on oncological outcomes and toxicity in non-muscle invasive bladder cancer

Authors: Azuri W et al.

Summary: The objective of this systematic review and meta-analysis was to explore the impact of dose reductions on the efficacy and toxicity of BCG among patients with NMIBC. Researchers identified 13 RCTs enrolling 2963 patients. Between patients administered a full dose and any dose reduction, there were no significant differences in recurrence (p=0.7) or progression (p=0.93), although patients in the full-dose group displayed higher frequencies of local (p<0.01) and systemic side effects (p<0.01). Researchers also found no significant differences in cancer outcomes between the different BCG strains included in the analysis.

Comment: An interesting systematic review showing that dose reductions in BCG for NMIBC are not associated with worse oncological outcomes. Needless to say, this is very welcome news in an era of seemingly permanent BCG shortages globally. Of course, the definition of dose reduction varies between studies, and this makes it challenging for clinicians to know how to apply these data in clinical practice; and the standard of care that we always strive to offer patients is for full-dose BCG treatment….is it fair to offer patients less than this without definitive randomised data?

Reference: Bladder Cancer. 2023;9(3):227-36
Abstract

Upcoming Webinar: Female urinary incontinence: conservative management in general practice and treatment options.

With urological surgeon Dr Henry Yao and Pelvic floor physiotherapist Lauren Clarke

Tuesday 12 March 2024

7.00pm-8.15pm

Online via Zoom

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