Bladder Cancer Research Review™

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In this issue:

Abbreviations used in this issue:

aMVAC = accelerated methotrexate, vinblastine, adriamycin & cisplatin;
ADC = antibody drug conjugate; **BCG** = bacillus Calmette-Guérin;
CFI = chart-derived frailty index; **CSS** = cancer-specific survival;
EAU = European Association of Urology;
ERAS = enhanced recovery after surgery;
FISH = fluorescence in situ hybridisation; **HR** = hazard ratio;
IHC = immunohistochemistry; **MDT** = multi-disciplinary team;
MMC = mitomycin C; **NAC** = neoadjuvant chemotherapy;
NGS = next-generation sequencing;
(N)MIBC = (non–)muscle-invasive bladder cancer;
QCI = quality control indicator;
TURBT = transurethral resection of bladder tumour;
UTUC = upper tract urothelial carcinoma.

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Welcome to this issue of Bladder Cancer Research Review.

We begin with a paper which reports on the mechanistic bases for durable disease-free treatment-free survival with cisplatin-based chemotherapy in patients with metastatic urothelial cancer. This is followed by an interesting study which evaluated the frequency of *HER2* expression in urothelial carcinoma, and associations with clinical characteristics and prognosis. The next paper reports on a phase 2 trial which assessed the efficacy of olaparib in patients with metastatic urothelial cancer and DNA damage response genes alterations. We conclude with a study which suggests that a hypofractionated radiation approach could be an effective treatment option in older, frailer patients with localised bladder cancer.

We trust you find this update in bladder cancer research informative and interesting, and we look forward to reading your thoughts and feedback.

Warm regards,

Associate Professor Ben Tran
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Antitumor immunity as the basis for durable disease-free treatment-free survival in patients with metastatic urothelial cancer

Authors: Anker J et al.

Summary: A phase 2 trial demonstrated that 4 of 36 patients with metastatic urothelial cancer achieved durable disease-free treatment-free survival and ongoing remission for >5 years with gemcitabine-cisplatin followed by gemcitabine-cisplatin with ipilimumab. These investigators performed whole exome sequencing on pretreatment archival tumour tissue to identify immunological and genomic features of "cured" patients. These patients showed an immune activated phenotype at pretreatment, with amplifications in immune checkpoint markers, costimulatory molecules and Th1 adaptive immunity. Following treatment, patients continued to show enhancements in adaptive immunity markers, together with T cell cytotoxicity. At all time points, *CD27* was enriched.

Comment: Many medical oncologists will have a few patients with metastatic urothelial cancer who sustain a complete response after first-line gemcitabine-cisplatin. I have a few patients who are now disease-free, 5 years after completing first-line gemcitabine-cisplatin. I have conducted NGS on these patients and interestingly, all of my patients have mutations in the same gene (that I won't share until I publish!). This might merely be a marker of good prognosis biology within a luminal subtype, rather than a predictive marker of benefit from chemotherapy. This study examined much more complex assays to determine if there are underlying immunological mechanisms that result in these functional "cures". They found that *CD27* was enriched in the "cured" patients. Identifying patients who can be cured with first-line gemcitabine-cisplatin may help these patients avoid maintenance avelumab, which may continue indefinitely. Lots to learn in this space.

Reference: J Immunother Cancer. 2023;11(8):e007613
Abstract

HER2 expression associated with clinical characteristics and prognosis of urothelial carcinoma in a Chinese population

Authors: Zhou L et al.

Summary: Previously, data have shown that 9-61% of all bladder cancers have *HER2* overexpression, however, there has been no evidence to date that traditional anti-*HER2* therapies result in clinical benefit for advanced urothelial carcinoma. This study of 284 patients with urothelial carcinoma and known *HER2* status evaluated the frequency of *HER2* overexpression, characteristics and prognosis. IHC detected *HER2*-positivity (2+/3+) in 44% of patients, with higher rates in urothelial bladder cancers than upper tract urothelial cancers (51% vs. 38%). Among metastatic patients, independent risk factors for prognosis included anaemia, liver metastasis and number of organs affected. An independent protective factor was disitamab vedotin therapy. Patients with low *HER2* expression administered disitamab vedotin also showed improved survival.

Comment: As a smoking-related cancer, urothelial cancer has several actionable mutations, similar to lung cancer. To date, only *FGFR3* has been successfully targeted, leading to the development of erdafitinib. However, *HER2* is another attractive target. In the past, targeting *HER2* in urothelial cancer did not lead to sufficient benefit. But I think that had a lot to do with the way we were targeting it, and the selection of patients. Now with novel *HER2* targeted antibody drug conjugates (ADCs), there appears to be a real role in urothelial cancer, with early data suggesting excellent outcomes for *HER2*-positive patients. Now it is time to better understand what proportion of patients are *HER2*-positive and agree on a definition of *HER2*-positivity. This real-world study performed in China showed that *HER2*-positivity is more frequent in bladder urothelial cancers rather than upper tract urothelial cancers. However, it is a small study. Previously, reports have focused on *HER2* amplification on NGS or FISH, or *HER2* mutations. But for ADCs... perhaps *HER2* over-expression on IHC is the best way to determine *HER2*-positivity.

Reference: Oncologist. 2023;28(8):e617-24
Abstract

Phase II trial of olaparib in patients with metastatic urothelial cancer harboring DNA damage response gene alterations

Authors: Doroshow DB et al.

Summary: This single-arm, open-label, phase 2 trial assessed the efficacy of olaparib in 19 patients with metastatic urothelial cancer and somatic alterations in DNA damage response genes. All patients had either progressed on prior platinum-based chemotherapy or were ineligible for cisplatin; nine patients had been administered prior cisplatin chemotherapy. Homologous recombination gene alterations were detected in ten patients, eight of whom harboured *BRCA1/2* alterations. A partial response was not achieved by any patient (primary endpoint). Stable disease occurred in six patients for a median of 7.69 months (range 2.13-16.1), median PFS was 1.9 months (0.8-16.1) and median OS was 9.5 months (1.5-22.1). It was concluded that the poor antitumour activity of olaparib in this population may be attributable to the high rate of prior platinum-based chemotherapy.

Comment: Olaparib is now a standard of care for prostate cancer patients harbouring somatic or germline *BRCA1/2* mutations. These mutations, along with mutations in other DNA repair genes, also occur in urothelial cancer - and perhaps there is a role for olaparib in these patients as well. In this small study of 19 patients, olaparib was prescribed to patients with somatic mutations in DNA repair genes. Surprisingly, no patients achieved a partial response. As the authors rightly state, this may be cross-resistance with platinum-based chemotherapy, which all patients would have received and progressed on or following. Still, I think this is an area worthy of ongoing research.

Reference: JCO Precis Oncol. 2023;7:e2300095
Abstract

Impact of chart-derived frailty index on 1-year mortality after radical cystectomy in 1004 patients with bladder cancer

Authors: Yu J et al.

Summary: These investigators retrospectively evaluated the efficacy of the chart-derived frailty index (CFI) to predict 1-year all-cause mortality after a radical cystectomy in patients with bladder cancer. The CFI was calculated from haematocrit, albumin and creatinine levels, age and BMI. Among a total of 1004 patients, 9.0% had a high CFI, while 91% had a low CFI. Those in the high CFI group had significantly higher 1-year all-cause mortality following radical cystectomy than low CFI (27.8% vs. 12.0%; p<0.001). According to multivariate analysis, 1-year all-cause mortality was associated with high CFI (p<0.001), red blood cell transfusion volume (p<0.001) and tumour stage (p=0.003).

Comment: Radical cystectomies are highly morbid, even in the best hands. A better way of predicting those who will do poorly from radical cystectomy is important, as it will help us to avoid surgery in these patients. The CFI measures preoperative frailty. This large retrospective study from Korea demonstrated that 9% of patients had a high CFI and that these patients had higher 1-year all-cause mortality after surgery. Certainly, there may be confounders, but this is food for thought. I wonder how a high CFI compares to other measures of fitness for an operation. It is unclear what the survival of these patients would have been without a radical cystectomy... and that is something that needs to be considered. These data don't necessarily tell us not to operate on patients with high CFI, but to consider alternatives given their poor survival.

Reference: Ann Surg Oncol. 2023;30(8):5295-303
Abstract

Quality control indicators for transurethral resection of bladder tumor

Authors: Muilwijk T et al.

Summary: Retrospective data from an embedded Belgian multicentre, prospective registry of TURBT procedures were used to assess adherence to six quality control indicators (QCIs) in non-muscle-invasive bladder cancer (NMIBC). Among a total of 1151 procedures for 907 patients, 271 were categorised as low-risk, 464 intermediate-risk, and 416 high-risk. The presence of detrusor muscle and start of BCG were both found to be suboptimal (35% and 51%, respectively). QCIs with the highest compliance rates were complete resection (97%), single instillation of MMC (65%) and therapy ≤6 weeks following diagnosis (88%), while the lowest rates of compliance were recorded for the presence of detrusor muscle (31%), re-TURBT (33%) and start of BCG therapy (39%). There was significant heterogeneity in compliance rates between centres. Over time, compliance for re-TURBT and MMC improved significantly, although it was noted that this may have occurred in only one centre. Recurrence-free survival was significantly associated with a single instillation of MMC.

Comment: In the MDTs that I am part of, there is regular discussion regarding reporting of muscle in the specimen, re-TURBT and single instillation of MMC. These are accepted as standard of care in the EAU guidelines - and it has been reported that adherence to guidelines is poor. This study examines the adherence to six QCIs in major Belgian cancer centres. They found that reporting of detrusor muscle in pathology specimens are suboptimal, but that most of this could be attributed to one centre! Interestingly, single instillation of MMC was quite high, reported in 65% of patients. I imagine that in Australia, this would be quite low. I think we need to find a better way to facilitate access to intravesical MMC. Anecdotally, I think this is a disconnect between oncology pharmacists/nurses and urologists. Often, I have been called upon by urologists to facilitate the single instillation of intravesical MMC... but the problem here is that only very few medical oncologists will prescribe intravesical treatments, or have an understanding of treatment for NMIBC. Should we be training medical oncologists in this field? Or better connecting urologists to oncology pharmacists and nurses?

Reference: Eur Urol Oncol. 2023;6(4):422-30
Abstract

Neoadjuvant chemotherapy with accelerated methotrexate, vinblastine, doxorubicin, and cisplatin in patients with muscle-invasive bladder cancer

Authors: Hemenway G et al.

Summary: This was a retrospective, age-stratified analysis which examined the safety and efficacy of neoadjuvant accelerated methotrexate, vinblastine, adriamycin and cisplatin (aMVAC) in older patients with MIBC. Eligible patients were stratified as <65, 65–74 or >75 years old; those with primary upper tract or metastatic disease were excluded. As this was a retrospective study, full safety data were not able to be assessed. Accelerated MVAC had similar efficacy across all age groups; there were no between-group differences in dose reductions, treatment interruptions, time to surgery or adverse events. However, older patients showed poorer renal function at baseline, and a greater decline in creatinine clearance.

Comment: Neoadjuvant chemotherapy (NAC) may be underutilised. However, I am starting to think that in all of the Australian analyses, the denominator might not be correct. Using the BLADDA registry, we are aiming to examine what the true use of NAC is in MIBC patients who are eligible for NAC. This would mean excluding patients with non-urothelial histology, and also those with renal impairment. I suspect that once we exclude these patients, the use of NAC would look better than what we expect. So, watch this space for these data. The study here examined the use of aMVAC. This is certainly increasingly used in Australia as an alternative to gemcitabine-cisplatin for NAC. While most of us would reserve aMVAC or dose-dense MVAC for younger and fitter patients, this study shows that in selected older patients, there is no difference in tolerability of aMVAC when compared to younger patients. If we truly believe aMVAC is better than gemcitabine-cisplatin, then we should start considering aMVAC in older patients as well.

Reference: Eur Urol Oncol. 2023;6(4):431-6
Abstract

Readmissions trends following radical cystectomy for bladder cancer unchanged in the era of enhanced recovery after surgery (ERAS) protocols

Authors: Chappidi MR et al.

Summary: This paper reports on changes in readmission trends among patients with bladder cancer who underwent radical cystectomy, during the era of ERAS protocol implementation. Investigators collected data for 20,957 patients between 2016-19. Across the study period, there were no significant changes in yearly 30- or 90-day readmission rates, even in patients who underwent radical cystectomy at high-volume centres (all p>0.05). The only cause of readmission which showed a significant change was wound readmission (2.7% in 2016 to 5.1% in 2019; p=0.02).

Comment: We are all aware, even us medical oncologists, that radical cystectomy can be a morbid procedure with relatively high complication rates, which can result in readmissions. In the modern era, ERAS is utilised to help reduce recovery and hopefully reduce the rate of late post-op complications. In this paper, it appeared that ERAS did not change the readmission rate or the cause of readmission. That means that different interventions are required in the post-discharge period. I know that some urologists consider anticoagulation and antibiotics in that immediate post-op period. Is that standard? Is that something that has been studied? Please reach out - I'm keen to be educated!

Reference: Urol Oncol. 2023;41(8):355.e19-28
Abstract

Independent commentary by Associate Professor Ben Tran

Ben is a medical oncologist in Melbourne, Australia with appointments at Peter MacCallum Centre and Walter and Eliza Hall Institute. He is actively involved in clinical trials and translational research, with special interests in genitourinary cancers, drug development and real-world evidence. Ben is currently the chair of the Phase 1 group within Cancer Trials Australia (CTA), and is also the Chair of the germ cell subcommittee within the Australian and New Zealand Urological and Prostate Cancer Trials (ANZUP) Group.

The efficacy and timing of adjuvant chemotherapy in upper tract urothelial carcinoma

Authors: Li H et al.

Summary: The objective of this retrospective analysis was to assess the efficacy of adjuvant chemotherapy initiated within 90 days after radical nephroureterectomy in patients with upper tract urothelial carcinoma (UTUC). Among a total of 428 patients, 132 initiated adjuvant chemotherapy with platinum in combination with gemcitabine within 90 days of surgery, while 296 did not initiate adjuvant chemotherapy. Patients who underwent adjuvant chemotherapy had significantly improved OS and CSS. There were no significant differences in OS or CSS between patients initiating chemotherapy within 45 days versus 45-90 days, and the incidence of adverse events appeared to increase with a shorter time interval.

Comment: I think that most medical oncologists would use 3 months as an arbitrary cut-off for the use of adjuvant chemotherapy across most cancers. I tend to like to start around the 6–8-week mark, if possible. These data presented here look at UTUC and the use of adjuvant chemotherapy within 45 days of surgery, versus 45-90 days post-op. They suggested that there was no difference in OS or CSS if adjuvant chemotherapy was started less than 45 days post-op compared to 45-90 days post-op. This is reassuring, and will allow clinicians to give their patients enough time to recover from surgery before starting adjuvant chemotherapy.

Reference: Urol Oncol. 2023;41(8):356.e1-9
Abstract

Real-world treatment patterns and clinical outcomes with first-line therapy in patients with locally advanced/metastatic urothelial carcinoma by cisplatin-eligibility

Authors: Morgans AK et al.

Summary: This retrospective, observational study explored the real-world first-line treatment patterns and OS in 4757 patients with locally advanced/metastatic urothelial carcinoma. A total of 3632 patients (76.4%) were administered first-line therapy, of whom 55.9% were cisplatin-ineligible. Compared to patients who were cisplatin-eligible, cisplatin-ineligible patients were older (74.9 vs. 68.8 years) and had lower creatinine clearance (46.4 vs. 87.0mL/min). Second-line treatment was administered to 43.8% of patients who received first-line treatment (37.6% cisplatin-ineligible vs. 51.6% cisplatin-eligible). Overall, those who received first-line treatment had a median OS of 10.8 months, and OS was shorter in cisplatin-ineligible patients (8.5 vs. 14.4 months; HR 0.9). Compared to other first-line treatments, cisplatin-based therapy was associated with longer OS, regardless of cisplatin-eligibility. It was concluded that there is a need for more effective first-line therapies in locally advanced/metastatic urothelial carcinoma.

Comment: This is an amazing real-world study of almost 5000 patients - makes the BLADDA registry look less impressive. Anyway, these data looked at first-line treatment in metastatic urothelial cancer. Three quarters of patients received first-line treatment, and over half of these patients were cisplatin-ineligible. Of those who got first-line treatment, less than half went on to receive second-line treatment. As an increasing number of treatment options become available in urothelial cancer, I think we will see this percentage increase. An interesting finding, which I am sure relates to patient selection, suggests that patients who received cisplatin lived longer. A similar analysis is currently being conducted within the BLADDA registry!

Reference: Urol Oncol. 2023;41(8):357.e11-21
Abstract

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Hypofractionated radiation therapy (Hypo-RT) for the treatment of localized bladder cancer

Authors: Moore A et al.

Summary: The efficacy and toxicity of definitive hypofractionated radiation therapy (55Gy in 20 fractions) for bladder cancer were evaluated in this retrospective review. A total of 40 patients were included in the analysis (median age 82 years [60-96 years]; median Charlson Comorbidity Index score 7; 80% nonsurgical candidates; 68% had undergone TURBT; 82.5% administered concurrent chemotherapy). A complete response was achieved by 77% of patients. At a median of 9.1 months, six patients (20%) developed disease recurrence. Estimated 2-year disease-free- and disease-specific survival were 59% and 78%, respectively. Improved disease-specific survival was associated with a complete response (p=0.018) and concurrent chemotherapy (p=0.003). Investigators state that the toxicity profile of hypofractionated radiation therapy was favourable; grade 2 genitourinary and gastrointestinal toxicities were each experienced by 40% of patients (primarily urinary frequency and diarrhoea) and rates of grade 3 genitourinary/gastrointestinal toxicities were low.

Comment: Radiotherapy is certainly an option for localised bladder cancer, ideally in combination with chemotherapy. In Australia, chemoradiotherapy is rarely used as a definitive treatment option and is often reserved for the frail and elderly patients. In this elderly population, sometimes chemotherapy is withheld, and sometimes a standard radiotherapy course might be too onerous. This study examined a hypofractionated approach for 55GY in 20 fractions. In this cohort, just over 80% of patients also received concurrent chemotherapy. Their data suggested generally good cancer outcomes and definitely improved toxicity profile. This is certainly an approach that can be considered for the frail and elderly.

Reference: Bladder Cancer. 2023;9(2):141-50
Abstract

