Bladder Cancer Research Review™

Making Education Easy

Issue 14 - 2024

In this issue:

Abbreviations used in this issue:

ADC = antibody drug conjugate; **DoR** = duration of response; **DSS** = disease-specific survival; **(e)PLND** = (extended) pelvic lymph node dissection; **EV** = enfortumab vedotin; **HR** = hazard ratio; **(HR)QOL** = (health-related) quality of life; **ICI** = immune checkpoint inhibitor; **IHC** = immunohistochemistry; **(N)MIBC** = (non-)muscle-invasive bladder cancer; **OR** = odds ratio; **ORR** = overall response rate; **OS** = overall survival; **PD-1/PD-L1** = programmed cell death (ligand)-1; **PFS** = progression-free survival; **RFS** = recurrence-free survival; **(TR)AE** = (treatment-related) adverse event; **TROP-2** = trophoblast cell surface antigen 2; **TURBT** = transurethral resection of bladder tumour.

Welcome to the latest issue of Bladder Cancer Research Review

We begin with the groundbreaking EV-302 trial which demonstrated that patients with untreated, advanced urothelial cancer achieved significantly better outcomes with EV + pembrolizumab than with standard of care chemotherapy. This is followed by a paper which suggests PD-L1 expression is associated with improved outcomes for patients with metastatic urothelial cancer who receive ICIs, although it is unlikely to be useful as a predictive biomarker. The next paper reports on the TROPHY-U-01 trial, detailing the efficacy and safety of sacituzumab govitecan for metastatic urothelial carcinoma. We conclude with a retrospective study which finds no difference in RFS or OS between patients who underwent a standard versus extended PLND during radical cystectomy for clinically lymph-node-positive bladder cancer, which leads one to wonder whether there are situations in which an ePLND is warranted.

We hope you find these and the other abstracts below interesting and informative for your clinical practice, and as always, we welcome your comments and feedback.

Warm regards,

Associate Professor Ben Tran
ben.tran@researchreview.com.au

Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer

Authors: Powles T et al., for the EV-302 Trial Investigators

Summary: In the phase 3, global, open-label, EV-302 trial, 886 patients with previously untreated locally advanced/metastatic urothelial carcinoma were randomised to either 3-week cycles of enfortumab vedotin (EV) + pembrolizumab (n=442) or chemotherapy (gemcitabine + cisplatin/carboplatin; n=444). At a follow-up of 17.2 months, patients administered EV + pembrolizumab achieved significantly longer median PFS than chemotherapy (12.5 vs. 6.3 months; HR 0.45; 95% CI 0.38—0.54; p<0.001), as well as longer OS (31.5 vs. 16.1 months; HR 0.47; 95% CI 0.38—0.58; p<0.001). Patients in the EV + pembrolizumab and chemotherapy arms received a median number of 12 and 6 cycles, respectively. No novel safety signals were reported. Grade ≥3 TRAEs occurred in 55.9% of those administered EV + pembrolizumab and in 69.5% of those who underwent chemotherapy.

Comment: Wow!!! Standing ovation at ESMO. Tom Powles named as one of Nature's top ten scientists. EV + pembrolizumab is truly groundbreaking. Back when I was a fellow, I'd watch practice-changing studies presented in colorectal cancer, breast cancer…bladder cancer barely featured. But every tumour has its day in the sun. Bladder cancer has had numerous advances in recent years, but nothing has been able to usurp platinum/gemcitabine as the standard of care for first-line treatment…until now. The dramatic survival curves demonstrated a 55% improvement in survival. Patients do not need perfect renal function as they might with cisplatin. Side effects do occur, but in my experience are tolerable. We look forward to HRQOL data to see if this holds true objectively. In Australia, this combination is not yet available, but we are all looking forward to being able to prescribe this for our patients.

Reference: N Engl J Med. 2024;390(10):875-88
Abstract

Significance of PD-L1 in metastatic urothelial carcinoma treated with immune checkpoint inhibitors

Authors: Maiorano BA et al., for the MeetURO Group

Summary: The objective of this systematic review and meta-analysis was to assess the association between PD-L1 status and response/survival in patients with metastatic urothelial carcinoma receiving immune checkpoint inhibitors (ICIs). A total of 14 studies were identified, enrolling 5271 patients, 2625 of whom had PD-L1-positive tumours. When ICIs were administered, patients with PD-L1-positive tumours showed significantly higher ORRs compared to those with PD-L1-negative tumours (13.8%-78.6% vs. 5.1%-63.2%, respectively; pooled OR 1.94; 95% CI 1.47—2.56; p<0.001), significantly longer OS (8.4-24.1 vs. 6.0-19.1 months; pooled HR 0.71; 95% CI 0.57—0.89; p=0.003) and significantly better PFS (HR 0.55; 95% CI 0.44—0.69; p<0.001). However, PD-L1 was not found to be a likely predictive biomarker of response to ICI.

Comment: We've been looking at a biomarker for immunotherapy in urothelial cancer for a long time. It appears logical that if you are going to use a PD-1/PD-L1 inhibitor, then demonstrating the target at a tumour tissue level should be associated with better responses/outcomes, and conversely a lack of the target should predict non-response. However, it isn't that simple. PD-L1 is dynamic. It changes. And IHC antibodies used to detect PD-L1 are not perfect and are all different. It is not a black-and-white biomarker. Some patients with high PD-L1 expression do not benefit, and some patients with no PD-L1 expression gain remarkable benefit. Subsequently, we offer PD-1/PD-L1 inhibitors regardless of PD-L1 expression, and hence, PD-L1 expression is not routinely tested in Australia.

Reference: JAMA Netw Open. 2024;7(3):e241215
Abstract

TROPHY-U-01, a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors

Authors: Tagawa ST et al.

Summary: This paper reports on the updated safety and efficacy outcomes from TROPHY-U-01, an open-label, phase 2 study of sacituzumab govitecan in patients with metastatic urothelial cancer who had progressed following platinum-based chemotherapy and checkpoint inhibitors. In Cohort 1, 133 patients were administered sacituzumab govitecan 10mg/kg on days 1 and 8 of 21-day cycles. At a follow-up of 9.1 months, patients demonstrated an ORR of 27% (primary outcome; 31 of 113; 95% CI 19.5—36.6), and 77% displayed a reduction in measurable disease. Median PFS was 5.4 months (95% CI 3.5—9.2), median OS 10.9 months (95% CI 9.0—13.8) and median DoR 7.2 months (95% CI 4.7—8.6). It was noted that sacituzumab govitecan demonstrated improved efficacy versus historical controls for this patient population. Treatment was discontinued by 6% of patients due to TRAEs. Grade ≥3 TRAEs most commonly included neutropenia (35%), leukopenia (18%), anaemia (14%), febrile neutropenia (10%) and diarrhoea (10%).

Comment: We are in the era of antibody drug conjugates (ADCs). Sacituzumab govitecan is an excellent TROP-2-targeted ADC that has very promising results in metastatic urothelial cancer. Here, the overall response rate is 27%. There is some exploration of toxicity in patients with *UGT1A1* gene mutations. Given the payload within sacituzumab govitecan is SN-38, an irinotecan metabolite, it might be important to know if toxicity is worse in those with *UGT1A1* mutations. For irinotecan given intravenously, mutations in this gene are linked to greater toxicity. In this study, the presence of *UGT1A1* mutations was not associated with increased toxicity.

Reference: J Clin Oncol. 2021;39(22):2474-85
Abstract

Enfortumab vedotin following platinum-based chemotherapy and immune checkpoint inhibitors for advanced urothelial carcinoma

Authors: Miyake M et al., on behalf of the Nara Urological Research & Treatment Group

Summary: These researchers explored data from a real-world, Japanese, multicentre cohort, regarding the use of EV for unresectable/metastatic urothelial cancer. Between 2008-23, researchers identified 35 patients with metastatic urothelial cancer who had been treated with EV, for a median of five cycles. Overall, safety profiles and tumour responses reflected those shown in previous clinical trials. A partial response was achieved by 19 patients (56%), while five (15%) experienced stable disease and ten (29%) progressive disease. Following the first EV dose, median PFS and OS were 9 and 16 months, respectively. There was no association between EV relative dose intensity and survival outcomes. Following initiation of first-line platinum-based chemotherapy, median OS was 42 months. TRAEs were experienced by 76% of patients. Grade 3-4 toxicities occurred in eight patients (24%), the most common of which was skin toxicity (12%).

Comment: These real-world data from Japan show that when EV is used as a single agent following platinum-based chemotherapy and likely immunotherapy, the response rates are excellent - similar to those reported in clinical trials. Additionally, toxicity data are also similar, with only 12% of patients experiencing a grade 3-4 rash. We hope that with increasing prescribing of EV over time, the Australian advanced urothelial cancer database BLADDA will also describe similar results.

Reference: Jpn J Clin Oncol. 2024;54(3):329-38
Abstract

Interruptions in bladder cancer care during the COVID-19 public health emergency

Authors: Gore JL et al.

Summary: In order to ascertain the impact of the COVID-19 pandemic on bladder cancer care, these investigators invited US urology centres participating in a wider clinical trial to complete monthly surveys. From a total of 32 invitations, 21 sites provided eligible responses. In May 2020, January 2021 and January 2022, general elective surgery was paused at 76%, 48% and 52% of sites, respectively. In contrast, bladder cancer care was less restricted: across these three timepoints, TURBT was restricted at 10%, 14% and 14% of sites, respectively, radical cystectomy was restricted at 10%, 14% and 19%, and cystoscopy was restricted at 33%, 0% and 10%.

Comment: During the height of the COVID-19 pandemic, patients stopped going to their GP for routine checkups and all their screening tests. I think it has been well documented that this greatly impacted on some cancers, like prostate cancer. But my thinking was that for bladder cancer, there might be minimal impact. If I started peeing blood, I know I'd be straight to ED! And this study showed that in the US, there was minimal impact on the treatment of urothelial cancer.

Reference: Urol Oncol. 2024;42(4):116.e17-21
Abstract

Earn CPD

Royal Australasian College of Physicians (RACP) MyCPD participants can claim the time spent reading and evaluating research reviews as CPD in the online MyCPD program. Please contact MyCPD@racp.edu.au for any assistance.

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.

Follow us at:

Longer time to radical cystectomy in patients treated with neoadjuvant chemotherapy is associated with worse oncological outcomes

Authors: Nuijens ST et al.

Summary: As part of the nationwide, prospective BlaZIB study in The Netherlands, this research assessed the impacts that a delay in radical cystectomy had among patients with muscle-invasive bladder cancer (MIBC) undergoing neoadjuvant chemotherapy. Across a total of 237 evaluable patients, the median time from diagnosis to radical cystectomy was 23 weeks, and 2-year OS was 67% (95% CI 59—74). For each week of delay in the time from diagnosis to radical cystectomy, 2-year OS significantly worsened (HR 1.07; p=0.03). Sensitivity analysis also found that each week of delay between neoadjuvant chemotherapy and radical cystectomy was associated with shorter 2-year OS (HR 1.13; p<0.0001) and poorer pathological lymph node status (OR 1.21; p=0.01).

Comment: This is a big concern. It is critical to have excellent communication between medical oncology and urology for patients receiving neoadjuvant chemotherapy. I am constantly updating urology about how patients are tracking, and when they would be ok for a radical cystectomy. I normally aim for 2 weeks after completion of the last cycle of chemotherapy, but I can see how delays can happen if there is inadequate communication. If urology only finds out about the end of chemotherapy when it happens, it might be difficult to schedule surgery promptly. This study showed that there was a median of 23 weeks from diagnosis of MIBC to radical cystectomy. Assuming 3-4 weeks post-TURBT to neoadjuvant chemotherapy and 12 weeks of chemotherapy, that is a gap of 7 weeks between end of chemotherapy and radical cystectomy. As a community, we can do better! Communicate, communicate and communicate. Medical oncologists…get the MIBC patients seen quickly to start neoadjuvant chemotherapy quickly… and make sure you let the surgeons know when they should be booking surgery!!!

Reference: Urol Oncol. 2024;42(4):117.e11-16
Abstract

The role of neoadjuvant chemotherapy for patients with variant histology muscle invasive bladder cancer undergoing robotic cystectomy

Authors: Cooke I et al.

Summary: The objective of this retrospective review was to examine the role of neoadjuvant chemotherapy before robot-assisted radical cystectomy for patients with variant histology MIBC. Between 2004-23, 988 patients in the International Robotic Cystectomy Consortium underwent robot-assisted radical cystectomy for MIBC, of whom 35% had variant histology. The most common variant histology subgroups were squamous (n=94), adenocarcinoma (n=64), micropapillary (n=34) and sarcomatoid (n=21). Data showed that when comparing patients who underwent neoadjuvant chemotherapy with those who did not, there were no significant differences in OS, RFS or DSS. However, those with squamous histology who underwent neoadjuvant chemotherapy had a higher likelihood of pathological downstaging on final pathology (p<0.01).

Comment: I have been waiting for data like this. There are always concerns over the presence of micropapillary histology and other variant histology and the use of neoadjuvant chemotherapy. I think some education is needed here: squamous-differentiated urothelial cancer is not the same as squamous cell carcinoma! For those with squamous-differentiated cancer, neoadjuvant chemotherapy should be pursued. However, for squamous cell carcinoma or adenocarcinoma, I tend to suggest initial surgery and consider adjuvant chemotherapy later, given uncertain response (and likely lesser response). For sarcomatoid, I also think neoadjuvant chemotherapy should be pursued, as these are generally platinum-sensitive. Micropapillary is a tricky one. My view is that if micropapillary represents a smaller percentage of tumour, then neoadjuvant chemotherapy is still appropriate. I'm interested in hearing the views of others!

Reference: Urol Oncol. 2024;42(4):117.e17-25
Abstract

Maximizing efficiency and ensuring safety: Exploring the outcomes of 2 consecutive open radical cystectomies by the same team within a single surgical day

Authors: Egen L et al.

Summary: This retrospective analysis explored the safety and outcomes of two consecutive open radical cystectomies within 1 day performed by the same surgical team. The final cohort included a total of 657 patients, with 64 paired radical cystectomies and 593 single cystectomies. When comparing paired and single cystectomies, there were no significant between-group differences in major complication rates, transfusion rates, 30-day readmission, 30-day mortality or histopathology; although paired radical cystectomies had significantly shorter operative times (p=0.001) and lengths of stay (p=0.047). The authors concluded that two consecutive open radical cystectomies within a single day, by one surgical team, is a safe approach.

Comment: Even I, as a mere medical oncologist, understand radical cystectomies are big surgeries! This study examined surgical teams who conducted two in a day! They demonstrated this was not an issue, but the study was conducted in very large, high-quality centres!

Reference: Urol Oncol. 2024;42(4):118.e1-7
Abstract

Earn CPD

Nursing and Midwifery Board of Australia (NMBA) Journal reading and watching videos (including Research Reviews') may be considered a self-directed activity set out in the NMBA Registration Standard: Continuing Professional Development. One hour of active learning will equal one hour of CPD. Details at NMBA CPD page.

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.

Health-related quality of life after a diagnosis of bladder cancer

Authors: Rogers Z et al.

Summary: The HRQOL of patients with a new bladder diagnosis was explored in this prospective, longitudinal UK study conducted over the first year. Patients were invited to complete questionnaires at 3, 6, 9 and 12 months. Among a total of 349 patients, 80% underwent TURBT ± intravesical therapy, 17% radical cystectomy/radiotherapy and 2% palliation. At baseline, poorer HRQOL was reported by patients requiring radical treatment than those who underwent TURBT, including increased fatigue (p=0.03), greater worries about the future (p=0.005) and reduced social function (p=0.002). Following treatment, those in the TURBT group showed no significant changes in HRQOL scores, while those who underwent radical treatment continued to show deteriorations, particularly in male sexual function (p<0.001) and body image (p=0.007). Compared with the general UK population, radically treated patients reported more problems with usual activities, and poorer QOL scores. It was concluded that appropriate supportive and clinical care is necessary for those requiring radical treatment.

Comment: This study recruited mostly NMIBC patients, with cystectomy/radiotherapy only representing 17% of the cohort. They showed that patients needing the more intensive treatments had lower HRQOL compared to those who only needed TURBT. I think it is important to recognise the impact that radical treatment can have on QOL. We need to do more work to address this. For instance, while I am quick to discuss erectile dysfunction with my prostate cancer patients, I rarely remember to discuss it with my post-cystoprostatectomy patients. I need to do better!

Reference: BJU Int. 2024;133(4):460-73
Abstract

Impact of the extent of lymph node dissection on survival outcomes in clinically lymph node-positive bladder cancer

Authors: von Deimling M et al., on behalf of the CLIPOLY Study Group Collaborators

Summary: These investigators retrospectively compared survival outcomes following standard pelvic lymph node dissection (PLND; internal/external iliac & obturator lymph nodes) versus extended pelvic lymph node dissection (ePLND; PLND + common iliac & presacral nodes) during radical cystectomy in patients with clinically lymph node-positive bladder cancer. A total of 510 evaluable patients were 1:1 matched on propensity scores. Compared to PLND, ePLND did not improve OS (primary outcome; p=0.06) or RFS (p=0.5), and these outcomes did not change when patients were stratified according to use of chemotherapy.

Comment: Lymph node yield is important in patients undergoing radical cystectomy, but do we need an extended pelvic lymph node dissection (ePLND)? This study suggests that an ePLND does not improve survival. I wonder whether it might worsen HRQOL, given all the complications that might arise. Are there situations where an ePLND is warranted?

Reference: BJU Int. 2024;133(3):341-50
Abstract