Bladder Cancer Research Review™

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Issue 13 - 2024

In this issue:

Abbreviations used in this issue:

ADC = antibody drug conjugate; **AE** = adverse event;
BCG = bacillus Calmette–Guérin; **DCR** = disease control rate;
ddMVAC = dose-dense methotrexate, vinblastine, doxorubicin & cisplatin;
DOR = duration of response; **ECOG** = Eastern Cooperative Oncology Group;
HR = hazard ratio; **NAC** = neoadjuvant chemotherapy;
(N)MIBC = (non-)muscle-invasive bladder cancer;
ORR = objective response rate; **OS** = overall survival;
PFS = progression-free survival; **RFS** = recurrence-free survival;
SqCC = squamous cell carcinoma.

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Welcome to the latest issue of Bladder Cancer Research Review

This month we begin with an updated 5-year analysis of the VESPER trial, which demonstrated improved OS with ddMVAC versus cisplatin/gemcitabine in the neoadjuvant setting for patients with MBIC. This is followed by the LUX-Bladder 1 study which evaluated the use of afatinib in advanced urothelial cancer, reporting that patients with basal-squamous tumours and *ERBB2*/*EGFR* aberrations showed superior responses. The next paper reports on the phase 2 FIGHT-201 trial, which concluded that patients with previously treated, unresectable/metastatic urothelial cancer and *FGFR3* alterations experience promising clinical activity with pemigatinib, although I feel that this agent does not confer substantial benefits over erdafitinib. We conclude with an intriguing retrospective study which found that concurrent chemo-radiotherapy was associated with improved OS versus radiation alone among patients with high-grade cT1 urothelial cancer.

We hope you enjoy these updates in bladder cancer research, and we value your comments and feedback – please continue to send them in.

Warm regards,

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

Perioperative dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin in muscle-invasive bladder cancer (VESPER)

Authors: Pfister C et al., for the VESPER Trial Investigators

Summary: In previously reported data from the phase 3 VESPER trial, patients with muscle-invasive bladder cancer (MIBC) who received neoadjuvant chemotherapy (NAC) showed a 3-year PFS benefit (primary endpoint) with dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (ddMVAC) versus cisplatin/gemcitabine. This abstract presents the secondary endpoints from 5 years of follow-up regarding OS and bladder cancer-related mortality. A total of 500 eligible patients (89% received NAC) were randomised to receive either ddMVAC every 2 weeks for 6 cycles in total, or cisplatin/gemcitabine every 3 weeks for 4 cycles. The 5-year data were consistent with the earlier analysis. At a median follow-up of 5.3 years, there was no significant between-group difference in 5-year OS between ddMVAC versus cisplatin/gemcitabine in the perioperative setting (64% vs. 56%; HR 0.79; 95% CI 0.58—1.05), however 5-year OS was improved in the neoadjuvant subgroup (66% vs. 57%; HR 0.71; 95% CI 0.52—0.97). The 5-year cumulative incidence of death was improved with ddMVAC versus cisplatin/gemcitabine in both the perioperative (27% vs. 40%; HR 0.61; 95% CI 0.45—0.84) and neoadjuvant settings (24% vs. 38%; HR 0.55; 95% CI 0.39—0.78). Data were unable to be compared in the adjuvant subgroup as the sample sizes were small.

Comment: In recent years, the messaging in Australia is to ensure patients with MIBC are referred for consideration of NAC. Not all patients will proceed to NAC, but it is important that all patients are considered and see a medical oncologist given the survival advantages associated with NAC. ddMVAC for 4 cycles in selected patients has been deliverable, and given that it is over in 8 weeks, any breakdown in communication between medical oncology and urology regarding planned surgical dates is minimised. VESPER now explores 6 cycles of ddMVAC versus 4 cycles of cisplatin/gemcitabine, both 3 months in duration. Six cycles of ddMVAC is definitely less deliverable than 4 cycles, and that is reflected in VESPER. This update shows an OS advantage for the NAC subgroup for 6 cycles of ddMVAC. Patients who would tolerate this would be a very select subgroup, but regardless, this option should be considered for these very well patients. The focus though, should be on continuing to promote the use of NAC and encouraging referrals to medical oncology for discussion. As medical oncologists we need to make sure we see these patients promptly and make a decision quickly, so as not to delay cystectomy in both those not suitable for NAC, and also those who will go on to receive NAC.

Reference: Lancet Oncol. 2024;25(2):255-64
Abstract

Phase II trial of afatinib in patients with advanced urothelial carcinoma with genetic alterations in *ERBB1-3* (LUX-Bladder 1)

Authors: Font A et al.

Summary: LUX-Bladder 1 was an open-label, phase 2, single-arm trial which examined the efficacy and safety of second-line afatinib in the treatment of metastatic urothelial carcinoma with *ERBB2/ERBB3* alterations/amplification (cohort A; n=34) or *EGFR* amplification (cohort B; n=8). Patients in cohort A only proceeded to stage 2 if they demonstrated antitumour activity. The primary endpoint of 6-month PFS was 11.8% and 12.5% in cohorts A and B, respectively, while the ORRs were 5.9% and 12.5%, DCRs 50.0% and 25.0%, median PFS 9.8 and 7.8 weeks and median OS 30.1 and 29.6 weeks. Partial responses were achieved by three patients, two of whom harboured *ERBB2* amplifications, while one showed *EGFR* amplification. Researchers noted that patients with basal-squamous tumours also experienced a superior response to afatinib. AEs occurred in all patients; the most common AE was diarrhoea (any grade 76.2%; grade 3 9.5%). AEs led two patients to discontinue treatment, and one patient died due to acute coronary syndrome which was considered unrelated to treatment.

Comment: *ERBB1-3/HER2* is back in trend as a target for urothelial cancer. Most excitement revolves around the use of ADCs targeting *HER2*, but we still have *HER2* small molecular inhibitors which will demonstrate activity in cancers strongly driven through *HER2*. This phase 2 study shows that patients harbouring *HER2* amplification (a driver genetic aberration) will achieve reasonable response rates to afatinib. But I still think the ADC approach towards *HER2* will be more effective, both more broadly across the population (as it will not rely on genetic drivers, but rather expression will be sufficient) but also in terms of tolerability (maybe!).

Reference: Br J Cancer. 2024;130(3):434-41
Abstract

Pemigatinib for metastatic or surgically unresectable urothelial carcinoma with *FGF/FGFR* genomic alterations

Authors: Necchi A et al.

Summary: The open-label, single-arm, phase 2 FIGHT-201 study assessed the safety and efficacy of pemigatinib (oral *FGFR1-3* inhibitor) for previously treated, unresectable or metastatic urothelial carcinoma with *FGF/FGFR* alterations. Eligible patients (n=260) with *FGFR3* (cohort A) and other *FGF/FGFR* alterations (cohort B) were administered pemigatinib either continuously or intermittently. All patients discontinued treatment, with 68.5% stopping due to progressive disease. The continuous and intermittent groups showed ORRs of 17.8% and 23.3%, respectively. Among those with *FGFR3* alterations (n=107), ORRs were comparable between the continuous and intermittent schedules (23.9% vs. 24.6%, respectively). In the continuous and intermittent schedules in cohort A, PFS was 4.0 and 4.3 months, respectively, DOR 6.2 and 6.2 months and OS 6.8 and 8.9 months. Patients in cohort B did not demonstrate substantial clinical activity. At progression, samples were available for 26 patients, eight of whom had developed *FGFR* secondary resistant alterations. Overall, pemigatinib was well-tolerated; treatment-emergent AEs most commonly included diarrhoea (44.6%), alopecia (42.7%), stomatitis (42.7%) and hyperphosphatemia (42.7%).

Comment: Pemigatinib is another *FGFR* inhibitor. Erdafitinib has already demonstrated an OS advantage compared to chemotherapy as a third-line treatment, post-platinum and PD-1 inhibitors. In my opinion, pemigatinib does not have substantial differences or advantages over erdafitinib. In this phase 2 study, response rates in those with known *FGFR* drivers was 17%-23%. As expected, an intermittent strategy to dosing did not limit activity, with these patients achieving a 23% response rate compared to 17% for continuous dosing. The development of *FGFR* secondary resistant mutations represented a recurring mechanism of resistance, and next-generation *FGFR* inhibitors are designed to overcome this.

Reference: Ann Oncol. 2024;35(2):200-10
Abstract

The Double Antibody Drug Conjugate (DAD) phase I trial

Authors: McGregor BA et al.

Summary: These investigators explored the safety and efficacy of sacituzumab govitecan + enfortumab vedotin in patients with metastatic urothelial carcinoma. Eligible patients included those who had progressed on platinum-based/immunotherapy with ECOG ≤1. A total of 23 evaluable patients (median age 70 years; 11 had received ≥3 prior lines of therapy) were administered sacituzumab govitecan + enfortumab vedotin on days 1 and 8 of a 21-day cycle. Grade ≥3 AEs were experienced by 18 patients (78%) and occurred regardless of dose level; one patient experienced grade 5 pneumonitis which may have been attributable to enfortumab vedotin. Investigators stated that the recommended doses of sacituzumab govitecan and enfortumab vedotin were 8mg/kg and 1.25mg/kg, alongside granulocyte colony-stimulating factor support. The maximum tolerated doses in combination were 10mg/kg and 1.25mg/kg, respectively. Sixteen patients responded overall (ORR 70%; 95% CI 47—87), with three patients achieving a complete response. At a median follow-up of 14 months, nine patients showed ongoing response, with six showing a response duration >12 months.

Comment: ADCs are all the rage at the moment. The DAD study looks to combine two very active ADCs in urothelial cancer, both sacituzumab govitecan and enfortumab vedotin. As expected, this study shows AEs were difficult, however, there may be a path forward with lower doses of sacituzumab govitecan. Certainly, the response rate of 70% in this small study is eyebrow-raising!

Reference: Ann Oncol. 2024;35(1):91-7
Abstract

Erdafitinib in BCG-treated high-risk non-muscle-invasive bladder cancer

Authors: Catto JWF et al., for the THOR-2 Cohort 1 Investigators

Summary: In the phase 2 THOR-2 trial, patients with recurrent, BCG-treated, papillary-only, high-risk NMIBC and select *FGFR* alterations who were ineligible for/refused radical cystectomy were randomised 2:1 to either erdafitinib (*FGFR* inhibitor; n=49) or investigator's choice of intravesical chemotherapy (mitomycin C or gemcitabine; n=24). At a median follow-up of 13.4 months, patients demonstrated prolonged median RFS (primary endpoint) with erdafitinib versus chemotherapy (not reached [95% CI 16.9 months—not estimable] vs. 11.6 months [95% CI 6.4—20.1]; HR 0.28; p=0.0008). Those in the erdafitinib arm also demonstrated longer 6-month RFS (96% vs. 73%, respectively), and 12-month RFS (77% vs. 41%). There were no novel or unexpected safety signals. AEs occurred in all patients administered erdafitinib and in 83% of those administered chemotherapy. Grade ≥3 AEs with erdafitinib most commonly included stomatitis (10%), glossitis (4%) and nail dystrophy (4%); most AEs were grade 1-2 and were managed with dose reductions/interruptions. Serious AEs occurred in a higher proportion of those who received erdafitinib versus chemotherapy (22% vs. 13%). A total of 14 patients (29%) in the erdafitinib arm discontinued treatment due to AEs, predominantly as a result of stomatitis (6%).

Comment: Full disclosure: I am an author of this study and have been a passionate advocate of trialling *FGFR* inhibitors in NMIBC patients since my days in Toronto back in 2011. The THOR-2 study studying erdafitinib in NMIBC patients was very satisfying for me academically, and did show that erdafitinib is very active in NMIBC patients harbouring *FGFR* aberrations - it was certainly better than mitomycin C or gemcitabine. However, the ongoing dosing of an oral agent in patients not expecting ongoing low-grade side effects did result in general poor tolerability, with discontinuations leading to a reduction in dose. Interestingly, this dose reduction did not compromise activity; however given the tolerability issues in this patient population, we are now exploring different ways to give erdafitinib to NMIBC patients.

Reference: Ann Oncol. 2024;35(1):98-106
Abstract

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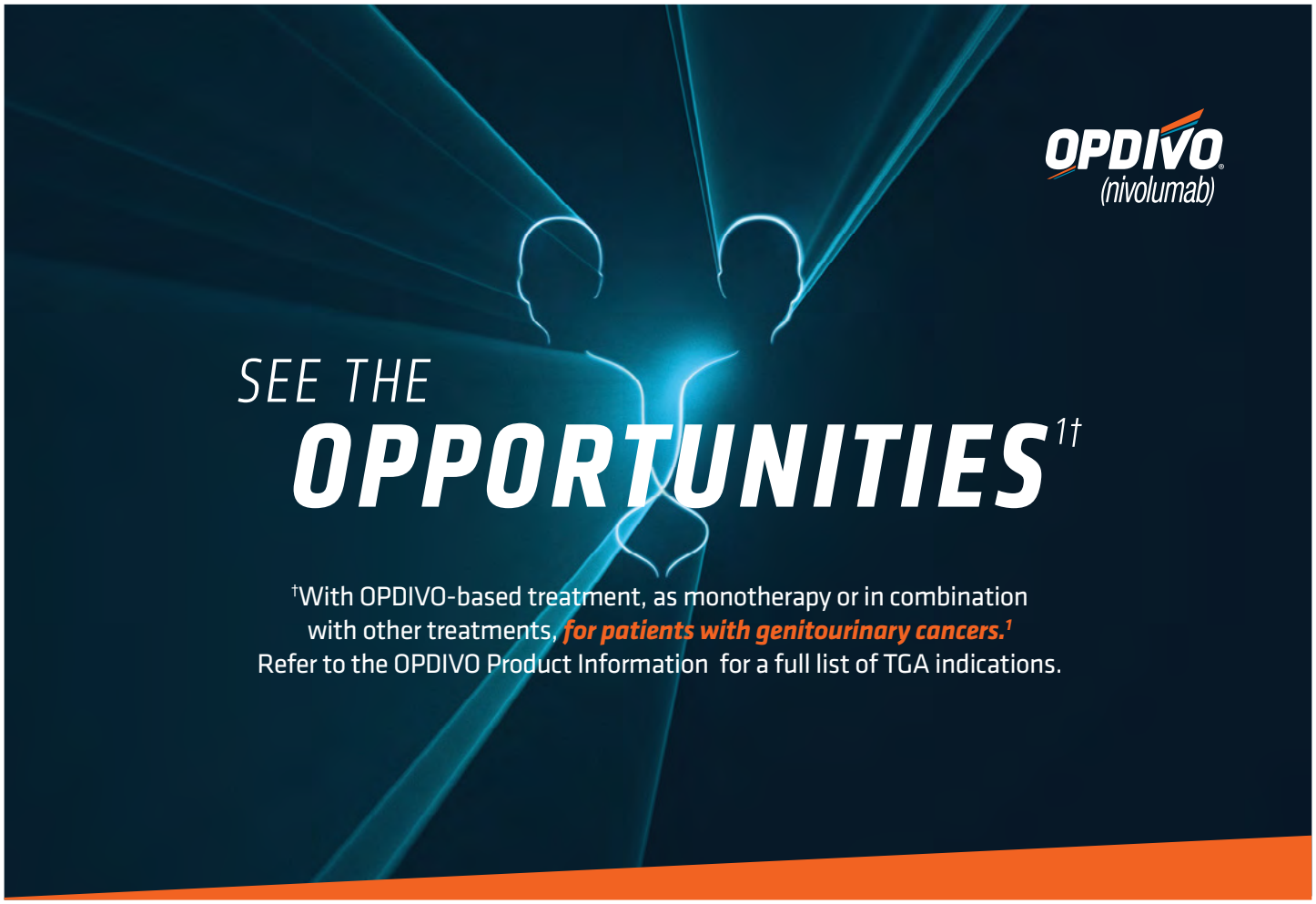

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†mDFS 22.0 months vs 10.9 months with placebo at median follow-up 36.1 months (HR 0.71, 95% CI 0.58–0.86, p-value not reported);‡ 3-year landmark DFS rate 45% vs 35% with placebo (p-value not reported)[3]

Grade ≥3 TRAEs rate 18% with OPDIVO (vs 7% with placebo) and rate of any grade TRAEs leading to discontinuation 14% with OPDIVO (vs 2% with placebo); p-values not reported.[2,3]

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‡Primary disclosure at median follow-up ~20–21 months was statistically significant for DFS vs placebo: HR 0.70, 98.22% CI 0.55–0.90; p<0.001.[2] DFS was also investigated in patients with PD-L1 ≥1% as a primary endpoint.
*High-risk MIUC was defined as pathological stage of pT3, pT4a, or N+ and not eligible for or declined adjuvant cisplatin-based combination chemotherapy for patients who had not received NAC and pathological stage of ypT2 to ypT4a or N+ for patients who received cisplatin-based NAC.[2]

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CI = confidence interval; **DFS** = disease-free survival; **HR** = hazard ratio; **IO** = immuno-oncology; **mDFS** = median disease-free survival; **NAC** = neoadjuvant chemotherapy; **PD-L1** = programmed death-ligand 1; **pT** = pathological tumour stage; **TGA** = Therapeutic Goods Administration; **TRAE** = treatment-related adverse event; **ypT** = post-treatment pathological tumour stage.

References: 1.OPDIVO® (nivolumab) approved Product Information (https://rss.medsinfo.com.au/bq/pi.cfm?product=bqpopdiv). **2.** Bajorin *et al. N Engl J Med* 2021;384:2102–14.
3. Galsky *et al.* Extended follow-up results from the CheckMate 274 trial. Presented at ASCO GU Cancers Symposium, Feb 16–18, 2023: Abs LBA443.

Erdafitinib versus pembrolizumab in pretreated patients with advanced or metastatic urothelial cancer with select *FGFR* alterations

Authors: Siefker-Radtke AO et al., for the THOR Cohort 2 Investigators

Summary: This paper reports on findings from cohort 2 of the randomised, phase 3 THOR trial, in which evaluable patients with unresectable, advanced/metastatic urothelial cancer and select *FGFR* alterations who had progressed following platinum-based chemotherapy were randomised to either erdafitinib (n=175) or pembrolizumab (n=176). At a median follow-up of 33 months, patients in the erdafitinib and pembrolizumab arms showed similar OS (primary outcome; 10.9 vs. 11.1 months; p=0.18). The respective ORRs with erdafitinib and pembrolizumab were 40.0% and 21.6%, median PFS 4.4 and 2.7 months and median DOR 4.3 and 14.4 months. One or more grade 3/4 AEs occurred in 64.7% of patients administered erdafitinib and 50.9% of those who received pembrolizumab; 2.9% and 6.9% experienced AEs which led to death.

Comment: This is another study I was involved with - this time a little disappointing. The theory with *FGFR* mutations and amplifications is that patients harbouring these did not respond as well to checkpoint inhibitors. Subsequently, there was a hypothesis that erdafitinib would be more active and result in better survival in these patients when compared to pembrolizumab. Unfortunately, in the THOR study pembrolizumab performed much better than expected, and subsequently, the hypothesis was disproven. In my experience *FGFR* aberrations tend to occur in patients with very rapidly-progressing cancers or very slow-growing cancers. In both scenarios, perhaps the type of anti-cancer agent makes no difference? In the rapidly-progressing cancers the aggressive biology might mean that any gains for erdafitinib over pembrolizumab might not be durable, and in the slow-growing cancers the indolent biology might mean that patients will do very well regardless of erdafitinib or pembrolizumab. The short answer is, no one knows at the moment - and much more work needs to be done to understand the biology of these cancers.

Reference: Ann Oncol. 2024;35(1):107-17
Abstract

The immune-related adverse events paradox in locally advanced or metastatic urothelial cancer after atezolizumab immunotherapy

Authors: Robesti D et al.

Summary: The objective of this analysis was to explore the association between immune-related AEs and oncological outcomes among patients administered atezolizumab for advanced urothelial cancer, and to determine whether any treatment effect is reduced by systemic corticosteroids. Investigators evaluated data from 896 eligible patients across the IMvigor210 and IMvigor211 trials. Immune-related AEs occurred in 195 patients overall, at a median time of 64 days. Multivariable analysis revealed that those who experienced immune-related AEs were at a lower risk of disease progression (HR 0.50; p<0.001), with lower overall mortality (HR 0.51; p<0.001) and lower cancer-specific mortality (sub-distributional HR 0.55; p<0.001). The use of systemic corticosteroids did not significantly alter PFS (p=0.629), OS (p=0.613) or cancer-specific survival (p=0.630).

Comment: I think we have known this for a while, but it is good to see these data. Patients who develop immune-related AEs to atezolizumab in metastatic urothelial cancer are less likely to have disease progression and are more likely to live longer. This likely speaks to a healthy immune system that is activated by checkpoint inhibitors. Interestingly and very reassuringly, the use of corticosteroids to overcome any immune-related AEs did not impact oncological outcomes.

Reference: BJU Int. 2024;133(2):158-68
Abstract

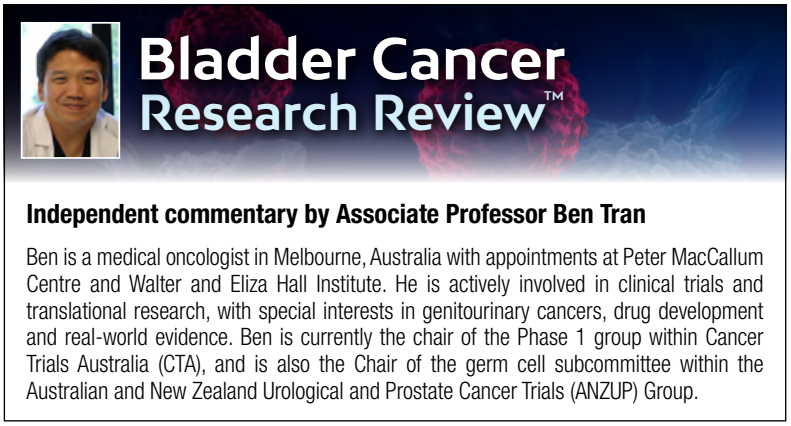
Long-term oncological outcomes in patients diagnosed with nonmetastatic plasmacytoid variant of bladder cancer

Authors: Sood A et al.

Summary: There is a paucity of data on the treated natural history of non-metastatic, plasmacytoid variant of bladder cancer. This was a retrospective chart review of 56 patients who were treated with curative intent over 20 years (1998-2018) at the University of Texas MD Anderson Cancer Centre. At presentation, 39.3% of patients had stage ≤cT2N0 disease, 26.8% had cT3N0, 23.2% had cT4N0 and 10.7% had ≥cN1. Chemotherapy was administered to 87.5% of patients and 75% underwent planned surgery. At the time of surgery patients had primarily pN+ disease (52.4%); only 7.2% had stage pT0. At a follow-up of 36 months, 28.4% of patients remained alive and 22.2% were metastasis-free. Metastasis-free survival was dependent on disease stage at the time of surgical excision: in patients with localised/locally advanced disease, 36-month metastasis-free survival was higher among those who underwent successful surgery following chemotherapy (32.4% vs. 0%; p<0.001), however, surgery showed no benefit for those with regionally advanced disease (12.5% vs. 10%; p=0.49). Metastasis occurred at a median of 6.5 months following the end of primary treatment. Patients with recurrence/metastasis had high rates of peritoneal lesions (76.1%), and their risk of death was significantly decreased by salvage immunotherapy (HR 0.11; p=0.001).

Comment: It is always good to see data about rare variants. In my experience, plasmacytoid urothelial cancer is very aggressive and has the potential to spread intraperitoneally. The two patients I have treated with this variant responded very well to platinum-based chemotherapy, but then progressed very quickly after its cessation. I think it is important to act quickly in these patients and to be aggressive with systemic therapy, and to work closely and collaboratively within a multi-disciplinary team.

Reference: J Urol. 2024;211(2):241-55
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.

Clinicopathologic and survival after cystectomy outcomes in squamous cell carcinoma of the bladder

Authors: Agrawal P et al.

Summary: This single-centre, retrospective cohort study explored the clinicopathologic and survival outcomes of 1034 patients following cystectomy for MIBC, 3.58% of whom had squamous cell carcinoma (SqCC) histology, 87.81% urothelial carcinoma histology and 8.61% urothelial carcinoma with squamous differentiation. A higher proportion of SqCC patients were female and of Black ethnicity, whereas a higher proportion of patients with squamous-differentiated urothelial carcinoma had a lower BMI, and a higher proportion of patients with urothelial cancer had a lower clinical T, cN, pathological T and pN stage. Intravesical therapy was more likely to be administered to patients with urothelial carcinoma, whereas those with SqCC had a lower likelihood of receiving NAC. All groups had comparable rates of adjuvant chemotherapy. Analyses found that patients with squamous-differentiated urothelial carcinoma had poorer OS, RFS and cancer-specific survival.

Comment: This is another variant for which we need more data! We always worry about how to treat SqCC histology. It is very important to differentiate this from squamous-differentiated urothelial carcinoma which should be treated like standard urothelial cancer; however, distinct SqCC is a different entity. Chemotherapy regimens for SqCC are not well described and there is a general feeling that MIBC patients with distinct SqCC histology should proceed straight to surgery. However, these data demonstrate that these patients do poorer post-operatively and are more likely to experience recurrence. We need to work towards producing data on an effective NAC protocol for this subgroup of patients.

Reference: Clin Genitourin Cancer. 2023;21(6):631-8
Abstract

Does chemo-radiotherapy improve survival outcomes vs. radiotherapy alone for high-grade cT1 urothelial carcinoma of the bladder?

Authors: Andruska N et al.

Summary: These investigators conducted a retrospective analysis to compare the OS of patients with high-grade, cT1 NMIBC treated with either radiotherapy alone (n=123) or chemo-radiotherapy (n=126) following transurethral resection of bladder tumour. Those who underwent chemo-radiotherapy experienced significantly longer OS compared to radiotherapy alone (HR 0.62; 95% CI 0.44—0.88; p=0.007), with 4-year OS rates of 36% and 19%, respectively (p<0.008).

Comment: Radiotherapy for T1 disease! I can already hear the urologists groaning. But there are certainly some patients for whom there are no other options, and there are certainly some patients who might not want to proceed to cystectomy for BCG-refractory disease. As a medical oncologist I am very interested in discovering better intravesical options for these patients, but perhaps I should also pay attention to the work exploring chemo-radiotherapy. This is a very select patient population in a retrospective analysis, albeit propensity-weighted. It is certainly hypothesis-generating, suggesting that if you are going to have radiotherapy for pT1 disease, you should consider adding chemotherapy as well. The plan is to explore this in a randomised phase 2 study.

Reference: Clin Genitourin Cancer. 2023;21(6):653-9
Abstract

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