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In this review:

Abbreviations used in this review:

AUC = area under the ROC curve; **BAT** = bipolar androgen therapy; **BCG** = Bacillus Calmette-Guérin; **HR** = hazard ratio; **HRQOL** = health-related quality of life; **IMDC** = International Metastatic RCC Database Consortium; **ISUP** = International Society of Urological Pathology; **mccRCC** = metastatic clear cell renal cell carcinoma; **mCRPC** = metastatic castration-resistant prostate cancer; **(m)RCC** = (metastatic) renal cell carcinoma; **NEPC** = neuroendocrine prostate cancer; **NMIBC** = non-muscle-invasive bladder cancer; **OS** = overall survival; **PDX** = patient-derived xenograft; **PFS** = progression-free survival; **PIRADS** = Prostate Imaging-Reporting & Data System; **PSMA** = prostate-specific membrane antigen; **(TR)AE** = (treatment-related) adverse event.

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Welcome to our review of the 2024 Australian and NZ Urogenital and Prostate Cancer Trials Group (ANZUP) Annual Scientific Meeting held on the Gold Coast, Australia.

This year ANZUP hosted a robust programme with a number of fascinating abstracts in the field of urogenital and prostate cancer research. Here I have selected ten presentations which were particularly interesting and relevant for our readers. We begin with an interesting presentation on a nurse-led clinic designed to address cardiovascular disease risk factors in prostate cancer, achieving improved rates of risk factor modification and high quality of care. Another highlight included a pre-clinical study which reports potentially crucial insights into mechanisms underlying response or resistance to 177Lu-PSMA in prostate cancer, through the use of patient-derived xenografts (mouse models). We conclude with important findings from a study at Monash Health, which reveal that men undergoing active surveillance with ISUP grade group 1 prostate cancer and a PIRADS 4/5 lesion have significantly higher rates of upgrading to clinically significant disease on repeat biopsy than those with PIRADS 1/3 disease; these results suggest that such patients need very close monitoring.

I hope you find this conference review informative and of clinical value, and I encourage you to send in your thoughts.

Kind Regards,

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Rapid access nurse led cardio-oncology clinics

Speaker: Trent Williams (University of Newcastle, Callaghan, NSW)

Summary: A high prevalence of cardiovascular disease risk factors is seen in patients undergoing treatment for prostate cancer. Trent Williams discussed the implementation of a nurse-led clinic for patients with prostate cancer, which aims to manage these risk factors and provide education, clinical assessment and referral to allied health providers. Cancer clinicians may refer their patients to the clinic, whereby they undergo cardiovascular assessment and other tests, with interviews on medical history, dietary habits, general function and physical activity. Between June 2020-February 2023, a total of 140 prostate cancer patients visited the clinic. At least one cardiovascular risk factor was observed in 85% of patients, and these patients began treatment for risk factor modifications, with 84% achieving guideline targets. Invasive revascularisation interventions (bypass grafting, stenting) were carried out in nine patients. Overall, 95% of patients rated the care they received as high quality, and the nurse-led clinic achieved high satisfaction and acceptability scores.

Comment: As survival has improved significantly for patients with advanced prostate cancer, the risk of death from non-cancer causes will undoubtedly increase. Cardiovascular disease is a particular issue for patients with advanced prostate cancer, and will likely become more prevalent due to the competing effects of an older population cohort and side effect profile of androgen deprivation therapy. Therefore, identifying and pre-emptively managing cardiovascular disease in advanced prostate cancer patients is paramount. This study looked at a rapid access, nurse-led clinic for 140 prostate cancer patients (85% with at least one risk factor for cardiovascular disease). Risk factor modification led to 84% of patients attaining guideline-based targets. A small number of patients required revascularisation procedures, and patient satisfaction was very high at 95%. These data show that early intervention for prostate cancer patients via a nurse-led clinic can help to optimise cardiovascular disease risk factors. The key remaining question – which could not be answered by this study – is whether early nurse-led intervention can reduce cardiovascular events, but this will require a much larger study with longer follow-up.

Abstract #55

Prognostic and predictive immune-based biomarkers to assess the benefit of adding mitomycin to Bacillus Calmette-Guérin as intravesical therapy for high-risk, non-muscle-invasive urothelial bladder cancer

Speaker: Cameron Redfern (Fiona Stanley Hospital, Murdoch, WA)

Summary: In this pilot cohort of the BCG-MM trial, patients with high-risk, non-muscle-invasive bladder cancer (NMIBC; relapsing n=23; non-relapsing n=23) were administered intravesical mitomycin + Bacillus Calmette-Guérin (NCG) or BCG alone. Immunohistochemistry revealed a significantly higher recurrence of low stromal cytotoxic T-cells in relapsing patients versus non-relapsing patients (65% vs. 35%, respectively; p=0.02), alongside higher total NK cell counts (62% vs. 36%; p=0.04), and higher intra-tumoural counts of the pan-macrophage CD68 marker (70% vs. 30%; p=0.004) and the M2-differentiated macrophage marker CD163 (65% vs. 35%; p=0.02). Numerically higher rates of relapse were seen in patients with high versus low tumoural CD163:CD68 ratios, although this did not reach statistical significance (63% vs. 41%; p=0.07). Outcomes showed no significant association with higher regulatory T-cells. It was noted that none of the biomarkers showed differential impacts between the two treatment arms.

Comment: BCG is a standard-of-care intravesical treatment for NMIBC; however, outcomes are highly variable, with some patients having primary resistance and others early treatment failure. Identifying biomarkers that correlate with clinical outcomes would be invaluable to better optimise the use of BCG, which as we all know is permanently in short supply. Using a cohort of relapsing and non-relapsing patients enrolled on the BCG-MM trial (BCG + mitomycin vs. BCG), the investigators examined tumour and stromal biomarkers associated with clinical outcomes. They found that low cytotoxic T-cells in stroma, increased macrophages in tumours and higher NK cell counts were linked to worse outcomes with BCG-MM. Importantly, these biomarkers were only prognostic, as no predictive biomarker was identified that showed a differential effect in either treatment arm. Overall, this is interesting work but needs validation in larger/independent series. In addition, identifying prognostic but not predictive biomarkers is unlikely to have much clinical utility in this disease space.

Abstract #52

Can proteomics predict metastatic relapse in prostate cancer? Development of a 6-protein prognostic signature in a >250 sample proteomic study including a validation cohort

Speaker: Elizabeth Connolly (University of Sydney, NSW)

Summary: These researchers attempted to identify a protein signature of metastatic relapse in prostate cancer to aid in risk stratification. A total of 6101 proteins from prostatectomy samples across two cohorts (discovery cohort PCA1; validation cohort PCA2) were evaluated via mass spectrometry. The final analysis set included non-relapsing patients only who had a follow-up of ≥12.5 years (PCA1 n=123; PCA2 n=71). At median follow-up periods of 15 (PCA1) and 13 years (PCA2), 61 and 71 metastatic relapse events were reported. In a multi-variate analysis of PCA1, the protein signature 6-PS was found to be associated with metastasis-free survival (HR 4.7; 95% CI 2.5—8.5; p<0.0001), and was predictive when used alongside EAU risk group classification (AUC 0.81). 6-PS was also associated with metastasis-free survival in the PCA2 cohort (HR 3.4; 95% CI 1.2—9.5; p=0.02), with similarly strong predictive performance alongside EAU risk stratification (AUC 0.78).

Comment: Following radical prostatectomy, approximately 1/3 to 1/2 of patients with clinically localised prostate cancer will relapse. In this study, the authors used proteomic analysis to profile 6101 proteins in discovery and validation cohorts of radical prostatectomy specimens. They developed a protein signature (called 6-PS) that they then applied to the respective clinical cohorts and correlated with clinical outcomes. They found that 6-PS was independently associated with metastasis-free survival in both the discover and validation cohorts. The signature also performed well when combined with EAU risk group classification. The results of this study are impressive; however, there are a plethora of prognostic biomarkers for patients with clinically-localised prostate cancer, and whether 6-PS outperforms those is unknown, and should be a priority for future work.

Abstract #21

Radiobiological responses to Lutetium-PSMA-I&T: the impact of underlying tumour biology on treatment response

Speaker: Laura Porter (Monash University, Melbourne, VIC)

Summary: Using patient-derived xenograft (PDX) mouse models, these investigators attempted to identify mechanisms underlying therapeutic response or resistance to 177Lu-PSMA in prostate cancer. A total of 70 PDXs received 177Lu-PSMA, and responses were compared with PSMA expression, tumour radiation uptake and differential gene expression. Immunohistochemistry revealed wide variation in tumour PSMA expression across all stages of progression. Among tumours with low PSMA expression, no response was observed to 177Lu-PSMA. In contrast, a range of responses were seen in tumours with high PSMA, from non-response through to complete and sustained tumour regression. Response was found to be affected by whole tumour radiation uptake, and heterogenous spatial expression of PSMA. Responsive tumours also displayed changes in gene expression and microenvironment composition, including downregulation of pathways related to DNA damage repair, and upregulation of inflammation pathways.

Comment: 177Lu-PSMA has transformed the management of mCRPC and is now established as a standard of care agent. However, not all patients respond to treatment, and the durability of benefit in many responders can be short-lived. Understanding the disease biology of cancers with and without a good response to 177Lu-PSMA remains a priority. In this pre-clinical study, the authors took patient-derived xenografts (PDXs, which are created by taking small amounts of human cancer and growing them in a mouse) and treated them with 177Lu-PSMA. They found that even in tumours with high PSMA expression, responses to treatment were highly variable. In addition, PSMA expression within cancer cells was variable, as was radiation uptake by cancer cells. In tumours that responded well to treatment, upregulation of inflammatory pathways and downregulation of DNA damage repair pathways on gene expression assays were observed. Altogether, this is a really important pre-clinical study that may offer crucial insights into mechanisms underlying response or resistance to 177Lu-PSMA in the clinic.

Abstract #54

Analysis of combination immunotherapy availability in Australia and time to treatment commencement in metastatic clear cell renal cancer

Speaker: Evon Jude (Austin Health, Melbourne, VIC)

Summary: In 2019, combination immunotherapy was approved for patients with metastatic clear cell renal cell carcinoma (mccRCC) at poor- or intermediate-risk. In this session, Evon Jude shared a study which explored the impacts that this approval had on treatment initiation and outcomes among 472 eligible mccRCC patients in the Australian Kidney Cancer Database (KRAB). Before and after 2019, the mean time to systemic therapy decreased significantly (14 to 4 months; p<0.05), and there was a significant reduction in the proportion of patients with a delay of ≥12 months to systemic treatment (27% to 7%). Among those who had an IMCD score of 1, a greater proportion received systemic treatment within 12 months after 2019 (38% vs. 24%). In spite of these trends, there have been no significant differences before and after 2019 in either PFS (31.8 vs. 30.7 months) or OS (21.7 vs. 20.5 months).

Comment: Among the treatment options for mccRCC is a period of initial observation in patients with low-volume, asymptomatic disease. With an increasing number of systemic options available, however, it is plausible that medical oncologists will feel obligated to offer systemic treatment earlier. This real-world analysis using the Australian KRAB database confirms this, showing that since the reimbursement of nivolumab and ipilimumab for first-line mccRCC, the time to initiation of systemic therapy has significantly decreased. The authors speculate that this might be due to wanting to start treatment within 12 months of diagnosis so that patients are classified as IMDC intermediate-risk, and can access nivolumab and ipilimumab through the PBS. That is certainly possible, but in my mind, it's more due to effective treatment options being available and using them earlier as a consequence. Either way, I think it's important to remember that a period of observation with or without metastasis-directed therapy remains a very viable and sensible option for low-volume, asymptomatic mccRCC.

Abstract #9

Registry-based randomised study of enzalutamide vs abiraterone assessing cognitive function in elderly patients with metastatic castration-resistant prostate cancer (REAL-Pro)

Speaker: Angelyn Anton (Monash University, Melbourne, VIC)

Summary: In the prospective, registry-based REAL-PRO trial, 76 eligible men from an Australian prostate cancer database aged ≥75 years with mCRPC were randomised 1:1 to either abiraterone or enzalutamide. Following slow accrual, recruitment was closed early. To assess cognitive impairment, depression, falls and cardiovascular risks, telephone assessments were conducted at baseline and at 12 weeks; 74% of men completed both assessments (each group n=28). At 12 weeks, a greater proportion of those in the enzalutamide arm showed worsening scores in the Geriatric Depression Scale (13.36% vs. 8.29%) and in the Blessed-Orientation-Memory-Concentration assessment (11.39% vs. 8.29%) versus abiraterone. A higher rate of falls was reported in patients administered enzalutamide (6.21% vs. 3.11%).

Comment: Androgen receptor pathway inhibitors (ARPIs), especially enzalutamide, have been associated with higher levels of cognitive dysfunction, depression and falls in older patients with mCRPC. The REAL-Pro study was a prospective, registry-based, randomised trial comparing the effects of enzalutamide and abiraterone on cognition, depression and falls in mCRPC patients aged ≥75 years. Although the study was closed early due to slow accrual (likely due to the fact that clinicians and patients did not feel there was clinical equipoise between the two treatments in this population), it did confirm that enzalutamide was associated with higher risks of cognitive decline, lowered mood and falls compared with abiraterone. None of this was a great surprise, so I do not feel this will have a major impact on clinical practice, as these particular issues with enzalutamide are well known to clinicians treating prostate cancer.

Abstract #61

Bipolar androgen therapy in combination with carboplatin chemotherapy retains activity in late line metastatic castrate-resistant prostate cancer

Speaker: Samantha Shekar (St Vincent's Hospital, Darlinghurst, NSW)

Summary: This session shared the interim analysis results from arm B of HIGH-TeCH, a phase 2 trial examining the safety and efficacy of bipolar androgen therapy (BAT) + carboplatin in heavily pre-treated mCRPC. At the time of data cut-off, treatment had been administered to 21 patients (median age 71 years; median 4 prior lines of treatment; 71% prior Lu-PSMA). At a median follow-up of 13.9 months, one patient remained on treatment, 19 patients had discontinued treatment due to disease progression and one patient discontinued with a serious AE. Overall, patients were administered a median of six cycles of BAT + carboplatin. PSA50 responses were seen in 24% of patients. Median PFS was 165 days, and median OS was not reached. It was noted that BAT + carboplatin had a tolerable safety profile. Predictive biomarker and quality of life analyses are currently underway, and the trial has met its endpoint for further expansion.

Comment: Bipolar androgen therapy (BAT) has emerged as a promising, albeit still unproven treatment for mCRPC. As BAT induces DNA double-strand breaks, a combination approach with carboplatin (which also induces DNA double-strand breaks) may be of particular utility. This rationale underpins arm B of the HIGH-TeCH study, which evaluated BAT + carboplatin in heavily pre-treated mCRPC. The investigators reported a PSA50 response rate of 24% and median PFS of approximately 5.5 months. Treatment was well tolerated, with only 7% of patients having grade 3 TRAEs. Overall, the efficacy of this approach seems limited, without any suggestion of synergy. Identifying predictive biomarker(s) may help, but otherwise it is difficult to see this combination moving forward in clinical development.

Abstract #18

A novel targeted therapy for treatment-emergent anaplastic forms of castration-resistant prostate cancer

Speaker: Brett Hollier (Queensland University of Technology, Brisbane, QLD)

Summary: Neuroendocrine prostate cancer (NEPC) tumours often have low PSMA expression, and to date, no molecular targeted agents have been approved for clinical treatment. Here, Brett Hollier presented his team's work on a therapeutic target which inversely correlates with expression of PSMA, named the FAcilitates Chromatin Transcription complex (FACT). Following promising preclinical findings, this study examined the use of CBL0137, a FACT-inhibitor, in five patient-derived xenograft (PDX) mouse models of NEPC. In vivo, CBL0137 monotherapy was found to significantly reduce the growth of PDX tumour tissue; results were similar in ex vivo PDX organoid cultures, with further benefits seen with cisplatin. It was concluded that CBL0137 shows promise as a potential mono- or combination therapy in anaplastic phenotypes of cancer, including NEPC.

Comment: Effective treatment options for NEPC remain a huge unmet need, with clinical outcomes remaining extremely poor for these patients. The investigators in this study identified FAcilitates Chromatin Transcription complex (FACT) as a novel therapeutic target in NEPC, and evaluated CBL0137 (a FACT inhibitor) in pre-clinical models of NEPC. Promisingly, they saw single-agent activity of CBL0137 in a range of PDX models of NEPC. Using organoid cultures obtained from NEPC PDXs, they also reported activity of CBL0137 in combination with cisplatin. Although there is a long way to go with this work, the results are promising, and it will be important to see if a FACT inhibitor suitable for use in the clinic emerges.

Abstract #3

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Independent commentary by Associate Professor Arun Azad

Associate Professor Arun Azad is a medical oncologist and translational researcher based at Peter MacCallum Cancer Centre and University of Melbourne with a subspecialist interest in urological malignancies.

Remote physical activity program for patients with metastatic renal cell carcinoma undergoing immunotherapy

Speaker: Paulo Bergerot (Medica Scientia Innovation Research, Sao Paulo, Brazil)

Summary: These researchers examined the effects of a 12-week remote, supervised exercise intervention in 19 patients (median age 67 years; 57.9% male) with metastatic renal cell carcinoma (mRCC) undergoing immuno-oncologic therapy (ipilimumab/nivolumab 21.1%; nivolumab/cabozantinib 15.8%; nivolumab 15.8%). The intervention included mobility, aerobic and resistance exercises. Patients displayed a range of adherence rates, with 57.9% showing high adherence. At 12 weeks, patients showed significant improvements in overall health-related quality of life (HRQOL; p=0.001), fatigue (p=0.001), anxiety (p=0.02), appetite (p=0.01), sleep quality (p=0.02), depression (p=0.01) and shortness of breath (p=0.01), however no changes were reported in nausea (p=0.1) or pain (p=0.1).

Comment: The benefits of exercise for patients with cancer are increasingly recognised. In this study, 19 patients with mRCC receiving immune checkpoint inhibitor-based therapy underwent a 12-week remote, supervised exercise programme, and were assessed for changes in HRQOL. Somewhat surprisingly, given that this was such a small study, significant improvements were seen in overall HRQOL and multiple symptoms including fatigue, anxiety, appetite, sleep quality, depression and shortness of breath. Although this is the first study to evaluate the impact of exercise on HRQOL in mRCC patients receiving immune checkpoint inhibitors, ultimately, we already know that exercise has lots of benefits for our patients with cancer, and further work in larger cohorts (as suggested by the investigators) almost seems unnecessary.

Abstract #62

Active surveillance in ISUP 1 prostate cancer and PI-RADS 4/5 lesion

Speaker: Shaoting Zhang (Monash Health, Melbourne, VIC)

Summary: The objective of this study was to investigate the rates of disease upgrading in men undergoing active surveillance with ISUP grade group 1 prostate cancer and a PI-RADS 4/5 lesion. A total of 228 men with ISUP 1 disease were enrolled, whom 135 (57.6%) had a PIRADS 4-5 lesion, while 93 (42.4%) had a PIRADS 1-3 lesion. Patients with PIRADS 4-5 lesions had a higher rate of biopsy upgrading to clinically significant prostate cancer than those with PIRADS 1-3 (58.3% vs. 40.4%; p=0.04), as well as a shorter time to upgrading of disease (p=0.001).

Comment: Active surveillance is standard of care for grade group 1 prostate cancer, and in countries like Australia, there has been rapid uptake of active surveillance for grade group 1 disease. One issue that is particularly relevant to Australian urologists, however (given the widespread use of multiparametric MRI [mpMRI] in the diagnostic algorithm for prostate cancer), is whether patients with a PI-RADS 4/5 lesion and grade group 1 disease are suitable for active surveillance. In this series of 228 patients, more than half had a PI-RADS 4/5 lesion and, when compared to patients with a PI-RADS 1-3 lesion, these patients were significantly more likely to be upgraded to clinically significant disease on repeat biopsy, and also had a significantly shorter time to disease upgrading. These are important results, and while active surveillance should be the standard of care for all grade group 1 prostate cancers, patients with PI-RADS 4/5 lesions need very close monitoring.

Abstract #6

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