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Metastatic CRPC: Contemporary Therapeutic Options and Optimal Sequencing

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Introduction

Prostate cancer (PC) is the most common malignancy among men worldwide. In Canada, an estimated 27,900 new diagnoses were projected in 2024, accounting for approximately 22% of all new cancer cases, with nearly 5,000 related deaths, making PC the fifth leading cause of cancer mortality.[1] Approximately 8% of patients present with metastatic disease at diagnosis.[2] Moreover, rates of *de novo* metastatic PC have increased in recent years, likely reflecting both the widespread adoption of advanced imaging modalities and reduced systematic screening practices.[2,3]

Initial treatment for recurrent or *de novo* metastatic castration-sensitive prostate cancer (mCSPC) typically consists of androgen-deprivation therapy (ADT) combined with an androgen receptor pathway inhibitor (ARPI). In patients with high-volume disease, which is defined as ≥4 bone metastases (including ≥1 outside the vertebral column) or the presence of visceral metastases, triplet therapy with ADT, an ARPI, and docetaxel chemotherapy may be employed.[4-6] In contrast, biochemical recurrence without radiographic metastases is generally managed with ADT alone, with treatment intensification using enzalutamide for patients with a prostate-specific antigen (PSA) doubling time between 3 and 9 months, as supported by the EMBARK trial.[7]

Despite initial disease control, most patients ultimately progress while maintaining castrate testosterone levels, a state known as castration-resistant prostate cancer (CRPC), which may be metastatic (mCRPC) or non-metastatic (nmCRPC). Over 84% of patients are estimated to have metastatic disease at the time of CRPC diagnosis.[8]

This review summarizes the current and evolving treatment landscape for mCRPC and proposes an evidence-based approach to treatment sequencing in accordance with the 2025 Canadian Urological Association Canadian Uro-Oncology Group guidelines and the National Comprehensive Cancer Network (NCCN) recommendations.[9,10]

General Principles for Treatment Selection

Metastatic CRPC is defined by disease progression despite ongoing ADT and castrate serum testosterone levels (<50 ng/dL or <1.7 nmol/L). Persistent androgen receptor signaling remains a key driver of disease progression, partly due to intratumoural autocrine and paracrine androgen synthesis.[11] Consequently, ADT is maintained indefinitely in patients with mCRPC.

Biochemical progression is defined as a PSA rise of ≥2 ng/mL or ≥50% above nadir, confirmed by three consecutive measurements at least one week apart.[12] Radiographic progression is assessed according to Prostate Cancer Working Group 3 (PCWG3) criteria.[13]

For patients who developed mCRPC, biopsy of metastatic lesions is recommended when feasible, along with molecular testing for homologous recombination repair (HRR) gene mutations (particularly *BRCA*1/2) and microsatellite instability (MSI)/mismatch repair (MMR) deficiency.[9,10] HRR testing may be performed on archival primary tumour tissue, fresh metastatic biopsy, or circulating tumour DNA when tissue is unavailable or non-informative.

Given the increasing use of ARPIs and chemotherapy in earlier disease states, treatment sequencing in mCRPC has become increasingly complex and must account for prior therapies, response duration, toxicity, and patient comorbidities.

Androgen Receptor Pathway Inhibitors

Abiraterone acetate plus prednisone (AAP) was the first ARPI to demonstrate survival benefit in mCRPC. In a phase III trial involving post-chemotherapy patients, AAP significantly improved progression-free survival (PFS) and overall survival (OS) compared with placebo.[14] Subsequently, the COU-AA-302 trial showed that AAP significantly prolonged median PFS in patients with chemotherapy-naïve mCRPC (16.5 vs. 8.3 months; hazard ratio [HR]: 0.53, 95% confidence interval [CI]: 0.45–0.62), leading to its approval in this setting.[15]

Enzalutamide, a second-generation ARPI, also demonstrated OS and PFS benefits in mCRPC after chemotherapy in the AFFIRM trial.[16] In the PREVAIL trial, enzalutamide significantly improved OS in patients with chemotherapy-naïve mCRPC, with a median OS of 35.2 versus 31.0 months (HR: 0.71, 95% CI: 0.60–0.84).[17,18]

In nmCRPC, enzalutamide, apalutamide, and darolutamide have all demonstrated clinically meaningful improvements in metastasis-free survival and OS when added to continuous ADT in patients with high-risk disease (PSA doubling time ≤10 months), forming the standard of care in this setting.[19-21]

For patients presenting with *de novo* mCRPC who have previously received ADT alone, first-line treatment typically consists of an ARPI (AAP or enzalutamide), either alone or in combination with a poly (ADP-ribose) polymerase (PARP) inhibitor in the presence of HRR mutations.

Taxane Chemotherapy

Taxane chemotherapy remains a cornerstone of mCRPC treatment. Docetaxel demonstrated a median OS improvement of approximately 3 months over mitoxantrone in the TAX 327 trial and is most commonly used as first-line chemotherapy.[22]

Cabazitaxel, a next-generation taxane developed to overcome docetaxel resistance, has demonstrated efficacy across multiple trials. In the TROPIC trial, cabazitaxel improved OS compared with mitoxantrone in post-docetaxel patients (15.1 vs. 12.7 months; HR: 0.70, 95% CI: 0.59–0.83).[23] The PROSELICA trial established non-inferiority of the 20 mg/m² dose compared with 25 mg/m², with improved tolerability.[24] Importantly, the CARD trial showed that cabazitaxel was superior to switching to an alternative ARPI in patients previously treated with docetaxel and one ARPI, improving both radiographic PFS (8.0 vs. 3.7 months; HR: 0.54, 95% CI: 0.40–0.73) and OS (13.6 vs.11.0 months; HR: 0.64, 95% CI: 0.46–0.89).[25]

Targeted Therapies

HRR Gene Mutations and PARP Inhibitors

Up to 30% of patients with metastatic PC harbour germline or somatic DNA repair gene alterations, most commonly involving *BRCA2* or *BRCA1*.[26-29] These mutations are associated with poorer prognosis but confer sensitivity to PARP inhibition.

In the post-ARPI setting, the PROfound trial demonstrated that olaparib significantly improved radiographic PFS (7.4 vs. 3.6 months; HR: 0.34, 95% CI: 0.25–0.47) and OS (18.5 vs. 15.1 months;

HR: 0.69, 95% CI: 0.50–0.97) compared with switching to another ARPI in patients with *BRCA1/2* or *ATM* alterations, despite crossover.[30]

First-line combinations of PARP inhibitors with ARPIs have also shown benefit in first-line treatment of mCRPC. The PROpel trial demonstrated improved radiographic PFS with olaparib plus abiraterone compared with abiraterone alone (24.8 vs. 16.6 months; HR: 0.66; 95% CI: 0.54 to 0.81), with the greatest benefit observed in HRR-mutated tumours.[31] This combination is approved by Health Canada for *BRCA1/2*-mutated mCRPC.

Similarly, the MAGNITUDE trial showed improved PFS with niraparib plus AAP in HRR-mutated mCRPC.[32] Recently, the TALAPRO-2 trial demonstrated that talazoparib plus enzalutamide improved both PFS and OS compared with enzalutamide alone, irrespective of HRR status. This treatment resulted in radiographic mPFS of 33.1 vs. 19.5 months (HR: 0.667, 95% CI: 0.551–0.807) and an OS of 45.8 vs. 37.0 months (HR: 0.796, 95% CI: 0.661–0.958).[33] The benefit was most pronounced in HRR-mutated tumours, where the combination produced a deeper and more durable radiographic PFS advantage compared with HRR-non-mutated disease.

PSMA-Targeted Radioligand Therapy

Patients with mCRPC progressing after ARPI and taxane chemotherapy may be eligible for PSMA-targeted radioligand therapy (RLT), contingent upon PSMA positron emission tomography (PET) imaging demonstrating PSMA-positive disease without discordant PSMA-negative lesions.

In the phase III VISION trial, beta-emitter lutetium-177-PSMA-617 plus standard of care significantly improved radiographic PFS (8.7 vs. 3.4 months; HR: 0.40, 99.2% CI: 0.29–0.57) and OS (15.3 vs. 11.3 months; HR: 0.62, 95% CI: 0.52–0.74) compared with standard care alone.[34] Although higher rates of grade ≥3 adverse events were observed, quality of life was preserved.

In taxane-naïve mCRPC, the PSMAfore and SPLASH trials demonstrated significant improvements in radiographic PFS compared with ARPI switching, though no OS benefit was observed, likely due to crossover.[35,36]

Immunotherapy

MMR deficiency, MSI-high status, or high tumour mutational burden (TMB) are identified in a minority of patients with mCRPC (1.2–12.0%) and may predict benefit from immune checkpoint inhibition.[28] Pembrolizumab has tumour-agnostic approval for these patients, with retrospective data demonstrating meaningful PSA and radiographic responses.[28,37] However, phase III trials of pembrolizumab combinations in unselected mCRPC populations have not demonstrated survival benefit.[38-40]

Other Therapies

Alpha-emitter Radium-223 dichloride (^{223}Ra) demonstrated improved OS and delayed skeletal-related events in the ALSYMPCA trial for patients with symptomatic bone-only mCRPC.[41] ^{223}Ra is an option for patients with mCRPC with symptomatic bone metastases and/or lymph nodes ≤3 cm in the absence of visceral disease.

Mitoxantrone, an anthracenedione antineoplastic agent, provides palliative benefit without OS improvement and is now rarely used.[42,43] The cellular therapy sipuleucel-T improved OS in asymptomatic mCRPC in the IMPACT trial but is not approved by Health Canada.[44]

Supportive Therapy

Bone metastases occur in approximately 90% of patients with mCRPC and these patients are thus subject to skeletal-related events.[45-47] These include pathological fractures, debilitating bone pain requiring palliative radiation therapy, and spinal cord compression, all of which may significantly affect quality of life.

Zoledronic acid and denosumab reduce skeletal-related events, with denosumab demonstrating superiority over zoledronic acid in delaying time to first event.[46,47] Bone-modifying agents should be routinely considered, with appropriate dental evaluation to mitigate the risk of osteonecrosis of the jaw.

Treatment Sequencing

Treatment sequencing in mCRPC is largely driven by prior systemic therapy exposure and should be individualized based on clinical and biological characteristics, as well as patient comorbidities.

Approximately 20–50% of patients treated with curative intent ultimately develop biochemical recurrence and progress to mCRPC, most often after prior exposure to ADT and an ARPI. Upon development of castration resistance, these patients typically transition to docetaxel chemotherapy while continuing ADT.

Similarly, patients presenting with (mCSPC) are now frequently treated upfront with ADT in combination with an ARPI, with the addition of docetaxel in those with high-volume disease. At progression to mCRPC, docetaxel is initiated, if not previously administered, or may be reintroduced in selected patients who achieved a durable prior response.

In contrast, for patients harbouring a pathogenic *BRCA1* or *BRCA2* mutation who experience progression following ARPI therapy, treatment with a PARP inhibitor, most notably olaparib, is recommended in lieu of immediate taxane chemotherapy.

As discussed earlier, lutetium-177-PSMA-617 may be considered in patients with prior exposure to an ARPI and at least one line of chemotherapy.

Finally, cabazitaxel and ^{223}Ra represent established therapeutic options that can be incorporated into the treatment sequence based on disease characteristics, prior therapies, symptom burden, and patient fitness.

Conclusion

Therapeutic advances have substantially improved outcomes for patients with mCRPC, offering prolonged survival and improved quality of life. Nonetheless, the disease remains incurable, and optimal sequencing of increasingly complex treatment options requires careful consideration of prior therapies and molecular features. Participation in clinical trials remains essential to further advance care for this population.

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