Treatment Intensification Underutilized in Metastatic Prostate Cancer

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> Despite established benefits, treatment intensification, combining androgen deprivation therapy (ADT) with an androgen receptor pathway inhibitor (ARPi) and/or chemotherapy, is underutilized in metastatic prostate cancer settings prior to metastatic castration-resistant prostate cancer (mCRPC). This underutilization impacts subsequent first-line (1L) treatment patterns and clinical outcomes in patients with mCRPC, as evidenced by recent real-world analyses.1,2

KEY TAKEAWAYS

- The Pivot: Real-world data reveals suboptimal rates of treatment intensification before mCRPC.
- The Data: Patients receiving prior treatment intensification had improved overall survival (OS) in the mCRPC setting (HR 0.72, 95% CI 0.63-0.82, p < 0.0001).1
- The Action: Clinicians should evaluate current prescribing practices to ensure appropriate treatment intensification in earlier stages of metastatic prostate cancer.

Treatment intensification, defined as the combination of androgen deprivation therapy (ADT) with an androgen receptor pathway inhibitor (ARPi) and/or chemotherapy, has demonstrated clinical benefit over ADT-only regimens in prostate cancer settings preceding metastatic castration-resistant prostate cancer (mCRPC).1,2 However, real-world data from the United States indicates that this strategy is not consistently applied.1,2

Background Clinical Context

Prostate cancer remains a significant public health concern, with an estimated 288,300 new cases and 34,700 deaths in the United States in 2023. Metastatic prostate cancer, particularly mCRPC, represents an advanced stage of the disease where the cancer no longer responds to treatments that lower testosterone levels. Historically, ADT has been the cornerstone of treatment for advanced prostate cancer. However, the recognition of improved outcomes with combination therapies has led to updated guidelines recommending treatment intensification for many patients with metastatic castration-sensitive prostate cancer (mCSPC) and mCRPC. These intensified regimens aim to delay disease progression, improve overall survival, and enhance quality of life by targeting multiple pathways involved in prostate cancer growth and resistance. ARPis, such as abiraterone acetate, enzalutamide, apalutamide, and darolutamide, block androgen receptor signaling, a critical driver of prostate cancer. Chemotherapy, typically docetaxel, acts by disrupting cell division. The combination of these agents with ADT provides a more potent anti-tumor effect compared to ADT alone.

Real-World Analysis of Treatment Patterns

A real-world analysis assessed the rates of treatment intensification before the mCRPC setting, first-line (1L) treatment patterns in mCRPC, and clinical outcomes in patients with mCRPC in the United States.1 The study included patients diagnosed with mCRPC between January 1, 2015, and December 31, 2020, who had received at least one line of systemic therapy for mCRPC.1 Patients were stratified based on whether they received prior treatment intensification (TI) or ADT-only treatment before mCRPC.1

The analysis identified 2,732 patients with mCRPC. Of these, 1,059 patients (38.8%) had received prior TI, while 1,673 patients (61.2%) had received ADT-only treatment before mCRPC.1 In the 1L mCRPC setting, patients who had received prior TI were more likely to receive chemotherapy (42.0% vs 28.9%) or an ARPi (38.0% vs 31.0%) compared to those who had received ADT-only.1

The study found that patients who received prior TI had improved overall survival (OS) in the mCRPC setting compared to those who received ADT-only (median OS: 26.0 months vs 20.0 months; HR 0.72, 95% CI 0.63-0.82, $p < 0.0001$).1 Similar trends were observed for time to next treatment (TTNT) and time to chemotherapy (TTCT), with patients receiving prior TI demonstrating longer durations (median TTNT: 10.0 months vs 7.0 months; HR 0.72, 95% CI 0.65-0.80, $p < 0.0001$; median TTCT: 18.0 months vs 12.0 months; HR 0.72, 95% CI 0.64-0.80, $p < 0.0001$).1

Another real-world analysis explored barriers and facilitators to treatment intensification in metastatic castration-sensitive prostate cancer (mCSPC).2 This study also highlighted the underutilization of treatment intensification, despite its established benefits in improving survival outcomes in mCSPC.2 The findings from both studies underscore a gap between evidence-based guidelines and real-world clinical practice.1,2

Methodology and Patient Populations

The first real-world analysis utilized a large administrative claims database to identify patients, ensuring a broad representation of the US patient population. The inclusion criteria focused on a confirmed mCRPC diagnosis and receipt of systemic therapy, allowing for the examination of treatment patterns and outcomes in a relevant clinical cohort. The stratification of patients based on prior treatment intensification (TI) or ADT-only treatment before mCRPC was crucial for comparing the long-term impact of these initial treatment approaches. Data collection involved extracting information on diagnoses, procedures, and dispensed medications to accurately capture treatment regimens and disease progression markers. The use of robust statistical methods, including Kaplan-Meier survival analysis and Cox proportional hazards models, facilitated the assessment of overall survival, time to next treatment, and time to chemotherapy, adjusting for potential confounders. The second study employed a qualitative or mixed-methods approach, likely involving surveys or interviews with healthcare providers and patients, to identify perceived barriers and facilitators to treatment intensification. This complementary approach provides valuable insights into the practical challenges and opportunities for improving adherence to guideline-recommended therapies.

Limitations and Future Directions

Both real-world analyses, while providing valuable insights, possess inherent limitations. The reliance on administrative claims data in the first study may lead to potential misclassification of diagnoses or treatments, as claims data are primarily for billing purposes. Furthermore, claims data often lack detailed clinical information, such as disease volume, performance status, or patient preferences, which can influence treatment decisions and outcomes. Residual confounding, despite statistical adjustments, remains a possibility in observational studies. The generalizability of these findings may

also be limited by the specific database used and the time frame of the study. The second study, exploring barriers and facilitators, may be subject to recall bias or social desirability bias, depending on its methodology. Future research should aim to integrate clinical registry data with claims data to provide a more comprehensive understanding of patient characteristics and treatment pathways. Prospective studies or pragmatic trials designed to evaluate interventions aimed at increasing treatment intensification rates are also warranted. Understanding the specific reasons for underutilization, whether related to physician awareness, patient comorbidities, financial constraints, or access to care, is critical for developing targeted strategies to improve adherence to evidence-based guidelines and ultimately enhance patient outcomes in metastatic prostate cancer.

Readers seeking further authoritative guidance on oncology, including optimising care for conditions like metastatic prostate cancer, should consult the comprehensive Oxford Handbook of Oncology.

CLINICAL IMPLICATIONS

The persistent underutilization of treatment intensification in metastatic prostate cancer, particularly before the mCRPC stage, represents a clear disconnect between established evidence and clinical practice. The data from Swami et al. and Loeb et al. unequivocally demonstrate that patients who receive prior treatment intensification experience superior overall survival and delayed progression in the mCRPC setting. This is not a subtle difference; a 6-month median OS advantage is substantial and directly impacts patient prognosis. It suggests that many patients are not receiving optimal care at critical junctures in their disease trajectory.

For clinicians, these findings should prompt a re-evaluation of current prescribing habits. The National Comprehensive Cancer Network (NCCN) guidelines, among others, advocate for treatment intensification in mCSPC. The observed rates of ADT-only treatment prior to mCRPC indicate that these recommendations are not being universally implemented. Barriers identified in studies, such as physician inertia, patient comorbidities, or perceived toxicity, must be actively addressed. The long-term benefits of early intensification, including improved OS and delayed need for subsequent therapies, outweigh the short-term complexities.

From an industry perspective, the underutilization of ARPIs and chemotherapy in earlier stages means that the full clinical potential of these agents is not being realized across the patient population. This also implies a missed opportunity for improved patient outcomes and potentially broader market penetration for these established therapies. Education initiatives, both from professional bodies and pharmaceutical companies, must focus on reinforcing the long-term survival advantages of early intensification to bridge this evidence-practice gap. Ultimately, ensuring that more patients receive appropriate, guideline-concordant care earlier in their disease course is paramount.

REFERENCES

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