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# The Current Landscape in Metastatic Castrate Resistant Prostate Cancer: What's New?

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## Historical Perspective: How Do We Treat This Disease?

Metastatic castrate resistant prostate cancer (mCRPC) is a significant cause of morbidity and mortality, with nearly 260,000 deaths annually worldwide [1]. From the first use of estramustine phosphate [2], a nitrogen mustard derivative of estradiol, in the early 1980s to the current employment of more sophisticated approaches employing agents such as abiraterone acetate [3], a cytochrome P-450c17 inhibitor, there has been a paradigm shift in the treatment of this disease, particularly in the last three years. Treating mCRPC from the 1980s to the early 1990s was challenging and disheartening, with minimum benefit achieved through a range of chemotherapy and radiotherapy approaches. However the United States Food and Drug Administration (FDA) approval of the taxane docetaxel for the treatment of mCRPC in 2004 represented a watershed, heralding a period of increasing efficacy in the control of this aggressive disease.

## A Glimmer of Hope: The Emergence of Docetaxel

TAX 327, the critical phase III randomized trial of more than 1,000 patients, provided the evidence base for the FDA's approval of docetaxel and demonstrated the superiority of docetaxel plus prednisone versus mitoxantrone plus prednisone by showing increased overall survival (OS), a greater reduction in prostate specific androgen (PSA) levels, a greater reduction in pain, and an increased quality of life (QoL) [4]. A second trial (SWOG 9916), comparing docetaxel plus estramustine versus mitoxantrone plus prednisone also demonstrated superiority in the docetaxel-containing arm [5]. The more favorable toxicity profile of mitoxantrone compared with docetaxel prompted consideration of initial treatment with mitoxantrone in order to capture the QoL benefit, followed by second-line docetaxel upon progression. Retrospective analysis of crossover data from the trials, however, indicated a much poorer second-line response to docetaxel [6]. Thus, docetaxel became the "gold standard" treatment of choice for patients with advanced CRPC.

## Docetaxel Plus: Can We Do Any Better?

After the documented success of docetaxel as a front-line agent for mCRPC, researchers investigated the potential for increasing efficacy using a number of combination approaches, including the incorporation of vitamin D analogs (e.g., calcitriol) [7], the use of antiangiogenic agents (e.g., bevacizumab) [8], vaccine combinations (e.g., engineered PC cells secreting granulocyte-macrophage colony-stimulating factor) [9], immunomodulatory drugs (e.g., lenalidomide) [10], and proapoptotic agents (e.g., BCL2 inhibitors) [11]. While initial studies yielded some promising results, increased efficacy as judged by prolonged survival in phase III trials proved elusive.

## The Last Three Years: The Times They Are a Changin'

Congruent with the evaluation of docetaxel combination approaches, researchers focused on developing newer agents and strategies to combat mCRPC. Sipuleucel-T was the first of the new agents to garner FDA approval in the context of metastatic but asymptomatic men. This trial demonstrated no benefit in progression-free survival (PFS), but prolonged OS [12] led to FDA approval. Cabazitaxel is a novel taxane that showed efficacy in docetaxel-resistant patients. TROPIC, a phase III trial randomizing 755 patients to cabazitaxel plus prednisone versus mitoxantrone plus prednisone, based on antitumor activity seen in a phase I trial in patients pretreated with docetaxel, demonstrated an improvement in OS [13]. A number of trials have also highlighted the role for abiraterone acetate in both the post- and pre-docetaxel "space." COU-AA-301 randomized 1,195 patients to abiraterone acetate plus prednisone versus prednisone alone in pretreated patients [14], while COU-AA-302 employed the same treatment arms in 1,088 chemotherapy-naïve patients [3]. In both cases, impressive improvements in radiographic PFS and OS were detected. The antiandrogen enzalutamide has also shown prolonged survival in the treatment arm of the

phase III AFFIRM trial (enzalutamide versus placebo) involving nearly 1,200 patients who have failed initial docetaxel chemotherapy [15].

Advances in the treatment of mCRPC are not limited to chemotherapy and biological agents. A recent study (ALSYMPCA) evaluated the efficacy of Radium-233, an alpha particle-emitting bone-targeting radioisotope. Radium-233 chloride demonstrated a significant increase in median OS in the ALSYMPCA phase III clinical trial, in which 921 patients were randomized to alpharadin or placebo [16]. ALSYMPCA enrolled patients who were either postdocetaxel or docetaxel-naïve, and in the stratified analysis, both groups of patients had a longer survival when treated with radium as compared with placebo.

## mCRPC: Where Next?

Significant progress has been made in the last three years for this group of patients with advanced disease. A number of effective agents with distinct biological mechanisms are now part of our armamentarium. The challenge for cancer physicians is to build on these initial successes. Which drug is best for which patient? Are combinations better than sequencing? If sequences are better, what is the proper sequence? A current guiding principle should be to ensure that the patient gets as many active agents as possible, thus offering the best chance of longer survival with improved quality of life.

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