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Management of castrate-resistant prostate cancer in older men

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ABSTRACT

Prostate cancer is the most common cancer diagnosed in men with the highest incidence in older men. Older men are more likely to present with metastatic disease compared with younger patients and eventually all will develop castrate resistant disease. In recent years, a number of new treatment options have demonstrated survival benefits for metastatic castrate resistant prostate cancer. However, the lack of randomized trials directly comparing the different available options results in some uncertainty on how best to choose and sequence therapy. In this paper, we outline the therapeutic options available to men with metastatic castrate-resistant prostate cancer, including cytotoxic therapy, hormonal agents and bone-directed therapy. We focus particularly on the evidence for specific treatment options and the challenges faced in choosing the appropriate therapy for the older patient.

Contents

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1. Introduction

Prostate cancer is the most common cancer diagnosed in men, with 180,890 new cases and 26,120 deaths estimated for 2016 in the US.[1] It affects older patients disproportionately with 57% being >65 years at diagnosis and 25% ≥ 75 years[2]. Moreover, older men are more likely to present with metastatic disease compared with younger patients.[4]

While men with metastatic prostate cancer usually respond to androgen deprivation therapy (ADT), most patients develop castrate-resistant disease within 18–24 months.[5] Castration-resistant prostate cancer is defined by disease progression despite castrate levels of testosterone.[6] It presents as a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of preexisting disease, and/or the appearance of new metastases. Treatment options in the setting of metastatic castrate-resistant prostate cancer (mCRPC) have expanded in recent years, with six different treatments now demonstrating improved survival in phase III trials. The lack of randomized trials directly comparing the different available options results in some uncertainty on how best to choose and sequence therapy. Thus, tumor characteristics, presence or absence of symptoms, disease burden in addition to patient characteristics, and toxicities all impact treatment decisions.

Here we outline the therapeutic options available to men with metastatic castrate-resistant prostate cancer with a particular focus on the evidence for and challenges facing the older patient.

2. Cytotoxic Therapy

Despite the number of new treatment options for mCRPC (Table 1), cytotoxic therapy still has an important role as evidenced from the results of recent trials reporting the benefit of docetaxel in combination with ADT in patients with hormone-sensitive disease. In the CHAARTED trial,[7] median age 63 years, median overall survival was 13.6 months longer with ADT plus docetaxel than with ADT alone (57.6 months vs. 44.0 months; $p < 0.001$). In the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial, median age 65 years, median survival was increased by 10 months with the addition of docetaxel.[8] While a third, smaller study was negative,[9] a systematic review and meta-analysis including all three studies[10] confirmed a significant overall

Table 1 – Treatment options for metastatic castrate-resistant prostate cancer.

Treatment	Indication	Median age (range), years	Proportion of older patients (%)	Median OS benefit	Elderly specific toxicities/concerns
Hormones					
Abiraterone	Post-docetaxel (COU-AA 301)[22]	69 (42–95)	28%, ≥75 years	4.6 months, HR 0.74 (95% CI, 0.64–0.86)	Cardiac toxicity Hypertension
	Pre-docetaxel (COU-AA 302)[23]	71 (44–95)	32%, ≥75 years	4.4 months, HR 0.81 (95% CI, 0.70–0.93)	Hyperkalemia Fluid retention Steroid side effects
Enzalutamide	Post-docetaxel (AFFIRM)[29]	69 (41–92)	25%, 75 years	4.8 months, HR 0.63 (95% CI, 0.53–0.75)	Fatigue Falls risk
	Pre-docetaxel (PREVAIL)[30]	72 (43–93)	35%, ≥75 years	2.2 months, HR 0.71 (95% CI, 0.60–0.84)	Diarrhea
Immunotherapy					
Sipuleucel-T	Pre- and post-docetaxel (IMPACT)[35]	72 (49–91)	50%, >71 years	4.1 months, HR 0.78 (95% CI, 0.61–0.98)	Feasibility of administration and access
Cytotoxic therapy					
Docetaxel	TAX 327[12]	68 (42–92)	20%,[a] ≥75 years	2.4 months, HR 0.76 (95% CI, 0.62–0.94)	Neutropenia Peripheral sensory neuropathy Diarrhea
Docetaxel and estramustine	SWOG 9916[11]	70 (47–88)	Not specified	1.9 months, HR 0.80 (95% CI, 0.67–0.97)	
Cabazitaxel	Post-docetaxel (TROPIC)[16]	68 (62–73)	18%, ≥75 years	2.4 months, HR 0.70 (95% CI, 0 · 59–0 · 83)	Neutropenia Diarrhea
Radioisotopes					
RAD223	Pre- and post-docetaxel (ALSYMPCA)[36]	71 (49–90)	28%, >75 years	3.6 months, HR 0.70 (95% CI, 0.58–0.83)	GI toxicity

[a] The 3 weekly docetaxel group.