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Anti-Tumour Treatment

New treatment developments applied to elderly patients with advanced prostate cancer

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ABSTRACT

Prostate cancer is a common disease amongst elderly men. Compared with younger patients, men over the age of 75 are more likely to present with advanced disease and have a greater risk of death from prostate cancer despite higher death rates from competing causes. Treatment options for advanced prostate cancer have improved considerably in the last two years. The immunotherapy sipuleucel-T, the cytotoxic cabazitaxel, the androgen biosynthesis inhibitor abiraterone acetate, the radioisotope radium-223 and the antiandrogen enzalutamide have all been shown to improve survival in randomized phase III studies for patients with metastatic castration-resistant prostate cancer. This review will focus on the clinical data regarding new treatment developments specifically applied to elderly patients with advanced prostate cancer.

Introduction

Prostate cancer is the second most common cancer in North American and European men after non-melanoma skin cancer, and is the second leading cause of male cancer-related death.[1,2] Prostate cancer incidence increases with age. Elderly patients with low-risk organ-confined disease have low cancer-specific mortality and are candidates for active surveillance rather than radical local therapy.[3] Recent prostate cancer data from the population-based surveillance, epidemiology, and end results (SEER) database in the United States indicated that compared with younger patients (<75 years), elderly men were more likely to present with advanced disease.[4] Elderly men contributed almost half (48%) of cases diagnosed with metastatic (M1) disease.[4] The cumulative incidence of death from prostate cancer was also higher in the elderly despite higher death rates from competing causes. These age-specific differences may be explained by more aggressive disease biology in older men and/or less frequent diagnostic evaluation in older compared with younger patients. PSA screening for prostate cancer is increasing, however remains controversial and is not recommended for men with a life expectancy <10 years.[5] The increase in diagnostic evaluation for younger patients may lead to over-diagnosis of low-risk disease, contributing to age-specific differences.

Suppression of gonadal androgens remains first-line therapy for patients who relapse following treatment of organ-confined disease and for those with metastatic disease at diagnosis, however responses are not durable and metastatic castration-resistant prostate cancer (mCRPC) remains fatal. In the last two years, sipuleucel-T, cabazitaxel, abiraterone acetate, radium-223 and enzalutamide have all been shown to improve survival in randomized phase III studies for patients with mCRPC, as shown in Table 1.[6–10] The optimal use and sequencing of these new agents has yet to be determined and treatment paradigms for advanced prostate cancer are changing rapidly. It is clear that median survival for patients with advanced prostate cancer has markedly improved with the advent of novel therapeutics, with median survival from diagnosis of CRPC exceeding 30 months in selected trial populations.[11,12]

Treatment selection for elderly patients who are more likely to suffer from other medical co-morbidities remains a considerable challenge; however age alone should not prevent patients deriving benefit from novel therapies. This review will focus on the clinical

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Table 1
Phase III clinical trials in castration resistant prostate cancer (CRPC) showing an improvement in overall survival.

Trial	Disease state	Trial design	HR	Elderly patients	Poor performance status patients	Survival (months)	Refs.
TAX327 $N = 1006$	mCRPC	Docetaxel/prednisone vs. mitoxantrone/prednisone	0.76	20% >75 years	14% KPS ⩽70%	18.9 vs. 16.6	44
IMPACT $N = 512$	Minimally symptomatic mCRPC	Sipuleucel-T vs. control	0.78	73% ⩾65 years	ECOG PS 2 patients excluded	25.8 vs. 21.7	6
TROPIC $N = 755$	Post-docetaxel mCRPC	Cabazitaxel/prednisone vs. mitoxantrone/prednisone	0.70	19% ⩾75 years	8% ECOG PS 2	15.1 vs. 12.7	7
COU-AA-301 $N = 1195$	Post-docetaxel mCRPC	Abiraterone/prednisone vs. placebo/prednisone	0.65	28% ⩾75 years	10% ECOG PS 2	14.8 vs 10.9	8
ALSYMPCA $N = 922$	Post-docetaxel or unfit for docetaxel mCRPC	Radium-223 vs. placebo	0.70	Mean age 71 years	13% ECOG PS 2	14.9 vs. 11.3	9
AFFIRM $N = 1199$	Post-docetaxel mCRPC	Enzalutamide vs. placebo	0.63	25% ⩾75 years	10% ECOG PS 2	18.4 vs. 13.6	10

KPS: Karnofsky performance status, ECOG PS: Eastern cooperative group performance status; HR: hazard ratio.

data regarding new treatment developments for advanced prostate cancer specifically applied to elderly patients.

Abiraterone

Abiraterone acetate (abiraterone; Zytiga®, Janssen) is an oral inhibitor of CYP17A1, a key enzyme in the testosterone biosynthesis pathway. Inhibition of CYP17A1 leads to reduction of testosterone both from adrenal steroid precursors and intratumoral production. Ketoconazole is a non-specific CYP inhibitor that showed modest activity in advanced prostate cancer with significant associated toxicity.[13] In partnership with Cancer Research UK, scientists at the Institute of Cancer Research designed abiraterone as a specific CYP17A1 inhibitor.[14,15] In the pivotal phase III COU-AA-301 study, published in 2011, abiraterone was shown to prolong survival in men with CRPC who had progressive disease following docetaxel chemotherapy.[8] In April 2011 abiraterone was approved by the United States Food and Drug Administration (US FDA) for use after docetaxel. From the outset, the clinical testing of abiraterone has included elderly men. Phase I testing included men in their 70s and 80s and no age-specific issues were identified in terms of pharmacokinetic profile or adverse effects.[16,17] In a dedicated renal impairment trial, renal dysfunction had no appreciable impact on pharmacokinetic parameters.[18] Phase II studies in both chemotherapy-naïve and post-docetaxel patients suggested similar rates of PSA decline and radiological response in elderly men compared to their younger counterparts.[19–21] In the double-blind randomized phase III COU-AA-301 trial, which tested abiraterone or placebo in combination with prednisone or prednisolone, 331 of the 1195 participants were at least 75 years of age and the median age of the overall study population was 69 years. Eligibility criteria reflected a representative 'real world' population, including 10% of participants with a baseline Eastern Co-operative Oncology Group (ECOG) performance status (PS) of 2. The main exclusion criteria were significant liver dysfunction, uncontrolled hypertension and clinically significant cardiac dysfunction.

The primary endpoint of COU-AA-301 was overall survival (OS), and the study was halted when the planned interim analysis met pre-specified criteria for efficacy, with a 3.9 month improvement in median OS. At final analysis the benefit had extended to 4.6 months.[22] All secondary efficacy endpoints favored the experimental arm at the time of study unblinding, including time to PSA progression (10.2 vs. 6.6 months; $p < 0.001$), progression-free survival (PFS; 5.6 months vs. 3.6 months; $p < 0.001$), and PSA response rate (29% vs. 6%, $p < 0.001$). Abiraterone treatment improved survival in all age groups. The hazard ratio (HR) for death associated with abiraterone treatment was 0.66 (95% CI 0.48–0.91) in patients under the age of 65, 0.67 (95% CI 0.55–0.82) for patients over the age of 65 and 0.52 (95% CI 0.38–0.71) for patients over the age of 75. Regardless of age, patients with a PS of 2 had significantly poorer outcomes, with median survival of 7.3 months on abiraterone, compared to 15.3 months for the patients with PS 0–1 treated with abiraterone.[8]

An important exploratory endpoint in COU-AA-301 was quality of life assessment using the functional assessment of cancer therapy – prostate version (FACT-P) and the brief pain inventory – short form (BPI). Pain palliation was significantly better in patients who received abiraterone, but FACT-P results have yet to be formally reported. Participants also completed brief fatigue inventory (BFI) and again there was significant improvement in men who received abiraterone compared to placebo.[23]

Despite the addition of prednisone, the most common side effects in patients receiving abiraterone related to mineralocorticoid excess including hypertension, fluid retention and hypokalemia. These toxicities were managed with increased glucocorticoid doses or by using the specific mineralocorticoid antagonist eplerenone. The incidence of hypertension was 10% with abiraterone (1% grade 3) compared to 8% with placebo (<1% grade 3). The incidence of fluid retention and edema was higher in the abiraterone group (31% vs. 22% in the placebo group; $p = 0.04$), however most of these events were grade 1 or 2 and easily managed. Hypokalemia occurred more commonly in men receiving abiraterone (17% vs. 8% in the placebo group; $p < 0.001$) with 30 patients experiencing grade 3–4 hypokalemia. The frequency of cardiac adverse events was not significantly different in abiraterone acetate and placebo patients (13% vs. 11% respectively, $p = 0.14$). For elderly patients who may be more likely to suffer from common co-morbidities such as hypertension and reduced cardiac function, evaluation and optimization of cardiac status prior to commencing abiraterone therapy is recommended. Careful monitoring of blood pressure and potassium once abiraterone treatment is started, with proactive management of treatment-related toxicities, should minimize treatment-related morbidity.

Abiraterone is orally administered once daily on an empty stomach, but clinical trial data indicated that a fed state increased the absorption of abiraterone.[17] This may have implications for patients on multiple other tablets. The concomitant corticosteroids may be problematic for certain patients, particularly those with diabetes. It is not yet known whether longer-term abiraterone will be associated with development of clinically important late toxicities. Certainly, the further lowering of testosterone in castrate patients may be associated with further morbidity in terms of bone and cardiovascular health which will need careful monitoring. In general, abiraterone is a well-tolerated treatment in patients of all ages.