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Efficacy and toxicity of abiraterone and docetaxel in octogenarians with metastatic castration-resistant prostate cancer

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ABSTRACT

Objective: To assess the efficacy and toxicity of abiraterone and docetaxel in men with metastatic castration-resistant prostate cancer (mCRPC) of age >80 compared to younger men.
Methods: Retrospective chart review of 116 men treated with abiraterone and 378 men treated with docetaxel at Princess Margaret Cancer Centre. Categorical outcome measures including PSA response rate (PSA-RR) and incidence of toxic side-effects were compared using Fisher's exact test. Overall survival (OS) and biochemical progression free survival (bPFS) were analyzed using the Kaplan–Meier method and log-rank tests.
Results: Thirty-four (29%) and 50 (13%) of the men treated with abiraterone or docetaxel, respectively, were octogenarians. For abiraterone there were no significant differences in PSA-RR (42% vs. 39%), bPFS (4.7 vs. 4.4 months) or OS (14.0 vs 20.7 months) between octogenarians and younger men, respectively. Toxicity was mild with no significant differences between age groups. For men treated with docetaxel PSA-RR and OS did not differ between age groups (40% vs. 45% and 12.0 vs. 14.1 months, respectively). However, rates of febrile neutropenia were 16% and 7% for octogenarians and younger men, respectively ($p = 0.048$). This difference was observed despite greater use of lower dose intensity and weekly docetaxel in the elderly cohort, with 20% of them receiving lower than standard dose during their first cycle compared to 7% of younger men ($p = 0.004$).
Conclusions: Treatment outcome on abiraterone and docetaxel did not differ in patients over and under the age of 80, but febrile neutropenia was more common in octogenarians treated with docetaxel despite lower dose intensity.

Abbreviations: bPFS, biochemical progression free survival; CI, confidence interval; ECOG PS, Eastern cooperative group performance status; EPR, electronic patient record; mCRPC, metastatic castration resistant prostate cancer; OS, overall survival; PM, Princess Margaret; PSA, Prostate specific antigen; PSA-RR, PSA response rate.

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1. Introduction

Prostate cancer (PC) is the second most common cancer in men in the western world and a leading cause of cancer-related death.[1,2] Increasing age is a risk factor for PC,[3] and as the life expectancy of men increases, the population of elderly men with PC is increasing.

Epidemiological studies show that compared with younger men, older men (>75 years) are more likely to present with advanced PC, have a greater risk of death from PC despite higher death rates from competing causes, and contribute more than half of all PC deaths.[4] Additionally, as more life-prolonging treatments become available,[5] the population of very elderly men with advanced PC is increasing.

Once PC has metastasized, the goals of treatment become palliative. The initial treatment of advanced or recurrent disease is with androgen deprivation therapy (ADT) leading to a castrate level of serum testosterone,[6] but resistance to castration-therapy inevitably develops. The chemotherapeutic agent docetaxel has been the mainstay of treatment of men with metastatic castration-resistant prostate cancer (mCRPC) for over a decade.[7] Recently several new hormonal, chemotherapeutic and radionuclide agents have been approved for such men (reviewed in Sridhar et al.[5]), thus increasing the therapeutic armamentarium. Abiraterone acetate (abiraterone), a novel hormonal agent, has been shown to increase overall survival (OS) in men with mCRPC[8] when administered both prior to and after chemotherapy[8,9] however its optimal place along the disease continuum of mCRPC is unknown.

Here we aim to compare the efficacy and toxicity of abiraterone and docetaxel in men over and under the age of 80 by performing a retrospective chart review of men with mCRPC treated with either of these two agents at Princess Margaret Cancer Centre (PM).

2. Methods

2.1. Setting, Participants, and Definitions

All men who received initial abiraterone at PM from November 2009 (first drug availability) until March 2013 were identified through the PM electronic patient records (EPR). All men who received at least one dose of docetaxel for first line chemotherapy treatment of mCRPC at PM before January 2012 were identified through pharmacy records. Men who received docetaxel in the context of neoadjuvant or adjuvant trials or as second-line chemotherapy for mCRPC were excluded. All data were extracted from the EPR. The institutional Research Ethics Board (REB) approved the study.

PSA response was defined as ≥50% decline of PSA compared with baseline maintained for at least 3 weeks. Men with a rise in PSA within the first 12 weeks of chemotherapy treatment were considered as PSA responders if subsequent values of PSA satisfied the above criterion, as recommended by the Prostate Cancer Working group 2 (PCWG2).[10]

Biochemical progression-free survival (bPFS) was defined as the time between drug initiation and PSA progression according to (PCWG2) criteria.[10] As most men were not treated under trial setting, radiological assessment was not performed at pre-determined intervals and radiological PFS could not be determined consistently. Overall survival (OS) was defined as the time between treatment initiation and death from any cause. Men who were alive or lost to follow-up were censored on their last day of contact.

Co-morbidities were defined as the pre-existing conditions of hypertension, dyslipidemia, active smoking, cardio-vascular disease, diabetes mellitus, COPD or any other significant disease (including other malignancies aside for non-melanoma skin cancer). Co-morbidities were collected from the initial patient visit with his treating oncologist, in which they were detailed in length as part of the medical note, and updated if more accumulated over time. The total number of co-morbidities was calculated for each patient at start of treatment with either abiraterone or docetaxel.

2.2. Outcome Measurements and Statistical Analysis

The primary outcome was PSA-RR. Secondary outcomes of interest were toxicity as well as bPFS (for men treated with abiraterone) and OS. PFS was not defined as an endpoint for docetaxel as many patients stopped treatment upon the completion of a set amount of cycles without progressive disease.

Monthly PSA measurements were performed during the first 3 months of abiraterone treatment, and thereafter every 1–3 months according to physicians' discretion. Continuous variables were reported as medians with range (for age) or interquartile range (for laboratory parameters). Categorical variables were described as counts and/or proportions and compared using Fisher's exact test. OS and bPFS were estimated by the Kaplan–Meier method and compared using log-rank tests. All p-values were 2-sided and considered significant if <0.05. No correction was made for multiple significance testing. Data analysis was performed using Statistical Analysis Software (SAS) Version 9.2 (SAS Institute, Inc., Cary, NC) or SPSS Version 20 (IBM Corp).

3. Results

3.1. Abiraterone

Of 116 men treated with abiraterone, 34 were octogenarians (29%). Baseline characteristics show that a higher percentage of octogenarians had more than one concurrent co-morbid condition, slightly lower hemoglobin and albumin levels than younger men and an Eastern Cooperative Group (ECOG) Performance Status (PS) of 2 or higher (Table 1). Octogenarians were more likely to be prescribed abiraterone at a reduced dose with a high-fat meal than at full-dose in the fasting state (Table 2), based on data showing similar pharmacokinetics of these two dosing regimens.[11] In these men, upfront dose reduction was not performed for medical reasons but because abiraterone was not reimbursed in Ontario for those who had not received prior docetaxel, mandating these men to purchase the drug out-of-pocket.

The PSA-RR was similar for the two age groups: 42% (95% confidence interval [CI] 26–60%) in octogenarians and 39% (95% CI 28–50%) in younger men (p = 0.8). Similarly, there were no significant differences in median bPFS: 4.7 (95% CI 1.8–6.4)