Original Study

Predictors of Chemotherapy-Induced Toxicity and Treatment Outcomes in Elderly Versus Younger Patients With Metastatic Castration-Resistant Prostate Cancer

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Abstract

The present study evaluated treatment outcomes in patients with metastatic castration-resistant prostate cancer treated with docetaxel in the everyday clinical setting. Medical records from consecutively treated patients were reviewed, and clinical predictors of severe nonhematologic toxicity and febrile neutropenia were identified. Overall survival was inferior to that observed in clinical trials. Older age and dose reductions did not affect the survival outcomes.

Background: In the present study, we examined possible predictors of chemotherapy-induced toxicity, treatment outcomes, and the consequences of dose reductions in patients with metastatic castration-resistant prostate cancer (mCRPC) receiving standard docetaxel. **Patients and Methods:** Medical records from 421 consecutive patients treated with first-line docetaxel (75 mg/m^2 every 3 weeks) and low-dose prednisolone from 2007 to 2013 at Herlev University Hospital were reviewed. Common Terminology Criteria for Adverse Events, version 4.0, and the Prostate Cancer Working Group 2 guidelines were used to evaluate treatment-related toxicity and efficacy. Logistic and Cox regression models were used to predict toxicity and survival. **Results:** Age $\geq$ 75 years (odds ratio [OR], 2.33), baseline levels of hemoglobin (OR, 0.89), and previous metastatic epidural spinal cord compression (MESCC; OR, 1.70) were predictive of grade 3 and 4 nonhematologic toxicity. Previous MESCC was associated with a greater risk of febrile neutropenia (OR, 2.74). The median progression-free survival (PFS) and overall survival (OS) were 6.4 and 15.4 months, respectively. Survival was similar in the older (age $\geq$ 75 years) and younger patients (P_{PFS} = .66, P_{OS} = .90; log-rank) and when comparing patients undergoing dose reductions with patients treated with standard docetaxel throughout their treatment course (P_{PFS} = .51 and P_{OS} = 0.52; log-rank). A longer interval from the primary diagnosis to the initiation of docetaxel (hazard ratio [HR], 1.00), baseline hemoglobin levels (HR, 0.85), Eastern Cooperative Oncology Group performance status > 0 to 1 (HR, 1.44), lactate dehydrogenase greater than the upper limit of normal (HR, 1.64), and prostate-specific antigen levels (HR, 1.00) were predictors of OS. **Conclusions:** OS in the everyday clinical setting was inferior to that observed in randomized trials. Our results indicate that elderly patients and patients with moderate anemia or a history of MESCC at baseline have a greater risk of treatment-induced toxicity. Dose reductions did not compromise survival.

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Introduction

Prostate cancer is the second most common male cancer in Western countries.[1] For primary or recurrent metastatic disease, treatment with androgen deprivation therapy has been recommended.[2] Disease progression despite castration levels of serum testosterone (< 50 ng/dL) is defined as metastatic castration-resistant prostate cancer (mCRPC).[3] After demonstrating a 2.4-month median overall survival (OS) benefit compared with

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treatment with mitoxantrone and prednisone,[4] the combination of docetaxel and prednisone was considered first-line standard chemotherapy for this group of patients for a decade. Additional systemic antineoplastic agents have now been approved as standard therapies,[5-7] and newly published data from 2 randomized trials have demonstrated a positive impact on OS from docetaxel in patients with newly diagnosed metastatic prostate cancer.[8,9] The survival of patients with mCRPC remains limited[10]; therefore, it is essential that the probability of clinical benefit from a given treatment always outweighs the risk of severe treatment-induced toxicity. When advising patients on such key issues, physicians adapt the results from clinical trials into usage in daily clinical practice. This process is not without challenges because patients participating in clinical trials are often highly selected by specific inclusion and exclusion criteria.[11,12] Only a few studies have addressed treatment results in patients with mCRPC treated with docetaxel-based chemotherapy outside of clinical trials. The results from such retrospective studies have pointed to diminished OS with greater rates of toxicity and dose reductions.[13,14] The treatment of elderly patients constitutes a specific challenge, because this group of patients has generally been underrepresented in randomized trials[15]; however, results seem consistent in demonstrating an equal benefit from docetaxel in older and younger patients, although with greater rates of toxicity and dose reductions in the former.[16]

To gain further insight into the treatment outcomes of patients treated outside of clinical trials, we conducted a retrospective study in which we evaluated treatment outcomes of a cohort of patients with mCRPC treated with standard first-line docetaxel. Treatment results for the entire cohort were analyzed, and a comparison between older (age $\geq$ 75 years) and younger patients was performed. Additionally, we aimed to identify possible predictors of chemotherapy-induced toxicity and elaborate on the consequences of dose reductions in the everyday clinical setting.

Patients and Methods

The records from 421 consecutive patients treated with docetaxel (75 mg/m^2 every 3 weeks) and low-dose prednisolone (5 mg administered twice daily) at Herlev University Hospital were reviewed. A part of the clinical data from 234 of these patients was also included in a study comparing patients with mCRPC treated with first-line docetaxel with and without coadministration of low-dose glucocorticoids.[17] Docetaxel was administered as standard first-line chemotherapy, and treatment was initiated from January 2007 to May 2013, at which point abiraterone acetate was introduced as first-line therapy.

During treatment with docetaxel, Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, was used to register grade $\geq$ 3 nonhematologic toxicity (NHT). Toxicity and the number of hospital admissions were registered until 4 weeks after the cessation of docetaxel. Dose reductions were standard (1 level dose reduction equaled a 25% reduction in docetaxel dosage).

The prostate-specific antigen (PSA) levels were measured before starting every new treatment cycle. Patients were evaluated after 4 cycles of chemotherapy, and an increase in the PSA level preceding this first evaluation was considered a flare if followed by a PSA decline. Clinical evaluations were in accordance with the guidelines defined by the Prostate Cancer Clinical Trials Working Group 2,[3] with the modification that in those with and without a PSA response, PSA progression was defined as a $\geq$ 25% increase from the nadir or baseline level, with a confirming increasing value measured $\geq$ 3 weeks later. A PSA response was defined as a confirmed 50% decrease in the baseline PSA level.

Progression-free survival (PFS) was defined as the interval from the initiation of docetaxel to disease progression (radiographic, PSA, or clinical progression), the initiation of second-line treatment, or death from any cause. OS was defined as the interval from the initiation of docetaxel to death from any cause.

The χ^2, Fisher exact, or Mann-Whitney U tests were used to compare the clinical variables across the subgroups. OS and PFS were calculated using the Kaplan-Meier method. Univariate logistic regression models were used to identify possible predictors of treatment-related toxicity, and Cox proportional hazards regression analysis was used to estimate the univariate hazard ratios (HRs) for OS. Variables with $P < .10$ were included in a multivariate analysis, and the odds ratios (ORs) and HRs, with the corresponding 95% confidence intervals and P values were calculated. Backwards stepwise selection was used to discard variables with $P \geq .05$ on multivariate logistic regression analysis. All statistical tests were 2-sided, and $P < .05$ was considered statistically significant. All statistical analyses were performed using SPSS, version 21 (IBM Corp., Armonk, NY). The Danish Health and Medicines Authority and Danish Data Protection Agency approved the study.

Results

Background Characteristics and Treatment History

Background clinical data are presented in Table 1. Previous treatment with estrogens was favored in the older age group (16.2% vs. 25.8%; $P = .021$), and the time interval from primary diagnosis to the initiation of docetaxel was also longer for this group of patients (32.0 vs. 53.5 months; $P < .0001$).

Although the proportion of patients with elevated levels of lactate dehydrogenase (LDH) at baseline was greater in the younger age group (60.0% vs. 42.7%; $P = .001$), the older patients had higher PSA levels when initiating docetaxel (283 ng/mL vs. 232 ng/mL; $P = .037$). A greater fraction of elderly patients also had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 (28.2% vs. 18.5%; $P = .027$) compared with the younger patients. The frequency of previous metastatic epidural spinal cord compression, including nerve root compression (MESCC), and the median number of vertebrae irradiated as a consequence of MESCC were equally distributed in the 2 age groups. The administered radiation dosage was 25 to 30 Gy in 5 to 7 fractions.

Number of Treatment Cycles, Toxicity, and Dose Reductions

A median of 7 treatment cycles was administered to the entire cohort of patients. The number of treatment cycles was similar in the 2 age groups (Table 2) and when comparing patients treated with standard docetaxel dosage throughout their whole treatment course with patients receiving a dose reduction. The rates of grade 3 to 4 NHT, hospital admissions, febrile neutropenia, and deaths within 28 days of the last administration of docetaxel, whether or not presumed treatment related, were 46.8%, 40.9%, 11.2%, and 5.2%, respectively (Table 2). Dose reductions before the initiation