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Original article

Low-dose prednisolone in first-line docetaxel for patients with metastatic castration-resistant prostate cancer: Is there a clinical benefit?

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Abstract

Background: Randomized studies have shown improved survival with the combination of docetaxel (D) and prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC). We retrospectively investigated whether coadministration of low-dose glucocorticoids has clinical benefits.

Material and methods: Records from 358 patients with metastatic castration-resistant prostate cancer treated consecutively with either D 75 mg/m^2 every 3 weeks ($n = 124$) (Rigshospitalet) or D and prednisolone (P) 10 mg daily ($n = 234$) (Herlev Hospital) given as first-line chemotherapy were reviewed. Of these, 15 patients treated with glucocorticoids at initiation of D at Rigshospitalet were excluded. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used to register any grade of peripheral edema, grade ≥ 2 sensory neuropathy, and grade ≥ 3 nonhematological toxicity. Background clinical data, rates of toxicity, hospital admissions, dose reductions, and post−D treatments were analyzed by the Chi-squared test or Mann-Whitney *U* test. Progression-free survival and overall survival were calculated by the Kaplan-Meier method.

Results: Patients treated with D alone had a higher incidence of peripheral edema (32% vs. 15%, $P < 0.001$) and grade 3 nonhematological toxicity (56% vs. 43%, $P = 0.022$). Patients treated with D alone were also more frequently hospitalized (53% vs. 41%, $P = 0.035$), mainly owing to a higher incidence of febrile neutropenia in this group (25% vs. 10%, $P < 0.001$). P did not influence progression-free survival ($P = 0.692$, log-rank test) or overall survival when adjusting for baseline levels of hemoglobin, alkaline phosphatase, lactate dehydrogenase, prostate-specific antigen, and Eastern Cooperative Oncology Group performance status (hazard ratio$_P$ = 0.98, 95% CI: 0.76–1.26, $P = 0.89$, Cox proportional hazard regression model).

Conclusions: Coadministration of low-dose P reduced the incidence of peripheral edema, grade 3 nonhematological toxicity, and the risk of being admitted owing to febrile neutropenia during treatment with D. Adjusted survival analysis did not indicate that P affected prognosis.

Keywords: Prostate cancer; mCRPC; Docetaxel; Prednisolone; Toxicity

1. Introduction

Suppressions of adrenal androgen biosynthesis and inflammatory pain are some of the mechanisms thought to be responsible for the beneficial effects of low-dose glucocorticoids (LDG) administered in patients with metastatic castration-resistant prostate cancer (mCRPC) [1,2]. LDG also influences fatigue, nausea, and the number of circulating granulocytes [3,4] and multiple clinical studies have confirmed an effect on prostate-specific antigen (PSA) levels [5]. No benefit in overall survival (OS) has been demonstrated from LDG as a sole treatment; however, in the recent COU-AA-302 study an unexpected long median OS was observed in the LDG-alone arm [6]. Prolonged treatment with systemic glucocorticoids leads to bone demineralization and elevated blood glucose levels, which, combined with the long-term effects of androgen deprivation therapy, are factors that could potentially

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increase patient morbidity and mortality [7,8]. Tannock et al. [9], reported 25 years ago a clinical benefit from treatment with low-dose prednisone in a small group of patients with symptomatic mCRPC. In the mid-1990s, mitoxantrone and prednisone were shown to be superior to prednisone alone regarding pain relief and improvements in quality of life [10]. As a consequence, this combinational regime served as a comparator in both the TAX327 and TROPIC trials preceding the approval of docetaxel (D) for mCRPC [11,12] Owing to the mentioned side effects related to systemic treatment with glucocorticoids it is of importance whether coadministration contributes positively to treatment with chemotherapy. In this study we hypothesize that inclusion of prednisolone (P) could protect from D-induced toxicity, specifically febrile neutropenia, without influencing treatment efficacy. To shed light on this possible clinical benefit from coadministration of P, we retrospectively compared toxicity and treatment results from 2 institutions with and without the routine use of daily P as part of first-line treatment with D.

2. Material and methods

Records from 358 consecutively patients with mCRPC treated with either D 75 mg/m^2/q3 weeks without P (Rigshospitalet, $n = 124$) or D 75 mg/m^2/q3 weeks and P 5 mg twice daily (Herlev Hospital, $n = 234$) were reviewed. Of these, 15 patients treated with glucocorticoids at initiation of D at Rigshospitalet were excluded from the analysis. D was initiated between 2007 and 2010 as first-line chemotherapy for mCRPC. During this time period, single-agent D was considered standard therapy at Rigshospitalet whereas standard therapy at Herlev Hospital was D and P (DP). Glucocorticoid premedication regimens were identical in both treatment groups. Sum of Gleason scores at diagnosis and treatment history including previous events of metastatic epidural spinal cord compression (MESCC) (including nerve root compression) were registered. When initiating chemotherapy, age, presence of bone metastasis, eastern cooperative oncology group (ECOG) performance status (PS), and levels of hemoglobin, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and PSA were registered. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used to register any grade of peripheral edema, grade ≥ 2 sensory neuropathy, and grade ≥ 3 nonhematological toxicity. Febrile neutropenia was defined as a temperature $\geq 38.5^{\circ}$C (or 38.0°C for >2 h) and a total neutrophilic count $<0.5 \times 10^9$ cells/ml, as described in the guidelines issued by the European Society for Medical Oncology [13]. Toxicity and number and causes of admissions were registered until 4 weeks after termination of D. Elective admissions and admissions owing to administrative procedures (e.g., imaging) were not registered unless prolonged owing to D-induced toxicity. During treatment with D, events with dose reductions and use of granulocyte colony stimulating factor (G-CSF) were registered. Finally, post−D treatments along with events of MESCC during and following treatment with D were registered. PSA was measured before starting a new treatment cycle in both groups. Patients in the D-only (DO) and DP groups were evaluated after 3 and 4 cycles of D, respectively, and an increase in PSA preceding this first evaluation was considered flare if it was followed by a decline. Clinical evaluations followed the guidelines defined by the Prostate Cancer Clinical Trials Working Group [14] with the modification that in both treatment groups, PSA progression was defined as a $\geq 25\%$ increase from the nadir/baseline with a confirming increasing value measured 3 or more weeks later. Progression-free survival (PFS) was defined as time from initiation of D to disease progression (radiographic, PSA progression or clinical progression) or death by any cause. OS was defined as time from initiation of D to death from any cause. The Chi-squared test or Fisher exact tests or Mann-Whitney U tests were used to analyze differences in clinical data. PFS and OS were calculated using the Kaplan-Meier method and differences were analyzed with the log-rank test. To adjust for differences in clinical background characteristics between the 2 treatment groups we performed a multiple Cox proportional hazard regression model test and a hazard ratio with 95% confidence intervals (95% CI) and P value was calculated. All statistical tests were 2 sided and a P value of less than 0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 19 (IBM Corp., Armonk, NY). The study was approved by the Danish Health and Medicines Authority and the Danish Data Protection Agency.

3. Results

3.1. Patient population and treatment history

All but 3 patients had pathologically confirmed adenocarcinoma of the prostate, with 1 patient in each treatment group having neuroendocrine differentiation. In spite of repeated biopsies of the prostate, prostate cancer was not pathologically confirmed in 1 patient. PSA levels in this patient though were 279 ng/ml and imaging (bonescan and magnetic resonance imaging) revealed multiple bone metastases. Background and baseline characteristics are presented in Table 1. A higher proportion of patients in the DO group had Gleason score ≤ 7 at diagnosis (38.7% vs. 25.7%, $P = 0.024$) and more patients in this group received treatment with second-line antiandrogens (14.8% vs. 7.9%, $P = 0.048$) or polyestradiolphosphat (62.4% vs. 21.2%, $P < 0.001$) before initiation of D. The time from diagnosis of prostate cancer to initiation of D though was similar in both treatment groups (38.7 vs. 34.5 mo, $P = 0.17$). Baseline levels of hemoglobin were lower in the DP group (11.8 vs. 12.6 g/dl, $P = 0.004$) and compared with