Original Study

The Effect of Therapeutic Anticoagulation on Overall Survival in Men Receiving First-Line Docetaxel Chemotherapy for Metastatic Castration-Resistant Prostate Cancer

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Abstract

We examined the effect of therapeutic anticoagulation on overall survival in men with metastatic castration-resistant prostate cancer (mCRPC) receiving first-line docetaxel chemotherapy. Anticoagulant use (low-molecular-weight heparin [LMWH] or warfarin) was retrospectively ascertained from a large single-institution database; all patients who were prescribed anticoagulants had a clinical indication for anticoagulation (ie, deep vein thrombosis or pulmonary embolism, or both). Our study found that anticoagulant use was an independent predictor of improved survival in men with mCRPC receiving docetaxel.

Background: Anticoagulants have been postulated to possess antitumor activity, although clinical data supporting this claim are conflicting. No definitive data exist on the clinical impact of anticoagulation therapy in patients with prostate cancer. The aim of this study was to investigate the association between therapeutic anticoagulant use and survival in men with metastatic castration-resistant prostate cancer (mCRPC) receiving docetaxel chemotherapy. **Patients and Methods:** We retrospectively reviewed the records of 247 consecutive patients with mCRPC who received first-line docetaxel chemotherapy between 1998 and 2010 at a single institution. Among them, 29 patients (11.7 %) received therapeutic anticoagulation (low-molecular-weight heparin [LMWH] or warfarin) for the treatment of venous thromboembolism. Univariate and multivariable Cox proportional hazards regression models were used to investigate the effect of anticoagulant use on overall survival. **Results:** In univariate analysis, anticoagulant use was associated with improved survival (hazard ratio [HR], 0.61; $P = .024$). Median survival was 20.9 months in the anti-coagulation group versus 17.1 months in the control group ($P = .024$). In multivariable analysis, anticoagulant use remained a significant predictor of survival after adjusting for other baseline prognostic factors (HR, 0.49; $P = .023$). When each anticoagulant was considered separately in the multivariable model, LMWH remained significantly prognostic for survival (HR, 0.48; $P = .035$), whereas warfarin use did not. **Conclusions:** Anticoagulant use (LMWH in particular) is an independent predictor of improved survival in men with mCRPC receiving docetaxel. These data provide the impetus to further explore the antitumor properties of anticoagulants in patients with prostate cancer and warrant validation in prospective studies.

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Introduction

Tumor-mediated activation of the coagulation cascade leads to dysregulation of hemostasis and could result in venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism in patients with cancer.[1] VTE is a major cause of cancer-related morbidity and mortality and has been

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validated as an independent risk factor for mortality.[2,3] In addition, various tumor-associated coagulation factors such as tissue factor, fibrin, thrombin, and plasmin are implicated in mechanisms of tumor cell survival and progression, including tumor stroma formation,[4] tumor cell migration and adhesion,[5-7] antitumor immune evasion,[8,9] induction of oncogenes,[10] and angiogenesis.[11-13] Furthermore, several anticoagulant agents have been found to possess various antitumor properties in addition to their antithrombotic effects.[14]

A number of studies have evaluated the association between the use of anticoagulants and clinical outcomes in patients with cancer. Low-molecular-weight heparin (LMWH) and unfractionated heparin have both been associated with enhanced tumor responses to chemotherapy and improved progression-free survival (PFS) when combined with various chemotherapy regimens in a number of cancer types.[15-18] In patients with VTE, LMWH has consistently demonstrated superior survival benefits over unfractionated heparin or warfarin, without a significant difference in VTE recurrence.[19-22] However, in patients who have no therapeutic or prophylactic indication for anticoagulation, anticoagulant use has produced conflicting survival outcomes in randomized controlled trials.[23-26] However, the majority of these trials included heterogeneous patient populations with various tumor types (and different disease stages) and included only a small number of patients with prostate cancer.

To date, no definitive data exist on the impact of anticoagulation therapy on overall survival in patients with advanced prostate cancer. Hence, we conducted a single-institution retrospective analysis to evaluate the impact of therapeutic anticoagulation on survival in patients with metastatic castration-resistant prostate cancer (mCRPC) receiving first-line docetaxel chemotherapy.

Patients and Methods

Patient Selection and Treatment

Data were retrospectively collected on consecutive patients diagnosed with mCRPC and treated with first-line docetaxel chemotherapy between 1998 and 2010 at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland. All patients had pathologically confirmed adenocarcinoma of the prostate with evidence of progressive metastatic disease either by prostate-specific antigen (PSA) or clinical/radiographic criteria. All patients received first-line docetaxel-containing chemotherapy at the US Food and Drug Administration–approved dose and schedule or as participants in clinical trials incorporating first-line docetaxel at the same dose and schedule (ie, docetaxel 75 mg/m^2 administered intravenously every 21 days together with prednisone 5 mg twice daily).

Data Collection and Analysis

Demographic data, type of primary treatment (surgery vs. radiation), Gleason score, Eastern Cooperative Oncology Group (ECOG) performance status, baseline PSA level, number and location of metastatic lesions, hematologic and metabolic laboratory parameters, previous treatment history, and number of chemotherapy cycles were determined from patient records. Data were also collected on anticoagulant use, type of anticoagulant, indication for anticoagulation therapy, and duration of anticoagulant use. Treatment response and disease progression characteristics were captured according to the recommendations of the Prostate Cancer Clinical Trials Working Group.[27]

Patients were divided into 2 groups: those who received therapeutic anticoagulation and those who did not. The distribution of baseline characteristics was compared between the groups (for descriptive purposes only) using a χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Overall survival (the primary outcome measure of interest) was defined as the time from the first chemotherapy treatment with docetaxel to the date of death from any cause. Patients who had not died at last follow-up were censored at that time point. Secondary outcome measures included PSA response rates, objective response rates, and PFS estimates. Survival analysis was performed using the Kaplan-Meier method, and differences between curves were sought using the log-rank test. Univariate and multivariable analyses were performed using Cox proportional hazards analysis to determine if anticoagulant use was an independent prognostic factor for survival. The specific anticoagulants used (LMWH or warfarin) were also studied with respect to their effect on survival.

All statistical tests were 2-sided, and a P value of $< .05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 20.0 (SPSS Inc, Chicago, IL).

Results

Patient Characteristics

Between 1998 and 2010, a total of 247 consecutive patients with mCRPC who had received docetaxel as first-line chemotherapy were identified. Among them, 29 patients (11.7 %) were receiving therapeutic anticoagulation for a concomitant VTE during the time of their chemotherapy treatment. The median age was 68 years (range, 44-84 years), and the majority of patients were white (76%). Baseline characteristics including ECOG status, PSA level, Gleason score, previous treatment history, location and number of metastatic lesions, and baseline laboratory values were well balanced between the anticoagulated and nonanticoagulated groups (Table 1).

At the time of docetaxel initiation, 39.3% of all men (97 of 247) had measurable soft tissue disease and were included in tumor response rate analysis according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria.[28] Median PSA level was numerically higher in the anticoagulated group than in the nonanticoagulated group (128 ng/mL vs. 91 ng/mL, respectively). Other disease-related characteristics are summarized in Table 1.

All patients receiving anticoagulation therapy had a concurrent or previous diagnosis of VTE. The indications for anticoagulation were DVT in 15 patients (51.7%), PE in 9 patients (31.0%), and both DVT and PE in 5 patients (17.2%). Seventeen patients (58.6%) received LMWH, and 12 patients (41.4%) received warfarin. The median duration of anticoagulation therapy was 5.7 months (range, 0.6-35.3 months) (Table 1).

Survival and Other Treatment Outcomes

In univariate analysis (Table 2), use of any anticoagulant (ie, either LMWH or warfarin) was associated with improved survival compared with no anticoagulant (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.40-0.94; $P = .024$) (Figure 1A). Median