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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 anticoagulation 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

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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.

Keywords

Anticoagulation; Docetaxel; Metastatic castration-resistant prostate cancer; Overall survival

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 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/m² 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 survival was 20.9 months in the group receiving anticoagulation versus 17.1 months in the group not receiving anticoagulation (log-rank $P = .024$). Furthermore, patients receiving > 6 months of anticoagulation had even superior survival compared with those receiving < 6 months of anticoagulation (HR, 0.47; 95% CI, 0.26-0.88; $P = .018$). When overall survival was analyzed for each anticoagulant separately, a significant improvement in survival was observed with LMWH use (HR, 0.58; 95% CI, 0.34-0.99; $P = .048$) but not with warfarin use (HR, 0.82; 95% CI, 0.55-1.28; $P = .23$) (Figure 1, B and C).

Other clinical factors that showed statistically significant correlations with survival in univariate analyses included number of chemotherapy cycles received, ECOG performance status, presence of anemia, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation, low serum albumin level, elevated alkaline phosphatase level, baseline PSA level, and presence of visceral (ie, liver or lung) metastases (Table 2).

Anticoagulant use remained a significant predictor of overall survival in multivariable Cox regression analysis (HR, 0.49; 95% CI, 0.26-0.90; $P = .023$) (Table 3). In addition, LMWH use was also significantly associated with survival (HR, 0.48; 95% CI, 0.24-0.95; $P = .035$), whereas warfarin use was not (HR, 0.53; 95% CI, 0.13-2.16; $P = .374$). Number of

chemotherapy cycles, AST/ALT elevation, ECOG score, and anemia also showed significant association with survival in multivariable analysis (Table 3).

Additional treatment outcomes, including objective tumor responses (in patients with measurable disease), best PSA response, and PFS, did not show statistically significant differences between the anticoagulation and control groups (Table 4)

Discussion

Tumor-associated dysregulation of the coagulation system has long been speculated to be associated with proliferation and spread of cancer cells.¹⁴ Thus the potential antitumor effects of anticoagulants have been explored, and several mechanisms besides their anticoagulating properties have been identified. For example, LMWH exerts an antiangiogenic effect through fibrin structure modification, inhibition of the endothelial/tissue factor pathway, and direct inhibition of ligand binding to the VEGF receptor.^{12,13,29} Heparin has also been shown to inhibit tumor metastasis through inhibition of vascular cell adhesion receptors P- and L-selectin,³⁰ modulation of chemokines,³¹ and inhibition of heparinase activity.³² Notably, Drago et al demonstrated that heparin significantly reduced metastasis in a murine CRPC model.³³

The antitumor properties of anticoagulants have been further supported by demonstration of improvements in clinical outcomes in patients with cancer in several prospective trials.²³ Prandoni et al first demonstrated the survival benefit of LMWH compared with unfractionated heparin in patients with cancer and VTE (without differences in recurrence rates of VTE).³⁴ Survival benefits of LMWH in patients with VTE have been further validated by subsequent meta-analyses,^{35,36} which has led to several randomized controlled trials to specifically assess the survival benefit of LMWH in patients without VTE. FAMOUS (Fragmin Advanced Malignancy Outcome Study), which randomized 385 patients with various advanced cancers to receive either dalteparin or placebo for 12 months, showed a nonsignificant trend toward a survival advantage in the group treated with dalteparin.²³ Furthermore, the MALT (Malignancy and Low Molecular Weight Heparin Therapy) trial showed that a 6-week course of nadroparin in 302 patients with advanced malignancy without VTE resulted in significant improvements in survival compared with placebo (HR, 0.75; 95% CI, 0.59-0.96).²⁴ However, a subsequent similar randomized study by Sideras et al evaluating dalteparin in patients with advanced cancers failed to confirm the survival benefit.²⁵ Both studies included only a small number of patients with prostate cancer (18 patients in each study). A more recent open-label randomized trial by van Doormaal et al included a significant proportion of patients with CRPC (n = 197) and showed a 21% relative reduction in risk of death among patients with prostate cancer receiving nadroparin versus no anticoagulation (median survival, 20.0 vs. 17.5 months), although this difference did not reach statistical significance.³⁷

Our retrospective analysis of 247 consecutive patients with mCRPC starting docetaxel-based chemotherapy showed that men who received therapeutic anticoagulation (all of whom also had a documented VTE) demonstrated improved survival compared with the control group that did not receive anticoagulation. This finding is particularly interesting because the

control group had comparable baseline prognostic characteristics but had no VTE (which is an indicator of poor survival in patients with cancer).^{2,3} This finding lends further support to the notion that anticoagulants may possess antitumor activity in men with mCRPC.

In our analysis, the survival benefit was more robust with LMWH use than with warfarin use (the survival trend with warfarin was not statistically significant). This observation is consistent with previous reports.³⁸⁻⁴⁰ Despite preclinical evidence of anti-metastatic^{41,42} and antiangiogenic⁴³ effects of warfarin, a survival benefit with warfarin has not been demonstrated in patients with cancer. The first randomized prospective study, the Veterans Administration Cooperative Study No. 75 (evaluating the effect of warfarin on survival in lung, colon, head and neck, and prostate cancers) showed significant improvements in survival only in patients with small-cell lung cancer.²⁶ However, subsequent randomized controlled trials failed to confirm the survival benefit of warfarin in patients with small-cell lung cancer.^{44,45} In addition, several randomized trials and meta-analyses comparing LMWH versus warfarin consistently showed a superior survival benefit of LMWH over warfarin in various solid tumor types.³⁸⁻⁴⁰

Despite the lack of specific recommendations for optimal duration of anticoagulation therapy in patients with cancer and established VTE, the majority of these patients receive anticoagulation therapy for 6 months or longer. Median duration of anticoagulation therapy in our study was 6 months, and the observed survival benefit was more pronounced in patients receiving anticoagulation for > 6 months. Previous prospective trials assessing the survival benefit of anticoagulants used various durations of anticoagulation (from 4 weeks to lifelong).^{46,47} This wide variation in duration of anticoagulation therapy for the purposes of cancer control precludes determination of appropriate anticoagulation duration and needs to be addressed in future studies.

Several prospective studies suggest that anticoagulation may also enhance the tumor response to cytotoxic chemotherapy. A phase II trial of single-agent docetaxel in combination with enoxaparin in patients with metastatic non—small-cell lung cancer showed a tumor response rate of 53% and a PFS duration of 5 months, which was longer than historical data in this setting, suggesting a synergistic effect of LMWH and docetaxel chemotherapy.¹⁷ An improvement in chemotherapy response as well as a survival benefit with the addition of LMWH has also been seen with various other chemotherapy regimens.^{15,16,18} A recent preclinical study also suggested that LMWH may prevent development of chemoresistance to cisplatin.⁴⁸ However, our data did not show improved tumor response rates or prolonged PFS with anticoagulation therapy, despite the observed improvements in overall survival. Therefore, it is not clear if the survival benefit demonstrated in our study is related to direct antitumor effects of anticoagulants or their ability to prevent further clinical thromboembolic events or micro-thrombotic phenomena that may potentially accelerate death in these patients.

Our study has the inherent limitations of a retrospective analysis and a relatively small sample size. However, to our knowledge, this is the first report of a significant survival benefit from therapeutic anticoagulation in patients with mCRPC receiving docetaxel chemotherapy. Our findings provide the rationale for further evaluation of anticoagulants

(especially LMWH) in patients with mCRPC in randomized prospective studies. In addition, evaluation of the safety and antineoplastic activity of next-generation oral anticoagulants (such as direct factor X inhibitors or thrombin inhibitors) may be warranted because increasing use of these novel agents in patients with cancer is anticipated.

Conclusion

Our retrospective analysis of 247 patients with mCRPC receiving docetaxel-based chemotherapy showed that patients who received therapeutic anticoagulation had improved survival compared with those not receiving anticoagulation therapy. The survival benefit was limited to LMWH use, whereas warfarin therapy did not appear to confer a survival benefit. Our findings are particularly interesting because the anticoagulated group also had concurrent VTE, which is a poor prognostic factor for survival in patients with cancer, further supporting the antitumor properties of LMWH in patients with mCRPC. Despite the inherent limitations of this retrospective analysis and a relatively small sample size, this study provides the impetus for further prospective evaluation of LMWH in patients with mCRPC.

Acknowledgments

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Clinical Practice Points

- Tumor-associated dysregulation of the coagulation system is associated with survival and spread of cancer cells.
- Various anticoagulants have been examined for potential antitumor effects, but no definitive data exist on the impact of anticoagulation therapy on survival in patients with advanced prostate cancer.
- Anticoagulation therapy resulted in improved survival in patients with mCRPC who received first-line docetaxel chemotherapy.
- The survival benefit appeared to be limited to LMWH use and not warfarin use.
- A larger effect on survival was observed in men receiving anticoagulation therapy for > 6 months.

Figure 1.
Kaplan-Meier Curves Depicting the Effect of (A) any Anticoagulation, (B) Low-Molecular-Weight Heparin (LMWH), and (C) Warfarin on Overall Survival

Table 1

Baseline Characteristics

Variable	Anticoagulation (n = 29)	No Anticoagulation (n = 218)	P Value
Clinical Characteristics			
Race, n (%)			.184
White	20 (71.4)	167 (77)	
Nonwhite	9 (28.6)	52 (23)	
Median Age, (range) years	65.7 (44.6-84.5)	68.5 (41.8-84.1)	.694
ECOG Performance Score, n (%)			.647
0	5 (31.2)	53 (37.1)	
1	11 (68.8)	90 (62.9)	
Gleason Score, n (%)			.353
6	3 (13)	10 (5.6)	
7	7 (30.4)	68 (37.8)	
8	13 (56.5)	102 (56.7)	
Treatment History			
Primary Treatment, n (%)			.564
Surgery	8 (29.6)	42 (20.7)	
Radiation	8 (29.6)	77 (37.9)	
Both	4 (14.8)	42 (20.7)	
None	7 (25.9)	42 (20.7)	
Median Number of Previous Hormonal Therapies (Range)	2 (1-4)	2 (0-5)	.872
Bisphosphonate Use, n (%)	6 (21.4)	69 (34.8)	.158
Median number Of Chemotherapy Cycles (range)	6 (2-18)	6 (1-19)	.869
Biochemical Values, median (range)			
Hemoglobin, g/dL	13 (8-15)	12 (7-16)	.280
AST (U/L)	26 (11-115)	25 (10-207)	.639
ALT (U/L)	21 (10-112)	20 (7-125)	.108
Albumin (mg/dL)	4.1 (3.2-4.9)	4.1 (3-5)	.981
Alkaline phosphatase (U/L)	126 (54-1949)	134.5 (12-2986)	.805
Baseline PSA (ng/mL)	128 (0-1377)	91 (0-5326)	.363
Metastatic Lesions, n (%)			
Presence of Bone Metastases	26 (92.9)	193 (89.8)	.606
10 lesions	3 (17.9)	31 (24.7)	.562
>10 lesions	23 (82.1)	162 (75.3)	
Presence of Lymph Node Metastases	18 (64.3)	106 (49.3)	.136
5 nodes	5 (27.8)	22 (20.8)	.504
>5 nodes	13 (72.2)	84 (79.2)	
Presence of Visceral Metastases ^a	3 (10.3)	34 (15.5)	.462
Presence of Measurable Disease ^b	12 (42.9)	85 (39.4)	.721
Anticoagulation Therapy Details			

Variable	Anticoagulation (n = 29)	No Anticoagulation (n = 218)	P Value
Indication for Anticoagulation, n (%)			
DVT	15 (51.7)	NA	
PE	9 (31.0)	NA	
Both DVT and PE	5 (17.2)	NA	
Type of Anticoagulant, n (%)			
Warfarin	12 (41.4)	NA	
LMWH	17 (58.6)	NA	
Duration of anticoagulation, mo, median (range)	5.7 (0.56-35.29)	NA	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; DVT = deep vein thrombosis; LMWH = low-molecular-weight heparin; NA = not available; PE = pulmonary embolism; PSA = prostate-specific antigen.

^aVisceral metastases consists of combined lung and liver metastases.

^bPresence of visceral or lymph node lesions, or both.

Table 2

Univariate Analysis of Overall Survival

Variable	Categories	HR (95% CI)	P Value
Anticoagulation use	Yes versus no	0.61 (0.40-0.94)	.024
LMWH	Yes versus no anticoagulation	0.58 (0.34-0.99)	.048
Warfarin	Yes versus no anticoagulation	0.82 (0.55-1.28)	.230
Length of anticoagulation, mo	>6 versus ≤6	0.47 (0.26-0.88)	.018
Age, years	≤65 versus >65	0.87 (0.65-1.17)	.354
Primary treatment	Radiation alone versus surgery ± radiation	1.19 (0.88-1.59)	.260
No. of chemotherapy cycles	6 versus <6 cycles	0.62 (0.46-0.84)	.002
Gleason score	7 versus ≤6	1.37 (0.71-2.62)	.347
	8-10 versus ≤6	1.60 (0.85-3.00)	.144
No. of hormonal therapies	Continuous	0.94 (0.78-1.13)	.510
Bisphosphonate use	Yes versus no	0.86 (0.63-1.17)	.340
ECOG score	1 versus 0	1.60 (1.10-2.35)	.013
Hemoglobin (g/dL)	<12.0 versus ≥12.1	2.18 (1.63-2.94)	<.001
Albumin (U/L)	<4 versus ≥4	2.64 (1.66-4.22)	<.001
Alkaline phosphatase (U/L)	≥140 versus <140	1.72 (1.30-2.28)	<.001
AST or ALT elevation, or both (≥40 U/L)	Yes versus no	2.45 (1.66-3.62)	<.001
Lymph node metastases	Yes versus no	0.96 (0.73-1.27)	.786
Visceral metastases	Yes versus no	1.98 (1.36-2.87)	<.001
Baseline (log) PSA	Continuous	1.11 (1.02-1.21)	.017

Bold values indicate statistically significant results.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; LMWH = low-molecular-weight heparin; PSA = prostate-specific antigen.

Table 3

Multivariable Analysis of Overall Survival

Variable	HR (95% CI)	P Value
Any anticoagulant versus no anticoagulation	0.487 (0.26-0.90)	.023
LMWH versus no anticoagulation	0.480 (0.24-0.95)	.035
Warfarin versus no anticoagulation	0.527 (0.13-2.16)	.374
Alkaline phosphatase: 140 versus <140 U/L	1.400 (0.94-2.08)	.097
AST or ALT elevation (>40 U/L), or both, present versus absent	2.638 (1.55-4.50)	<.001
Albumin: <4 versus 4 mg/dL	1.832 (0.95-3.53)	.103
Number of chemotherapy cycles: 6 versus <6 cycles	0.490 (0.33-0.72)	<.001
Hemoglobin: <12 versus 12 g/dL	1.511 (0.99-2.28)	.002
ECOG score: 1 versus 0	1.531 (1.03-2.29)	.037

Bold values indicate statistically significant results.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; LMWH = low-molecular-weight heparin.

Table 4

Treatment Response and Progression-Free Survival

Variable	Anticoagulation (n = 29)	No Anticoagulation (n = 219)	P Value
Objective tumor response, n (%)	5 of 12 (41.7)	35 of 80 (43.5)	.496
Best PSA response, % reduction, median (range)	57.1 (0-98.2)	57.2 (0-99.7)	.613
Progression-free survival, mo, median (range)	7.5 (1-36)	7.0 (0-79)	.535

Abbreviation: PSA = prostate-specific antigen.