Prognostic Value of Platelet Counts in Patients with Metastatic Prostate Cancer Treated with Endocrine Therapy

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Purpose: The endocrine therapy is effective for patients with advanced prostate cancer, but the disease eventually becomes refractory to treatment. The aim of this study was to investigate prognostic factors and to develop a risk stratification model for survival in patients with advanced prostate cancer undergoing endocrine therapy.

Materials and Methods: This study included 197 patients with stage IV prostate cancer who were treated with endocrine therapy as primary treatment at Tokyo Medical University, Tokyo, Japan, between January 1999 and November 2012. Prognostic values including baseline clinical laboratory values before endocrine therapy for stage IV prostate cancer were examined. Patients (n = 30) who were not followed or for whom data were unavailable or who were treated with radiotherapy were excluded from the study. Excluding these patients, we retrospectively analyzed 167 patients who were treated with endocrine therapy as the primary treatment. Disease-specific survival (DSS) was evaluated using the Kaplan-Meier method, and prognostic factors were identified using the Cox proportional hazard model analysis.

Results: In univariate analyses, patients with a performance status (PS) $\geq$ 2, platelet count $\geq$ 3.0× 105 μ/L, prostate specific antigen (PSA) > 50 ng/mL, alkaline phosphatase (ALP) > 350 U/L, lactate dehydrogenase (LDH) > 240 IU/L, and Gleason score (GS) $\geq$ 8, hemoglobin (Hb) < 12 g/dL, extent of disease (EOD) $\geq$ 3 and poorly differentiated adenocarcinoma showed significantly lower DSS than their respective counterparts. Neutrophil-to-Lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and white blood cell (WBC) count were not significantly associated with DSS. In a multivariate Cox proportional hazard model, PS and platelet count were independent prognostic factors. Based on the hazard rate (HR) calculated by the following formula: HR = exp (0.82 × PS + 1.38 × platelet count) patients were stratified into 3 risk groups. The differences in DSS rates among the 3 groups were statistically significant.

Conclusion: These results suggest that PS and platelet count are independent prognostic factors and that a combination of these factors can be used to stratify metastatic prostate cancer patients treated with endocrine therapy according to their DSS risk.

Keywords: advanced prostate cancer; endocrine therapy; platelet counts; prognostic value; risk stratification

INTRODUCTION

Although, endocrine therapy is initially effective for patients with advanced prostate cancer, some of them have an unfavorable prognosis; these patients need innovative therapeutic strategies to improve their prognosis, and they may be candidates for participation in clinical trials of novel therapies. Therefore, it is important to investigate prognostic factors and to develop a risk prediction model for survival in patients with advanced prostate cancer undergoing endocrine therapy in order to identify patients with a poor prognosis.

It has been reported that alkaline phosphatase (ALP), Gleason score (GS), hemoglobin (Hb) and extent of disease (EOD) are associated with prognosis in patients with advanced prostate cancer[1,2] in univariate analyses. In multivariate analyses, ALP and performance status (PS)[3], platelet-to-lymphocyte ratio (PLR)[4] and neutrophil-to-lymphocyte ratio (NLR)[5], were shown to be prognostic factors. Soloway et al. suggested that men with metastatic prostate cancer enrolled in trials designed to evaluate the impact of treatment on survival should be stratified based upon their EOD, as determined using a bone scan. Their analysis also indicates that patients in the EOD IV (super bone scan or similar super bone scan; equal to or more than 75% of total bone) category have particularly poor prognosis and may be candidates for alternative treatments. However, these studies did not develop tools for predicting prognosis, such as a risk stratification model, and it may therefore be difficult to accurately predict the prognosis.[1] Few reports have attempted to set up a risk stratification model for metastatic prostate cancer. Although EOD, ALP, GS, Hb, and PS are considered to be prognostic factors for survival, the oncologic significance of other potentially relevant variables such as peripheral

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Table1. Demographic and clinical characteristics

Characteristics	Number of patients (%)
Age, year; mean ± SD (range)	74.838 ± 0.629 (52-92)
T stage	
T1	19 (11.4)
T2	63 (37.7)
T3	67 (40.1)
T4	18 (10.8)
N stage	
N0	85 (50.9)
N1	82 (49.1)
M stage	
M0	32 (19.2)
M1	135 (80.8)
TNM stage	
TanyN1M0	32 (19.2)
TanyN0M1	85 (50.9)
TanyN1M1	50 (29.9)
bone metastasis (+/-)	
+	135 (80.8)
-	32 (19.2)
lymph node (+/-)	
+	99 (59.3)
-	68 (40.7)
Performance status, mean (range)	0.898 ± 0.089 (0-4)
≥ 2	49 (29.3)
≤1	118 (70.7)
Platelet, mean (range)	(241.329 ± 6.634) × 10^3 (6.1- 68.2× 10^3)
≥ 3.0× 10^5 /μL	32 (19.2)
< 3.0× 10^5 /μL	135 (80.8)
PSA, mean (range)	849.941 ± 185.612 (4.9-18910.0)
≥ 50 ng/ml	109 (65.3)
< 50 ng/ml	58 (34.7)
Alkaline phosphatase, mean (range)	589.874 ± 74.888 (106-7467)
> 350 U/L	62 (37.1)
≤ 350 U/L	105 (62.9)
Lactate dehydrogenase, mean (range)	252.698 ± 48.431 (86-8248)
> 240 IU/L	24 (14.4)
≤ 240 IU/L	143 (85.6)
Gleason score, mean (range)	8.281 ± 0.077 (6-10)
≥ 8	132 (79.0)
≤ 7	35 (21.0)
Hemoglobin, mean (range)	13.286 ± 0.146 (7.1-19.2)
≥12	133 (79.6)
< 12	34 (20.4)
White blood cell (WBC), mean (range)	(6.52 ± 1.84) × 10^3 (2.8-12.6)× 10^3
> 7.5 × 10^3 /μL	134 (80.2)
≤ 7.5× 10^3 /μL	33 (19.8)
Neutrophil-to-lymphocyte ratio (NLR)	2.757 ± 2.549 (0.883-27.059)
> 3.5 34 (20.4)	
≤ 3.5 133 (79.6)	
Platelet-to-lymphocyte ratio (PLR)	150 ± 73 (53-437)
> 150	64 (38.3)
≤ 150	103 (61.7)
Extent of disease (EOD)	1.653 ± 1.241 (0-4)
≥ 3	43 (25.7)
≤ 2	124 (74.3)
Histological differentiation	
poorly	80 (47.9)
well-moderately	87 (52.1)

Abbreviations: PSA: Prostate specific antigen

blood cell counts including platelet counts has not been fully evaluated. Platelet count has been reported to be a significant prognostic factor in renal tumors, malignant mesothelioma , diffuse large B cell lymphoma, upper tract urothelial carcinoma, epithelial ovarian cancer.[6-11] In several studies, platelets play a significant part in prostate cancer progression.[12]

However, to our knowledge, no report to date has investigated the relationship between platelet count and prognosis and developed a risk stratification model using platelet count.

In the present study, we sought to investigate prognostic factors including peripheral blood cell counts and to develop a risk stratification model for survival in patients with advanced prostate cancer undergoing endocrine therapy.

MATERIALS AND METHODS

This study was conducted at Tokyo Medical University. The medical records of 197 patients who were treated with endocrine therapy as primary treatment at Tokyo Medical University, Tokyo, Japan, between January 1999 and November 2012 were retrospectively reviewed after the study was approved by our facility's ethics committee. Prognostic values including baseline clinical laboratory values before endocrine therapy for stage IV prostate cancer were examined. Patients (n = 30) who were not followed or for whom data were unavailable or who were treated with radiotherapy were excluded from the study. Excluding these patients, we retrospectively analyzed 167 patients who were treated with endocrine therapy as the primary treatment (Table1). Endocrine therapy was LHRH analogue monotherapy or LHRH analogue with first-generation antiandrogen. Baseline demographic, clinical, and laboratory data were collected retrospectively for all patients.

Prostate cancer was diagnosed by using needle biopsy. The indication for a needle biopsy included an elevation of serum PSA level, a nodule felt on a digital rectal examination, and the existence of a low echoic lesion on transrectal ultrasonography (TRUS). Needle biopsy of the prostate was performed under TRUS guidance. Blood biochemistry was measured before the start of hormone therapy. Primary prostate cancer was evaluated by rectal examination, magnetic resonance imaging (MRI), and TRUS. Lymph node metastasis and distant metastasis were evaluated using computed tomography (CT) or MRI. The EOD, as determined using a bone scan was classified according to the method reported by Soloway et al. [1] PS was divided according to ECOG PS. [13]

We evaluated clinical and laboratory data before the start of hormone therapy retrospectively.

Baseline clinical data showed TNM stage, presence of bone metastasis, presence of positive lymph node, GS of biopsy on diagnosing prostate cancer, and histological differentiation. Baseline clinical laboratory data including platelet, prostate specific antigen (PSA), ALP, lactate dehydrogenase (LDH), Hb, white blood cell (WBC), NLR, and PLR before endocrine therapy were collected retrospectively for all patients. Disease-specific survival (DSS) defined the percentage of patients who have not died due to a specific disease at a certain point in the research participants or the treated group. We used DSS curves were constructed using the Kaplan-Meier method. Univariate analysis was performed using the log-rank test, and multivariate analysis was performed using the Cox regression analysis. To develop the risk stratification model, the optimal cut-off point was selected as the range of the 10th percentile to the 90th percentile for the distribution. Continuous variables were categorized by setting up effectual cut-off values[14]. We categorized effective cut-off values as described by Atzpodien J et al. Using the minimum p value approach, the selected cut-off value for all data was analyzed as a dichotomous variable. We identified significant prognostic factors in the multivariate analysis using a stepwise selection procedure. Therefore, all possible prognostic factors were evaluated in the multi-

Table 2. Result of univariate and multivariate analyses

Parameter	Univariate			Multivariate	
	P value	coefficient	Hazard ratio	95%CI	*P* value
PS (≧2 vs ≦1)	0.0129	0.82	2.27	1.36-4.21	0.0045
Plt (≧3.0× 10^5 vs < 3.0× 10^5)	< 0.0001	1.38	3.97	1.96-6.08	< 0.0001
PSA (> 50 vs ≦ 50)	0.0088				
ALP (> 350 vs ≦ 350)	0.0486				
LDH (> 240 vs ≦ 240)	0.0082				
GS (≧8 vs ≦ 7)	0.0141				
Hb (≧ 12 vs < 12)	0.0179				
EOD (≧3 vs ≦ 2)	0.0102				
poorly vs well or moderately	0.0294				
NLR (> 3.5 vs ≦ 3.5)	0.3772				
PLR (> 150 vs ≦ 150)	0.0502				
WBC (> 7500 vs ≦ 7500)	0.713				

Abbreviations: PS: Performance status, Plt: Platelet, PSA: Prostate specific antigen, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase, GS: Gleason score, Hb: Hemoglobin, EOD: extent of disease, NLR: neutrophil-to-Lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, WBC: white blood cell

variate analysis and a stepwise selection procedure was used. We calculated hazard rate (HR) of prognostic factors for DSS and developed a risk stratification model for survival by using the significant prognostic factors in patients with advanced prostate cancer treated with endocrine therapy as reported previously.[15,16] In all analyses, $P < 0.05$ was considered statistically significant. Analyses were performed with StatView.

RESULTS

The mean follow-up period was 54.3 months (range,

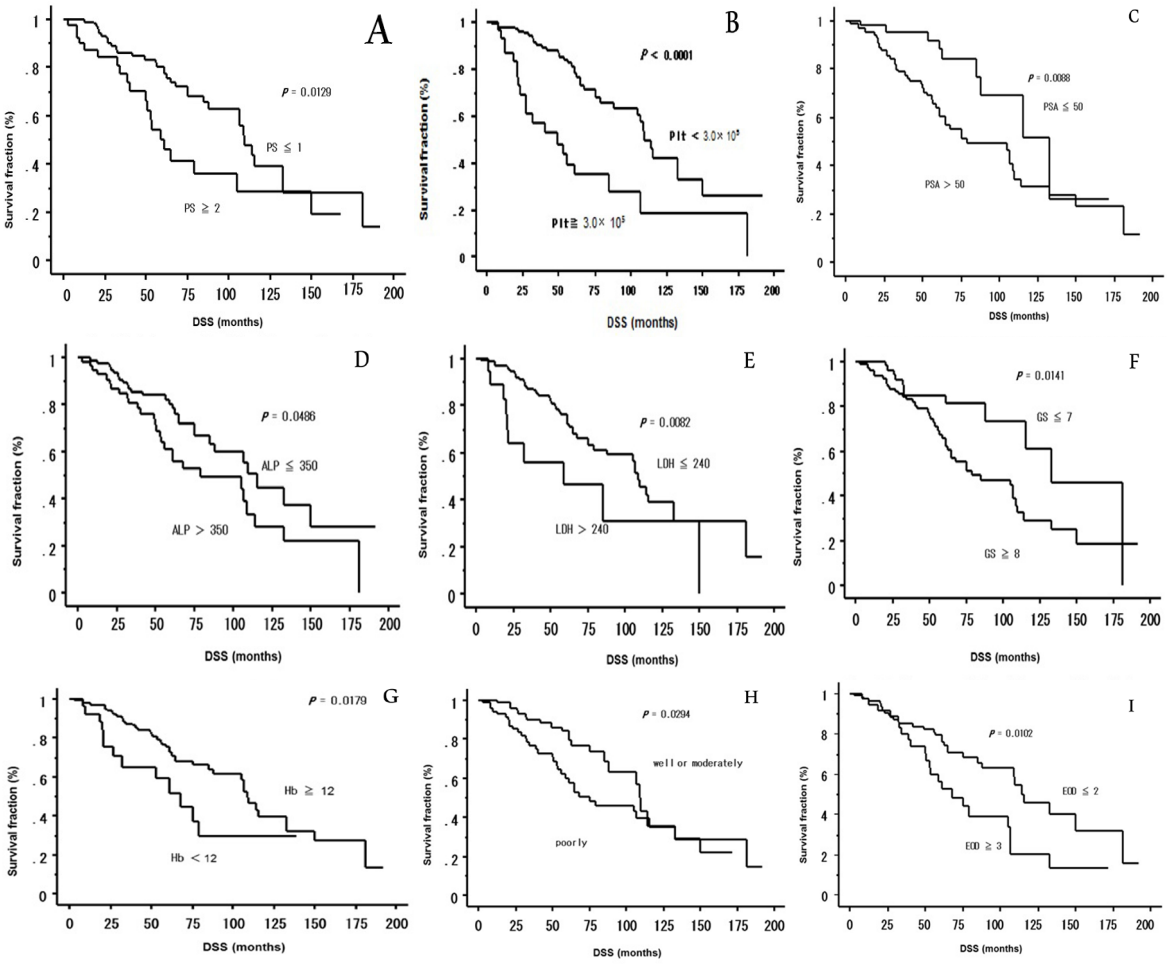

Figure 1. 1-A) Performance status (PS) and disease-specific survival, **1-B)** Platelet (Plt) and disease-specific survival, **1-C)** Prostate-specific antigen (PSA) and disease-specific survival, **1-D)** Alkaline phosphatase (ALP) and disease-specific survival, **1-E)** Lactate dehydrogenase (LDH) and disease-specific survival, **1-F)** Gleason score (GS) and disease-specific survival, **1-G)** Hemoglobin (Hb) and disease-specific survival, **1-H)** Poorly differentiated adenocarcinoma and disease-specific survival, **1-I)** Extent of disease (EOD) and disease-specific survival

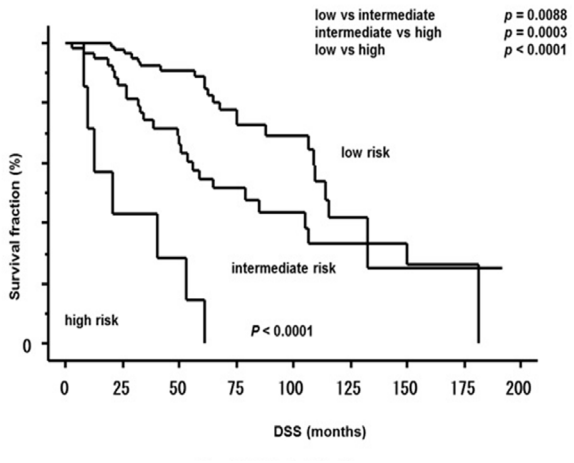

Figure 2. Disease-specific survival rates according to 3 risk groups. Using two statistically significant prognostic factors (Plt and PS), patients were stratified into 3 risk groups: a low-risk group, consisting of patients with neither of two unfavorable factors; an intermediate-risk group, consisting of patients with one of two unfavorable factors; and a high risk-group, consisting of patients with two of two unfavorable factors.

0–192 months). The mean survival time was 65.0 months. The mean age was 74.8 years (range, 52–92 years). The mean initial PSA was 849.9 ng/mL (range, 4.9–18910.0 ng/mL). T stage was T1 in 19 cases (11.4%), T2 in 63 cases (37.7%), T3 in 67 cases (40.1%), and T4 in 18 cases (10.8%); N stage was N0 in 85 (50.9%) cases, N1 in 82 cases (49.1%); and M stage was M0 in 32 cases (19.2%) and M1 in 135 cases (80.8%). T any N1M0 was 32 cases (19.2%), T any N0M1 was 85 cases (50.9%), and T any N1M1 was 50 cases (29.9%). LHRH analogue monotherapy was performed in 9 cases versus an LHRH analogue with first-generation anti-androgen in 158 cases.

In univariate analyses, patients with PS ≥ 2, platelet count ≥ 3.0 × 105 /μL, PSA > 50 ng/mL, ALP > 350 U/L, LDH > 240 IU/L, and GS ≥ 8, hemoglobin < 12 g/dL, EOD ≥ 3 and poorly differentiated adenocarcinoma showed significantly lower DSS rates than their respective counterparts (Figure 1). NLR, PLR and WBC count were not significantly associated with DSS. In a multivariate Cox proportional hazard model, PS (HR = 2.27, 95% confidence interval [CI]: 1.36 –4.21, P = 0.0045) and platelet count (HR = 3.97, 95%CI: 1.96 –6.08, P < 0.0001) were independent prognostic factors (Table 2). We calculated the HR for DSS by using the following formula: HR = exp (0.82 × PS + 1.38 × platelet count). In this equation, PS was assigned a value of 1 or 0 for ≥ 2 or ≤ 1, respectively. Platelet count was assigned a value of 1 or 0 for ≥ 3.0 × 10^5 /μL or < 3.0 × 10^5 /μL, respectively. Based on their PS and platelet count, patients were stratified into 3 risk groups: low-risk (HR = 1, PS ≤ 1 and platelet count < 3.0 × 10^5 μ/L), intermediate-risk (1 < HR ≤ 5, PS ≥ 2 and platelet count < 3.0 × 105 /μL or PS ≤ 1 and platelet count ≥ 3.0 × 10^5 /μL), and high-risk (HR > 5, PS ≥ 2 and platelet count ≥ 3.0 × 105 /μL). The differences in DSS rates among the 3 groups were statistically significant (**Figure 2**).

DISCUSSION

In previous reports, ALP, GS, Hb and EOD were related to prognosis in patients with advanced prostate cancer(1,7) in univariate analyses. In the present study, in univariate analyses, PS, platelet count, PSA, ALP, LDH levels, and GS were significantly associated with DSS rates, and in a multivariate Cox proportional hazard model, PS and platelet count were independent prognostic factors. Interestingly, platelet count was a prognostic factor in patients with metastatic prostate cancer treated with endocrine therapy.

Leblanc et al. revealed that patients with bone metastases (the most frequent in prostate cancer) have higher platelet count and bad prognosis.[17] In other malignancies, platelet count is also a prognostic factor. Bensalah et al. reported a correlation between platelet count and renal tumor characteristics, and evaluated the potential prognostic value of thrombocytosis in localized and metastatic tumors. The significance of the prognostic factors associated with survival was retained in multivariate analysis, suggesting that TNM stage, Fuhrman grade, tumor size, Eastern Cooperative Oncology Group score, and platelet count are independent prognostic factors in renal cell carcinoma.[6] Zhou et al. reported that high pretreatment platelet count resulted in poor overall survival in malignant mesothelioma.[7] Ochi Y et al. reported that platelet count and albumin levels are useful prognostic factors with diffuse large B cell lymphoma.[8] Georgios et al. assessed the impact of perioperative platelet count on recurrence-free survival after radical nephroureterectomy for upper tract urothelial carcinoma. In a comparison between patients with normal preoperative platelet counts and those with elevated platelet counts, the 5-year recurrence-free survival was significantly different for upper tract urothelial carcinoma.[9]

It was also reported that a group of patients with epithelial ovarian cancer and higher platelet counts had a significantly shorter median time to disease progression than a group of patients with normal platelet counts;[10] platelet counts were related to platelet derived growth factor, which may be the growth factor driving the pathogenesis of epithelial ovarian cancer.[11] Platelet-derived growth factors (PDGFs) and their receptors (PDGFRs) are key regulations of mesenchymal cells in the tumor microenvironment and have been associated with unfavorable outcomes in several cancers. A high expression of PDGFR-β, which was a specific manner with tyrosine kinase receptors of PDGFR family, is associated with biochemical recurrence in prostate cancer after radical prostatectomy.[18] PDGF-BB reportedly shows a significant predictive ability for prostate cancer.[19] It was also reported that thrombocytosis was associated with prognosis in patients with renal cell carcinoma.[20,21] Pardo et al. reported that higher platelet counts were associated with a poorer prognosis for those patients with hypopharyngeal cancer.[22] Platelet count has also been reported to predict postoperative survival in patients with gastric cancer.[23] Likewise, in the present study, patients with higher platelet counts showed significantly lower DSS rates than did those with lower platelet counts. In the past, it is revealed that platelets were related to prostate cancer progression.[12] In this study, PS and platelet count were independent prognostic factors in patients with metastatic prostate cancer. Recently, it has been reported that circulating tumor cells (CTC) counts have prognostic value in patients with castra-

tion-resistant prostate cancer (CRPC).[24] Future studies are expected to evaluate novel possible prognostic factors including CTC. We have calculated the HR of PS and platelet count and have successfully stratified patients with metastatic prostate cancer into 3 groups, using these prognostic factors based on the HR. The differences in DSS rates among the 3 groups were statistically significant. No reports to date have attempted to set up a risk stratification model using platelet count for metastatic prostate cancer. To our knowledge, the present study may be the first to establish a risk stratification model using PS and platelet count.

In recent years, it has been reported that abiraterone acetate[25,26] and enzalutamide[27] significantly prolong overall survival in patients with advanced prostate cancer. Our stratification model may facilitate more accurate predictions of unfavorable prognosis and identify patients who may be candidates for clinical trials of new strategies such as early induction of novel chemotherapeutics and hormonal agents that may eventually improve patients' DSS. We have demonstrated that platelet count is a novel prognostic factor and should be taken into consideration along with PS in the management of metastatic prostate cancer. Although this study provides important insights into the prognosis of patients with metastatic prostate cancer, it has several limitations. First, since it was a retrospective analysis of data collected from a single institution; the number of included cases was relatively small. Second, it is difficult to evaluate new strategies. It is not well known what new therapies are effective for metastatic prostate cancer patients with poor PS and a high platelet count treated with endocrine therapy at the primary treatment. The sequencing of metastatic castration-resistant prostate cancer (mCRPC) therapies was recently presented.[28] Furthermore, it is necessary to develop a novel treatment for patients with intermediate- or high-risk patients on the risk stratification to improve their prognosis. Further prospective studies are expected to validate externally the significance of our stratification model of DSS in patients with metastatic prostate cancer treated with endocrine therapy.

CONCLUSIONS

These results suggest that PS and platelet count are independent prognostic factors and that a combination of these factors can be used to stratify DSS risks in patients with metastatic prostate cancer treated with endocrine therapy.

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CONFLICT ON INTEREST

The authors report no conflict of interest.

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