Prognostic Impact of C-reactive Protein for Determining Overall Survival of Patients With Castration-resistant Prostate Cancer Treated With Docetaxel

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OBJECTIVE To verify the prognostic impact of C-reactive protein (CRP) for patients with castration-resistant prostate cancer (CRPC) treated with docetaxel in a single institution.

METHODS A group of 80 consecutive patients with CRPC were treated with docetaxel in our institution from January 2005 to May 2010. The patients received 75 mg/m^2 of docetaxel intravenously every 3 weeks. The prognostic value of all covariables, including CRP, was assessed using the Cox proportional hazard model. Risk stratification for overall survival was described from the results of the multivariable analysis.

RESULTS The median survival period for all patients was 14.5 months. The multivariable analysis showed that CRP and hemoglobin levels were independent prognostic factors for overall survival. Based on the presence of an elevated CRP concentration and/or a low hemoglobin level, all patients were stratified into 3 risk groups: those with no risk factors (low-risk group), those with 1 risk factor (intermediate-risk group), and those with 2 risk factors (high-risk group). The overall survival curves were clearly tiered according to the risk groups, with the 1-year overall survival rates being 86.3%, 60.5%, and 23.0% for the low-, intermediate-, and high-risk groups, respectively ($P < .001$).

CONCLUSION CRP is an independent prognostic factor for overall survival of patients with CRPC treated with docetaxel. Risk stratification based on CRP and hemoglobin could be helpful for estimating the overall survival. UROLOGY 78: 1131–1135, 2011. © 2011 Elsevier Inc.

Docetaxel is the first chemotherapeutic agent to demonstrate a survival benefit in patients with castration-resistant prostate cancer (CRPC),[1,2] yet the efficacy of docetaxel varies by patient. Because docetaxel is a cytotoxic agent, eventual adverse effects should not be ignored. In this regard, identification of prognostic factors would be an essential step in designing a therapeutic strategy for patients with CRPC being treated with docetaxel. It has been shown that pain, Gleason score, Eastern Cooperative Oncology Group performance status (ECOG PS), presence of visceral metastases, hemoglobin, albumin, and alkaline phosphatase (ALP) are prognostic factors for overall survival,[3-6] and several prognostic algorithms have also been proposed.[4,5,7,8]

Recently, the presence of a systemic inflammatory response that is measured by an acute-phase reactant has been recognized to be associated with a poor prognosis in various advanced cancers. C-reactive protein (CRP), which is a representative acute-phase reactant, has been shown to be 1 such significant prognostic factor.[9-11] We have also reported that CRP is an independent prognostic factor for patients with renal cell carcinoma and urothelial carcinoma of the upper urinary tract and bladder.[12-14] For patients with CRPC, 2 studies have previously reported that CRP is an independent prognostic factor.[15,16]

The aim of this study is to verify the prognostic impact of CRP for overall survival for patients with CRPC treated with docetaxel.

MATERIAL AND METHODS

Patients

A group of 80 consecutive patients with CRPC were treated with docetaxel at our institution from January 2005 to May

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Table 1. General characteristics of patients with castration resistant prostate cancer treated with docetaxel

		Number of Patients	CRP Status		
Variable	Category	All n = 80 (%)	Nonelevated (<5 mg/L) n = 34 (%)	Elevated (≥5 mg/L) n = 46 (%)	*P*
Age (y)	<70	41 (51)	16 (47)	25 (54)	.651
	≥70	39 (49)	18 (53)	21 (46)	
ECOG PS	0	66 (83)	32 (94)	34 (74)	.034
	≥1	14 (17)	2 (6)	12 (26)	
Gleason score	<8	14 (17)	6 (18)	8 (17)	.981
	≥8	66 (83)	28 (82)	38 (83)	
Analgesic consumption	−ve	40 (50)	23 (68)	17 (37)	.012
	+ve	40 (50)	11 (32)	29 (63)	
Bone metastasis	−ve	10 (12)	10 (29)	0 (0)	<.001
	+ve	70 (88)	24 (71)	46 (100)	
Visceral metastasis	−ve	57 (71)	23 (68)	34 (74)	.621
	+ve	23 (29)	11 (32)	12 (26)	
Prior estrogen	−ve	7 (9)	4 (12)	3 (7)	.451
	+ve	73 (91)	30 (88)	43 (93)	
PSA (ng/mL)	<80	48 (60)	25 (74)	23 (50)	.040
	≥80	32 (40)	9 (26)	23 (50)	
Albumin (g/dL)	≥3.6	52 (65)	27 (79)	25 (54)	.032
	<3.6	28 (35)	7 (21)	21 (46)	
ALP (IU/l)	<450	42 (53)	24 (71)	18 (39)	.007
	≥450	38 (47)	10 (29)	28 (61)	
Hemoglobin (g/dL)	≥11.0	44 (55)	24 (71)	20 (43)	.023
	<11.0	36 (45)	10 (29)	26 (57)	

NS = not significant.

2010 and comprised the current study cohort. In general, patients received 75 mg/m^2 of docetaxel intravenously every 3 weeks. If necessary, dose reduction and/or interval extension was allowed, based on a patient's overall condition. The median number of docetaxel chemotherapy cycles was 6 (range 1-23). Corticosteroid was simultaneously administered to all patients. In addition, zoledronic acid was administered to 30 patients (38%) with bone metastases. Seventy-three patients (91%) had already been given estrogen before docetaxel therapy was initiated. Forty patients (50%) had been using analgesics, including morphine, for pain control before the docetaxel therapy. All patients provided written, informed consent.

Variables

Prognostic variables were as follows: age at the beginning day of first cycle on docetaxel chemotherapy, ECOG PS, Gleason score, presence or absence of analgesic consumption, bone metastasis, visceral metastasis and prior estrogen therapy, pretreatment levels of serum prostate-specific antigen (PSA), hemoglobin, albumin, ALP, and CRP. For the statistical analysis, the categories of age, ECOG PS, and Gleason score were subdivided into 2 groups (age <70 years vs ≥70 years, ECOG PS 0 vs ≥1, and Gleason score 6-7 vs 8-10). The cut-off points of PSA, hemoglobin, albumin, ALP, and CRP were set at 80 ng/mL, 11.0 g/dL, 3.6 g/dL, 450 IU/L, and 5 mg/L, with the highest value of "sensitivity − (1 − specificity)" in the receiver operating characteristics (ROC) analysis using overall death as an endpoint, respectively.

Statistical Analysis

Because the primary endpoint of this study was overall survival, the follow-up period was defined as the initial day of the first cycle of docetaxel chemotherapy to the date of death or last visit. The associations among clinicopathological features were analyzed using the Fisher's exact test. The Kaplan–Meier curves were used to determine overall survival rate. The differences in overall survival rates were assessed using the log-rank test. Prognostic variables for overall survival were evaluated using the Cox proportional hazard model using backward elimination. For entry into a multivariable model, the *P* value of bivariate results was set to .25. The concordance index (c-index) was calculated as reported elsewhere.[17] For all analyses, the differences were considered significant at $P < .05$. All statistical analyses were performed using JMP software version 5.0 (SAS Institute, Inc., Cary, NC).

RESULTS

During the follow-up period (median 9.4 months, range 1-31 months), 37 of the 80 patients (46%) died of prostate cancer and 1 (1%) of another cause. The median survival period of all patients was 14.5 months (95% CI 10.7-21.8).

Characteristics of all 80 patients are summarized in Table 1. The median baseline CRP level was 6 mg/L (interquartile range 2-14 mg/L). CRP status was significantly associated with ECOG PS, presence or absence of analgesic consumption and bone metastasis, and pretreatment levels of serum PSA, hemoglobin, albumin, and ALP.

Bivariate and multivariable analyses for overall survival in patients with CRPC treated with docetaxel were shown in Table 2. The bivariate analysis revealed that ECOG PS, ALP, hemoglobin, albumin, PSA, and CRP were associated with overall survival. In the multivariable analysis using backward elimination, both CRP and hemoglobin were independent prognostic factors for overall survival. The hazard ratio of hemoglobin and

Table 2. Bivariate and multivariable analyses for overall survival in patients with CRPC treated with docetaxel

			Multivariable			
				Final Model		
Variable	Category	Bivariate *P*	Full Model *P*	Regression Coefficient	HR (95% CI)	*P*
Age (y)	<70 vs ≥70	.867				
ECOG PS	0 vs ≥1	.002	.138			
Gleason score	<8 vs ≥8	.404				
Analgesic consumption	−ve vs +ve	.117	.936			
Bone metastasis	−ve vs +ve	.125	.301			
Visceral metastasis	−ve vs +ve	.277				
Prior estrogen	−ve vs +ve	.299				
PSA (ng/mL)	<80 vs ≥80	.010	.994			
Albumin (g/dL)	≥3.6 vs <3.6	<.001	.089			
ALP (IU/l)	<450 vs ≥450	.005	.091			
Hemoglobin (g/dL)	≥11.0 vs <11.0	<.001	.089	0.486	1.63 (1.17-2.30)	.004
CRP (mg/L) (continuously)		.003				
CRP (mg/L)	<5 vs ≥5	<.001	.017	0.666	1.95 (1.33-2.96)	<.001

HR = hazard ratio; CI = confidence interval; NS = not significant.

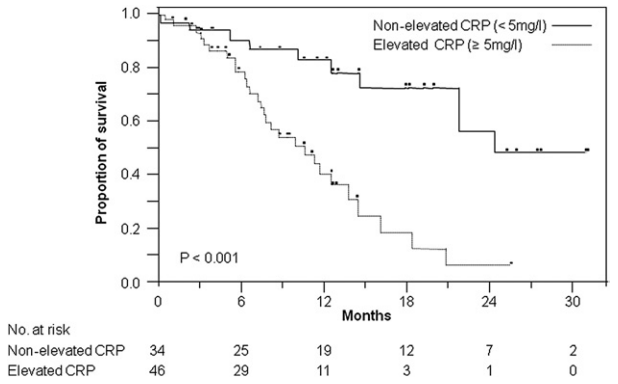

Figure 1. Overall survival curves for CRPC patients treated with docetaxel divided into nonelevated CRP (<5 mg/L) and elevated CRP (≥5 mg/L) groups.

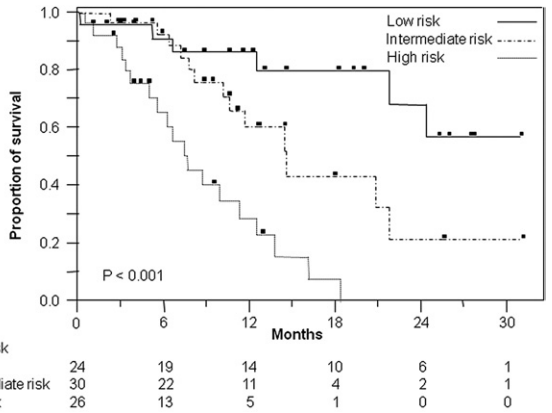

Figure 2. Overall survival curves for all patients with CRPC treated with docetaxel according to the risk groups. According to the presence of an elevated CRP (≥5 mg/L) concentration and/or a low hemoglobin level (<11.0 g/dL), each patient was assigned to low-, intermediate-, and high-risk groups.

CRP were 1.63 (95% CI 1.17-2.30, $P = .004$) and 1.95 (95% CI 1.33-2.96, $P < .001$), respectively. Median survival periods were 25 months in the nonelevated CRP (<5 mg/L) group and 11 months in the elevated CRP (≥5 mg/L) group ($P < .001$), respectively (Fig. 1).

Because CRP and hemoglobin were found to be 2 prognostic factors for overall survival, patients were divided into 3 risk groups according to CRP and hemoglobin levels. Both the elevation of CRP concentration (≥5 mg/L) and a low hemoglobin level (<11.0 g/dL) were assigned weight 1 because the regression coefficients of CRP and hemoglobin in the final multivariable model were nearly equivalent. According to the sum of their scores, patients were classified as low (0), intermediate (1), or high (2) risk. Overall survival curves according to the risk stratification were clearly tiered and statistically significant ($P < .001$), with 1-year survival rates of 86.3% (95% CI 56.8-95.8), 60.5% (95% CI 21.6-96.7), and 23.0% (95% CI 15.3-96.1) for low-, intermediate-, and high-risk groups, respectively (Fig. 2). Median survival periods of the patients with low-, intermediate-, and high-risk groups were not calculable, 15 months (95% CI 10-22) and 8 months (95% CI 5-11), respectively. The hazard ratio of intermediate and high risk to low risk were 1.66 (95% CI 1.04-2.83) and 3.03 (95% CI 1.90-5.21). The c-index of the risk stratification containing CRP and hemoglobin was 0.55 compared with those of 0.41 with hemoglobin alone and 0.40 with CRP alone.

COMMENT

In the present study, we demonstrated that an elevated CRP concentration and a low hemoglobin level are significant prognostic factors for overall survival in patients with CRPC treated with docetaxel. The elevation of CRP concentration and a low hemoglobin level were associated with poor patient survival. Risk stratification containing CRP and hemoglobin can be useful for estimating the length of overall survival of these patients.

As shown by the prognostic value of CRP in various advanced cancers,[9-12,18] the presence of a systematic in-

flammatory response as evidenced by an elevation of CRP concentration could be associated with a poor outcome in patients with CRPC treated with docetaxel. Granted, 2 reports have previously reported the prognostic value of CRP in patients with CRPC.[15,16] In the present study, we expanded upon the findings of those previous reports by describing risk stratification containing both CRP and hemoglobin.

Low hemoglobin level is one of the common conditions and is also an independent prognostic factor for survival in patients with various cancers.[19] In prostate cancer, a low hemoglobin level is associated with shorter overall survival.[20] In our study, a low hemoglobin level was also shown to be an independent prognostic factor for CRPC patients treated with docetaxel.

Systemic inflammatory response is caused by the stimulation of inflammatory cytokines. Among them, interleukin-6 (IL-6) is the potent inducer of CRP production and inversely correlated with hemoglobin level.[21-23] IL-6 regulates prostate cancer cell growth in vitro[24,25] and the prostate cancer cell itself also produces IL-6 in the process of bone metastasis.[26,27] Thus, the underlying inflammatory process could stimulate prostate cancer progression in an autocrine or paracrine manner. CRP, which is a representative acute-phase reactant, could reflect the aggressiveness of prostate cancer.

In the present study, we identified prognostic factors using only prechemotherapeutic factors in a single-institute cohort. In many prognostic models in patients with CRPC, postchemotherapeutic factors, namely, PSA decline, tumor response, and pain response, are often included to evaluate prognostic factors,[7,8] but it might be more beneficial for patients to predict the response or outcome before the initiation of treatment. The current results suggest that CRPC patients treated with docetaxel could be evaluated for risk of mortality using prechemotherapeutic factors, such as CRP and hemoglobin, which is already easily measured by standardized assays in most institutions.

Neither Gleason score nor PSA were associated with overall survival length in the present study. Previous reports demonstrated that a high Gleason score ($\geq$8) could be a negative prognostic factor for overall survival. Because the cut point of Gleason score using 6-7 vs 8-10 was common, we used this cut point in the current study. However, 83% of patients had high Gleason scores of 8 or more in the current cohort and it was unlikely that Gleason score could have been found to be significant because of power. Then we also considered the cut point using Gleason scores 6-8 vs 9-10, but the statistical significance was not found in bivariate analysis (P = .404). In the issue, we could not observe that Gleason score was prognostic in our current cohort. This might be a result of the small sample size. PSA is the important biomarker associated with disease status of prostate cancer. Indeed, PSA is a significant prognostic factor for overall survival in the bivariate analysis. However, PSA concentrations were significantly associated with both CRP concentrations (P = .040) and hemoglobin levels (P = .042) in the present study. Therefore, PSA might not have impact on overall survival compared with CRP and hemoglobin in the multivariable analysis.

There are a few limitations to this study. Given the small sample size, the retrospective nature and the data from a single institution of this study, additional larger confirmatory studies are warranted to validate our results. Because CRP and hemoglobin were evaluated as dichotomous variables with cut-off points, there might be possibilities of type-1 error or overfitting in this small cohort. Because CRP is a nonspecific inflammatory marker, we should also verify that the CRP value has not changed because of other diseases or conditions in which CRP might be elevated. Despite these concerns, CRP could still function as a useful and widely available biomarker.

CONCLUSIONS

We have identified that CRP, as well as hemoglobin, is an independent prognostic factor for overall survival of patients with CRPC treated with docetaxel. Risk stratification based on CRP and hemoglobin could be helpful for estimating the overall survival.

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