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CONFLICT OF INTEREST DISCLOSURE

Dr. Takeuchi is a scientific advisor for the anti-ALK iAEP immunohistochemistry kit (ALK Detection Kit, Nichirei Bioscience, Tokyo, Japan). All remaining authors have made no disclosures.

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Outcome of Antegrade Radical Prostatectomy with Intended Wide Resection in Prostate Cancer Patients with a Preoperative Serum PSA Level >100 ng/ml

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Key Words
Prostate cancer · Prostate-specific antigen · Prostatectomy · Survival

Abstract
Objective: It was the aim of this study to assess the outcome of prostate cancer patients with preoperative prostate-specific antigen (PSA) levels ≥100 ng/ml who were treated with antegrade radical prostatectomy with intended wide resection (aRP). ***Patients and Methods:*** Eighteen patients who underwent aRP had an initial PSA level ≥100 ng/ml. Overall survival, disease-specific survival and biochemical progression-free survival (bPFS) rates were determined, and predictors of treatment outcome were examined. ***Results:*** The median serum PSA level was 159.5 ng/ml. All patients but one had received neoadjuvant androgen deprivation therapy (ADT), while only 2 patients received adjuvant ADT. Five patients were classified as stage pT2, 6 as pT3a, 6 as pT3b and 1 as pT4. Four patients had locoregional lymph node metastases. Twelve patients developed PSA failure. Eight of them received salvage ADT. The estimated 10-year bPFS rate was 25.0% and the overall survival and disease-specific survival rates were 92.9 and 100%, respectively, at a median follow-up of 6 years. Multivariate analysis revealed only the clinical stage to be predictive of bPFS based on preoperative variables. On the other hand, surgical margin status, extracapsular extension and organ-confined disease were identified as being significant postoperative predictors. ***Conclusions:*** This study showed a comparatively satisfactory outcome for clinically non-metastatic prostate cancer with PSA levels ≥100 ng/ml treated by aRP.

Introduction

The preoperative serum level of prostate-specific antigen (PSA) is the critical variable in virtually all models predicting an advanced pathological stage and high Gleason grade and is considered a poor prognostic factor for biochemical relapse after radical prostatectomy (RP) [1]. Therefore, the initial PSA level at the time of prostate cancer (PCa) diagnosis has a great influence on clinical decision making. PCa with markedly elevated PSA levels harbors a high risk of locally advanced disease and micrometastasis, and therefore, would not ordinarily indicate RP to be a preferred course of treatment [2]. However, despite

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the roles that PSA plays in the decision-making process for PCa, no previous study has assessed the ability of PSA to predict the pathological stage or prognosis in patients with very high PSA levels. In fact, very high PSA levels have been shown to be insufficient indicators of appropriate treatment [3].

Surgical curability is one of the most promising avenues in the current oncological management of high-risk PCa. In particular, antegrade RP with intended wide resection of the vascular pedicles (aRP) might also contribute to improvement of the surgical outcome for locally advanced PCa. Therefore, the prevailing resistance towards advocating aRP for these patients may, in fact, be misguided.

Recently, remarkable long-term survival rates have been reported in locally advanced PCa with high preoperative PSA levels that have been treated by RP [4]. According to several studies, the 5-year biochemical progression-free survival (bPFS) rate has been shown to be about 50% in patients who underwent RP with a preoperative PSA level >20 ng/ml [5]. In addition, RP for PCa with a high preoperative PSA level can eliminate the primary source of systemic metastases and decrease the need for future procedural pelvic intervention for urinary retention or hematuria by providing good local controls. Therefore, a substantial proportion of these patients may benefit from RP. This is of particular concern for PCa patients without evidence of distant metastases presenting with initial PSA levels ≥100 ng/ml.

Therefore, we retrospectively analyzed our patients undergoing aRP with both a preoperative PSA level ≥100 ng/ml and no evidence of distant metastases, to assess the role of aRP in PCa patients with very high pretreatment PSA levels.

Patients and Methods

We retrospectively reviewed clinical records of 1,112 consecutive Japanese patients diagnosed with clinically and locally confined or advanced PCa treated by RP and bilateral lymphadenectomy between February 1994 and December 2008 at the Cancer Institute Hospital, Tokyo, Japan. Of the 1,112 patients, 18 patients (1.61%) had a preoperative PSA level ≥100 ng/ml without apparent or suspicious node/distant metastasis as shown by a preoperative imaging study.

To measure serum PSA levels, a Tandem-R Test (Beckman-Coulter, San Diego, Calif., USA) was used until July 2003, and an AxSYM kit (Abbot Laboratories, Japan) was used thereafter. Our extraperitoneal RP was performed as reported previously throughout this study period [6]. aRP is defined as 'antegrade radical retropubic prostatectomy with preliminary ligation of vascular pedicles', as we described previously [6]. In the current study, we used the term to emphasize an 'extended wide resection'. There are two important aspects of the technique utilized in our extraperitoneal RP. One is to ligate two main vascular pedicles, the dorsal vein complex and the posterolateral prostatic pedicles, before initiating the manipulation of malignant tissue. The other is to remove the prostatic pedicles and the bladder neck as widely as possible. The surgical technique reported by Serni et al. [7] with intended preservation of the bladder neck is different from ours mainly in the latter point. After the aRP, PSA measurements were performed at least every 3 months during year 2, every 6 months during years 3–5 and yearly thereafter. PSA failure was defined as either a PSA level >0.2 ng/ml or by performing adjuvant therapy with a PSA level <0.2 ng/ml. Imaging studies, including a CT and bone scan, were performed when PSA failure had been confirmed. In patients with persistently elevated PSA after aRP, the date of the surgery was considered to be the day of PSA failure.

aRP specimens were processed as reported previously [8]. Pathological grading of the aRP specimen was performed according to the Gleason score (GS) system by a single pathologist. When multiple cancer lesions were identified in an aRP specimen, GS was determined to be primary plus secondary Gleason grade in the index cancer, the largest cancer focus in the aRP specimen. Organ-confined disease (OCD) was defined as pT2 disease with a negative surgical margin (SM). Specimen-confined disease (SCD) was defined as pT2 or pT3a disease with negative SM.

Univariate and multivariate Cox's proportional hazard analyses were used to assess the association of variables to biochemical progression (PSA failure). Age, serum PSA value before aRP, clinical stage, biopsy GS, duration of neoadjuvant androgen deprivation therapy (ADT), SM (negative vs. positive), extracapsular extension (ECE) (negative vs. positive), pathological categories (OCD vs. non-OCD, and SCD vs. non-SCD), lymph node involvement (negative vs. positive) and seminal vesicle involvement (negative vs. positive) were evaluated as possible predictors of bPFS after aRP. bPFS, disease-specific survival (DSS) and overall survival (OS) curves were generated using the Kaplan-Meier method, and the difference between groups was assessed with the log-rank test. All p values were two-sided. A p value <0.05 was considered statistically significant. Statistical analyses were performed with JMP version 7.0.1 (SAS Institute Inc., Cary, N.C., USA).

Results

In a retrospective analysis of our institutional RP databases between 1994 and 2008, we identified 18 patients with preoperative PSA levels >100 ng/ml before neoadjuvant ADT. They all strongly wished for RP rather than ADT or radiation therapy (RT). The median age of these patients at the time of surgery was 69.5 years. The preoperative characteristics of the study cohort are shown in table 1. The median value of preoperative PSA was 159.5 ng/ml (range 115.0–660.0). All patients had palpable tumors in the prostate on digital rectal examination. The clinical stage was established as follows: T2 (n = 4), T3a (n = 7) and T3b (n = 7), according to the 1997 TNM clas-

sification. None showed initial signs of nodal (N1) or distant metastases (M1) in the preoperative imaging study, which included a chest X-ray, bone scan, CT scan and MRI. The median GS in prostatic biopsy specimens was 9 (range 5–9): 10 were Gleason 9, 8 were Gleason 7 and 1 was Gleason 5.

The characteristics of the pathology specimen, the neoadjuvant and adjuvant treatment, and applied salvage treatment are shown in table 2. We consider that a good clinical response of the neoadjuvant ADT contributes to the facilitation of surgical maneuver in aRP. Therefore, all patients except one had received neoadjuvant ADT. The median duration of neoadjuvant ADT was 8 months (range 1–13). Thirteen of these patients had received neoadjuvant ADT with a duration of >6 months. All patients treated by neoadjuvant ADT showed rapid PSA decrease within normal range before RP. All 18 of these patients underwent aRP with pelvic lymph node dissection. The mortality rate (within 30 days after RP) was 0%. Surgical pathology identified 5 (27.8%) with T2 (organ confined PCa), 6 (33.3%) with T3a (PCa extension through the capsule), 6 (33.3%) with T3b (PCa extension through seminal vesicle) and 1 (5.6%) with T4a (PCa involving bladder neck); 4 (22.2%) were N1. Four patients (22.2%) showed OCD (1 of 5 pT2 patients was excluded due to pN1). A positive SM was found in 10 of 18 (55.6%) patients. Only 2 patients received adjuvant ADT at the time of aRP without confirmation of PSA failure, whereas the remaining 16 patients were prospectively observed without any treatment until PSA failure was confirmed. We consider that the early salvage RT after PSA failure by local recurrence (suggested by slow PSA velocity or doubling time after RP) is not inferior compared with the adjuvant RT before PSA failure in quality of life and/or OS. Therefore, no patient in the entire cohort received immediate postoperative adjuvant RT. With a median follow-up of 6 years (range 1.4–15.3) after aRP, 12 patients (66.7%) were diagnosed with PSA failure. Salvage ADT was used in 7 patients, and additional salvage radiotherapy with ADT in 1 patient. Two patients who requested adjuvant ADT were defined as having PSA failure. Salvage therapy was initiated with a median PSA of 2.95 ng/ml (range 0.73–45). The treatment for the other 2 patients with PSA failure of between 0.2 and 0.4 ng/ml has been watchful waiting.

The median time to biochemical progression was 14.8 months. According to the Kaplan-Meier analysis, the bPFS rate at 3 and 4 years was 37.5 and 25.0%, respectively (fig. 1). Local and systemic recurrence occurred in 2 and 4 patients, respectively. Six patients (33.3%) were categorized as having no evidence of disease (NED). Of

Table 1. Preoperative characteristics of the patient cohort

Median age, years	69.5 [50–80]
Median PSA, ng/ml	159.5 [115.0–660.0]
1997 TNM clinical stage	
T1	0 (0%)
T2	4 (22.2%)
T3a	7 (38.9%)
T3b	7 (38.9%)
Biopsy GS	
≤6	1 (5.6%)
7	8 (44.4%)
8–10	9 (50.0%)

Figures in brackets are ranges.

Table 2. Postoperative characteristics of the patient cohort

1997 TNM pathological stage	
T2	5 (27.8%)
T3a	6 (33.3%)
T3b	6 (33.3%)
T4a	1 (5.6%)
Seminal vesicles	
Negative	11 (61.1%)
Positive	7 (38.9%)
Lymph nodes	
Negative	14 (77.8%)
Positive	4 (22.2%)
SM	
Negative	8 (44.4%)
Positive	10 (55.6%)
ECE	
Negative	5 (27.8%)
Positive	13 (72.2%)
OCD	
Yes	4 (22.2%)
No	14 (77.8%)
SCD	
Yes	5 (27.8%)
No	13 (72.2%)
Neoadjuvant ADT	
Yes	17 (94.4%)
No	1 (5.6%)
Adjuvant ADT	
Yes	2 (11.1%)
No	16 (88.9%)
Salvage external beam RT	
Yes	1 (5.6%)
No	17 (94.4%)
Salvage ADT	
Yes	8 (44.4%)
No	10 (55.6%)

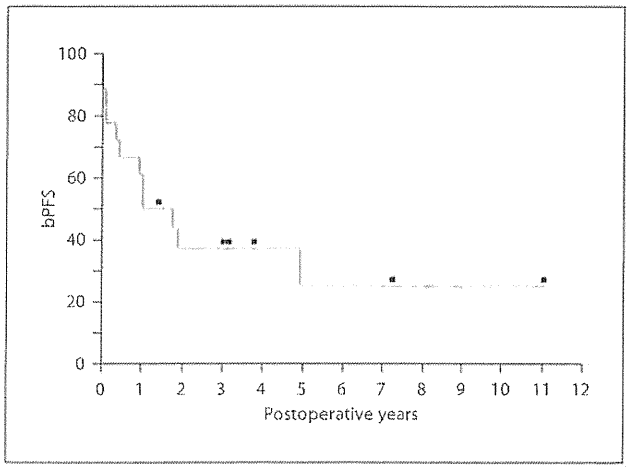

Fig. 1. bPFS rate.

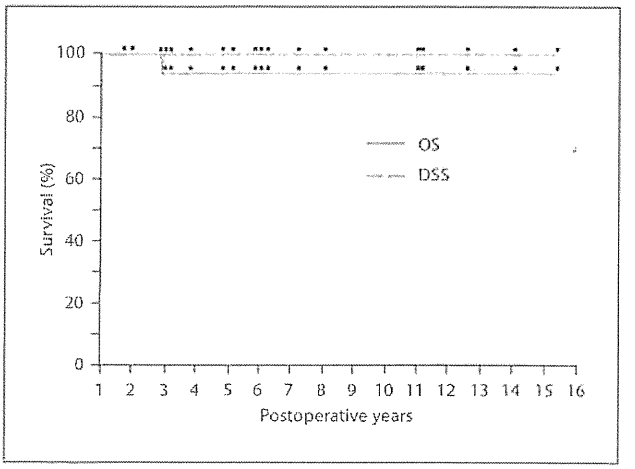

Fig. 2. DSS and OS rates.

Table 3. Preoperative factors predicting bPFS

Variables	3-year bPFS, %	p value (univariate)	p value (multivariate)
Age			
<69.5 years	44.4	0.05	0.0573
≥69.5 years	29.6		
Pre-PSA			
<159.5 ng/ml	14.8	0.9886	0.2487
>159.5 ng/ml	55.6		
cT stage			
<3	100	0.0333	0.0209
>3	17.9		
Biopsy GS			
<8	44.0	0.2723	0.4149
>8	37.5		
Duration of neoadjuvant hormonal therapy			
<8 months	20.0	0.2890	0.1530
≥8 months	44.0		

Table 4. Postoperative factors predicting bPFS

Variables	3-year bPFS, %	p value (univariate)	p value (multivariate)
SM			
Negative	50.0	0.0886	0.0344
Positive	30.0		
ECE			
Negative	80.0	0.1546	0.05
Positive	23.1		
OCD			
Yes	100	0.0493	0.0145
No	21.4		
SCD			
Yes	60.0	0.1129	0.216
No	28.9		
Pelvic lymph nodes			
Negative	38.2	0.0045	0.8245
Positive	0		
Seminal vesicles			
Negative	53.0	0.1571	0.2721
Positive	14.3		

these patients, 5 patients with NED for >3 years appeared to have been cured by neoadjuvant ADT followed by aRP. The serum testosterone level in all 5 of these patients has been confirmed to have recovered to within normal range after aRP. No patient had died from PCa at the time of their last follow-up visits. However, 1 patient died of gastric cancer. DSS and OS rates at 10 years were 100 and 92.9%, respectively (fig. 2).

Pre- and postoperative factors influencing bPFS were evaluated by logistic regression analysis (tables 3, 4). Age ($p = 0.05$) and clinical stage ($p < 0.05$) were predictive of bPFS in a univariate analysis of preoperative variables. Multivariate analysis revealed only the clinical stage to be predictive of bPFS from among the preoperative variables ($p < 0.05$). On the other hand, OCD and lymph node involvement was identified in a univariate analysis of postoperative variables. In addition, SM was indicated as being of borderline significance in predicting bPFS ($p = 0.1$).

Finally, SM, ECE and OCD were identified in multivariate analysis as being postoperative significant predictors. No other factors were statistically significant.

Discussion

Patients presenting with markedly elevated PSA levels undoubtedly have a higher likelihood of local extension and micrometastasis, which leads to earlier biochemical recurrence after radical treatment. D'Amico et al. [5] found that men with a PSA level >20 ng/ml have a >50% risk of PSA failure at 5 years. Therefore, ADT or the combination of ADT and RT has been advocated over RP for these patients [9]. However, the outcome of patients with a very high PSA level treated with RP is not actually well known. The ability to predict the pathological stage in patients with PSA levels >20 ng/ml has been reported to decrease significantly compared to patients with lower PSA values [10]. In fact, D'Amico et al. [5] did not include any men with preoperative PSA levels ≥50 ng/ml in their landmark study that defined PCa risk groups and led to the creation of their nomogram. In other words, markedly elevated PSA levels cannot necessarily indicate locally advanced or metastatic PCa [4, 10–12]. On the other hand, RP can provide accurate pathologic information (locally confined, locally advanced or metastatic disease) that can assist in determining whether or not patients would benefit from receiving adjuvant therapies.

With respect to the ability to predict the pathological stage in patients with a high PSA level, parameters that are not directly cancer-related, such as the volume of the prostate, can increase serum PSA levels. In our series, the mean surgically removed prostatic weight was high, 43.1 g (range 32–60), in spite of neoadjuvant ADT. The increased volume of benign prostate tissue could also cause high PSA levels in spite of localized cancer [13]. Furthermore, the transition zone cancers may acquire a greater volume than peripheral zone cancers and may be better differentiated and show lower GS [14]. The transition zone cancers may be associated with much higher PSA levels than otherwise expected for organ-confined cancer [15]. Therefore, although the cancer location in the prostate was routinely not available in our dataset, most of our cases with favorable pathological stage and bPFS after RP may be anteriorly located transition zone cancers rather than posteriorly located peripheral zone cancers. This could provide a possible explanation for why some patients present with very high PSA levels but have favorable/curable PCa.

A previous report from the Mayo Clinic showed that the bPFS rate with PSA levels ≥100 ng/ml was 36% at 10 years [4]. Another report from a European group showed that the bPFS rate with PSA levels ≥100 ng/ml was 11.3% at 10 years [12]. Our current study demonstrated that the bPFS rate was 25.0% at 10 years. All PCas with very high preoperative PSA values did not progress to biochemical recurrence. Therefore, we can conclude that there are PCas curable by performing aRP, even with markedly elevated PSA levels (≥100 ng/ml). In short, aRP should not be excluded as a therapeutic alternative for these PCa patients.

Although our preoperative PSA levels were much more elevated as compared to those in the other reports, our bPFS rate is comparable [4, 11, 12]. In a cohort of our series with PSA levels ≥100 ng/ml, we have demonstrated that 13 of 18 (72.2%) had ECE, 10 of 18 (55.6%) had positive SM, and 4 of 18 (22.1%) had nodal involvement. In terms of ECE rates, 70–100% have been reported in patients with initial PSA levels ≥20 ng/ml [11, 15–17]. With initial PSA levels ≥100 ng/ml, ECE was expected to be very high. However, our ECE appears to be consistent with previously reported cases with initial PSA levels ≥20 ng/ml. This may depend on the benefits of long neoadjuvant ADT administered in the majority of our patients. In this study, all patients treated by neoadjuvant ADT intended to perform aRP had shown a good clinical response, which might contribute to our satisfactory outcome. Therefore, a good clinical response to neoadjuvant ADT should be included into the selection criteria in the future. In addition, previous studies have clearly demonstrated a positive association between high initial PSA value and positive SM [11, 15–17]. Positive SM occurred in 50–70% of cases with initial PSA levels ≥20 ng/ml [11, 15, 18]. Therefore, our positive SM rate was expected to be even higher. However, positive SM in our patients with PSA levels ≥100 ng/ml was found in only 55.6% of the cases which seems to be very low, yet compares favorably to the results of the Mayo Clinic (82%) and the European group (84.6%) [4, 12]. These results have led us to believe that our particular surgical technique 'aRP' contributed to the satisfactory pathological findings.

Five patients with NED >3 years in our study are believed to have been cured by aRP with neoadjuvant ADT. Some patients with a high PSA level may be appropriate candidates for aRP as a curative treatment. bPFS, DSS and OS in our study were all favorable, which suggests the beneficial role of aRP with neoadjuvant ADT. Although our study was not highly reliable because of the small number of cases with a heterogeneity of adjuvant or neo-

adjuvant treatment modalities and the non-randomized retrospective study with a selection bias (such as patient's and urologist's wish for aRP), multivariate analysis revealed only clinically organ-confined cancer to be a significant positive preoperative predictor for bPFS after aRP. On the other hand, SM, ECE and OCD were identified as being postoperative significant predictors in multivariate analysis. In other words, aRP should be included as one of the therapeutic alternatives for clinically organ-confined PCa with good response to neoadjuvant ADT, even when markedly elevated PSA levels (≥100 ng/ml) are present.

In this study, local and metastatic recurrence occurred in only 2 and 4 patients, respectively. In the Mayo Clinic experience, RP provides an excellent local control, as evidenced by a local recurrence rate of only 13% [4]. However, the same cannot be said of primary RT. D'Amico et al. [19] showed a significantly lower 10-year prostate cancer-specific mortality rate in men treated with RP (10%) than in those who received RT (25%). In addition, RP can eliminate the primary source of systemic metastases, may improve therapeutic efficacy against residual locoregional disease by debulking cancer cells, and can decrease the need for future procedural pelvic intervention by providing good local controls. In addition, a recent German study showed that lymph node-positive PCa patients with complete RP had improved survival compared to patients with abandoned RP [20]. Therefore, aRP can provide durable local or locoregional control, and consequently, prolong CSS and OS.

The effect of prolonging survival by aRP in patients presenting with elevated PSA values cannot be definitively determined from this study. Therefore, a large randomized control study compared aRP to RT or ADT will be required in the future. However, the strength of our study is in the long-term follow-up. Patients were followed for a median of 6 years. In addition, we basically gave no adjuvant ADT and/or radiotherapy without confirmation of PSA failure in all except for 2 patients. PSA monitoring without adjuvant ADT even in pathologically advanced PCa after aRP seems warranted in order to prevent unnecessary ADT therapy with its accompanying side effects. This is supported by the fact that adjuvant ADT does not affect DSS as compared to deferred ADT, as previously reported [21]. We have preferred to employ early salvage ADT at the onset of a rise in PSA. Therefore, long-term follow-up and a lack of adjuvant therapy in our study provide urologists with accurate information regarding biochemical recurrence in PCa patients with preoperative PSA levels ≥100 ng/ml who were treated by aRP.

In conclusion, our study showed acceptable bPFS, DSS and OS for clinically non-metastatic PCa with initial PSA levels ≥100 ng/ml treated by aRP. aRP with neoadjuvant ADT may be an effective therapeutic option in patients with a very high serum PSA level but without apparent metastasis.

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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

Variable	Category	Bivariate *P*	Multivariable: Full Model *P*	Multivariable: Final Model: Regression Coefficient	Multivariable: Final Model: HR (95% CI)	Multivariable: Final Model: *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.

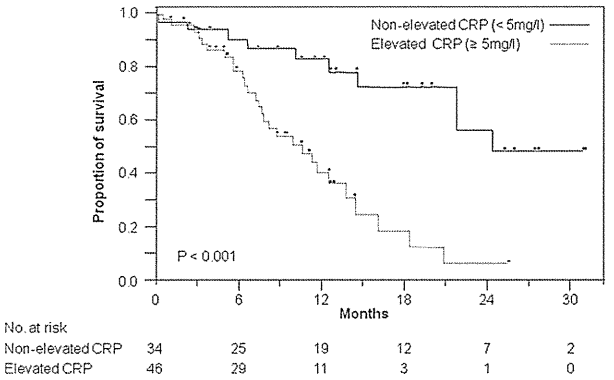

Figure 1. Overall survival curves for CRPC patients treated with docetaxel divided into nonelevated CRP (<5 mg/L) and elevated CRP (≥5 mg/L) groups.

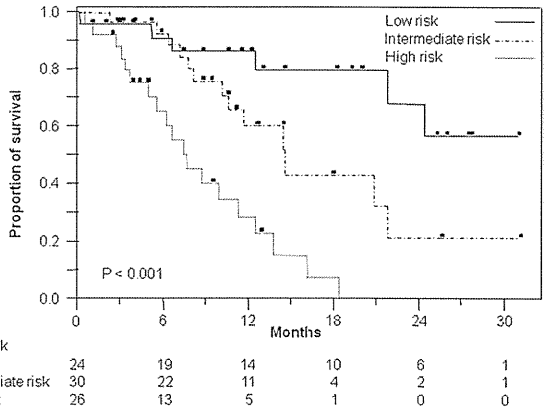

Figure 2. Overall survival curves for all patients with CRPC treated with docetaxel according to the risk groups. According to the presence of an elevated CRP (≥5 mg/L) concentration and/or a low hemoglobin level (<11.0 g/dL), each patient was assigned to low-, intermediate-, and high-risk groups.

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 (≥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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ORIGINAL ARTICLE

Outcome, clinical prognostic factors and genetic predictors of adverse reactions of intermittent combination chemotherapy with docetaxel, estramustine phosphate and carboplatin for castration-resistant prostate cancer

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Abstract
Objectives Docetaxel-based chemotherapy is effective in patients with castration-resistant prostate cancer (CRPC). This phase II study assessed the outcome and predictive factors for prognosis and toxicity following intermittent chemotherapy with docetaxel, estramustine phosphate, and carboplatin (DEC) in patients with CRPC.
Methods Thirty-five patients were treated with a DEC regimen that consisted of a 28-day cycle of drugs as follows: docetaxel (60 mg/m^2 on day 1), carboplatin (AUC 5 on day 1) and estramustine phosphate (560 mg daily). Treatment was continued intermittently. The end point was to test the effect of DEC on the response rate and overall survival (OS). Statistical correlations between the outcomes and predictive factors, including clinical parameters and 8 single-nucleotide polymorphisms (SNPs) related to drug metabolism, were assessed.
Results Prostate-specific antigen levels decreased by more than 30% in 65.7% of the patients. The median OS following DEC was 17.8 months, and the median total time of chemotherapy holiday was 7.7 months (range 1.7–35.8). On multivariate analysis, serum lactate dehydrogenase (LDH) was an independent prognostic factor for OS ($p = 0.007$). On SNP analysis, patients carrying the TT genotype of the *ABCB1* C3435T polymorphism showed a significantly more severe leukocytopenia during the first cycle of DEC therapy compared to patients with the CC + CT genotype ($p = 0.036$).
Conclusion Combination chemotherapy with DEC has a potential effect on CRPC with acceptable toxicity. Serum LDH may be a promising predictor of prognosis, and the *ABCB1* C3435T polymorphism may be a genetic predictor of the severity of leukocytopenia in patients with CRPC treated with DEC.

Keywords Chemotherapy · Prostate cancer · Single nucleotide polymorphism · Docetaxel

Introduction

Prostate cancer is currently the most common malignancy in men and the second or third leading cause of death in the Western world [1]. Although prostate cancer may be initially responsive to androgen ablation therapy, it can finally become refractory to hormonal manipulation. Two large phase III randomised trials showed that docetaxel-based chemotherapy enhanced survival in the treatment of castration-resistant prostate cancer (CRPC) [2, 3]. Furthermore, many combination therapies carry expectations of demonstrating the additive and synergistic effects of taxanes in patients with CRPC. To date, several studies have evaluated the benefit of combination chemotherapy with taxanes, estramustine phosphate (EMP) and carboplatin (TEC), of which the combination utilizing docetaxel as the taxane (docetaxel, EMP, carboplatin = DEC) was reported to have achieved particularly high response rates (58–98%) in patients with CRPC [4]. With regard to the schedule for the administration of docetaxel for CRPC, intermittent

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therapy has been conducted to reduce the side effects and maintain a high quality of life (QOL) [5].

Although taxane-based chemotherapy is promising for the treatment of CRPC, it remains open to debate what type of patients will have higher survival benefit. In addition, individual variation in response to chemotherapy may result in differences in the severity of adverse reactions (ARs). This individual variation has been partially explained by single nucleotide polymorphisms (SNPs). We previously reported that SNPs in drug metabolism-related genes were associated with prognosis and ARs in urological cancer [6, 7].

Here, we report the results of a phase II study evaluating the efficacy and patient tolerance of intermittent combination chemotherapy with DEC in patients with CRPC. We also evaluated the prognostic factors and predictors of ARs, including clinical parameters and SNPs in patients with CRPC.

Patients and methods

Patients

Our study included patients with CRPC treated at Akita University Hospital, Japan. A history of surgical or medical castration was required in all patients. Patients were diagnosed by biochemical and/or clinical progression following either (1) a second or subsequent cycle of hormonal therapy, or (2) other regimens including monotherapies of docetaxel, EMP, dexamethasone and prednisolone. The definition of diagnosis of CRPC and its progression were based on the criteria of the Prostate Cancer Clinical Trials Working Group [8].

Treatment regimen

The DEC regimen consisted of a 28-day cycle of docetaxel [60 mg/m^2 intravenously (IV) on day 1], carboplatin (IV to the area under the curve of 5 on day 1) and EMP (560 mg orally daily). Pre-medication consisting of dexamethasone (8 mg IV) was administered 30 min prior to each docetaxel infusion. Two consecutive DEC cycles were performed and efficacy and toxicity were assessed. Before further therapy with DEC, a chemotherapy holiday was taken from the treatment until the prostate-specific antigen (PSA) levels were elevated above the baseline. Dose-down regimens were prepared for elderly patients and for those with a history of severe ARs. Luteinzing hormone releasing hormone agonist was continued throughout the study. Treatment was stopped for any of the following reasons: progression of disease, severe adverse events, or withdrawal of consent.

Evaluation

A post-therapy change in PSA levels was defined on the basis of the maximum degree of change from baseline within 3 months of therapy. Tumour progression was defined by following RECIST guidelines. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 4.0 (NCI-CTC v4.0). Levels of pre-treatment platelet count, hemoglobin, serum alkaline phosphatase (ALP), serum lactate dehydrogenase (LDH) and PSA were measured prior to initial DEC therapy, and only PSA levels were measured every 3 months thereafter. The presence of bodily pain prior to initial DEC therapy was evaluated from the patient's medical records. The primary endpoint of the study was response rate. The secondary endpoints included safety and overall survival (OS) from the time of initiation of chemotherapy. For the evaluation of prognosis, the variables which were significant predictors in the univariate analysis were included in the multivariate analysis.

DNA extraction and genotyping

DNA was extracted from blood samples using a QIAamp Blood kit (Qiagen, Hilden, Germany). Patients were genotyped for polymorphisms of 8 SNPs in 6 genes (*MAP4*, *MAPT*, *ABCG2*, *CYP3A5*, *XRCC1* and *ABCB1*) considered to be involved in the metabolism of DEC (Table 1). The genotype of each SNP was determined either by polymerase chain reaction restriction fragment length polymorphism or by direct sequencing. Written informed consent for enrolment in this study and for the use of DNA and clinical information was obtained from all patients participating in this study, which was was approved by the institutional review board of Akita University School of Medicine. We examined the influence of age and genetic factors on OS and the development of severe toxicity during the first cycle of DEC therapy using univariate and multivariate analyses. Severe leukocytopenia was defined as greater than grade 3.

Statistical analysis

The Kaplan–Meier method was used to estimate OS. Each continuous independent variable was dichotomised at the median value. Differences in survival were tested using the log-rank test. Hazard ratios and 95% confidence intervals (Cis) for cancer death were assessed using the Cox proportional hazard regression model. Odds ratios and 95% CIs for dichotomised grades of ARs in each genotype grade were determined by multiple logistic regression analysis. Statistical analysis was performed using SPSS 15.0®. Differences were considered significant at $p < 0.05$.

Table 1 List of gene polymorphisms assessed in this study

Genes	Type and site	No.	Primers		Restriction enzyme
			Forward	Reverse	
MAP4	Intron	rs56313601	TGCATGGTTTCCTTTCCCCTA	TCTCTGAAACGTGTGTGGCTT	*Bcc*I
MAPT	Intron	rs3744460	AAAGTGGAGGCGTCCTTGCGA	CAGCTTCTTATTAATTATCTGC	*Mnl*I
ABCG2	V12M	rs2231137	GCTTTTCTGTCTGCAGAAAGAT	GAAGCTGTCGCGGGGAAGCC	*Tsp*RI
CYP3A5	A6986G	rs776746	ATGGAGAGTGGCATAGGAGATA	TGTGGTCCAAACAGGGAAGAAATA	*Ssp*I
XRCC1	C194T	rs1799782	ATGCTTGGCCAGTTCCGTGTGAAG	CACCTGGGGATGTCTTGTTGATCC	*Alu*I
XRCC1	A399G	rs25487	TCCTCCACCTTGTGCTTTCT	AGTAGTCTGCTGGCTCTGGG	*Nci*I
ABCB1	C3435T	rs1045642	TTGATGGCAAAGAAATAAAGC	CTTACATTAGGCAGTGACTCG	*Mbo*I
ABCB1	Intron	rs7779562	TGTTCTGCAATGAGAAGAATAA	ATTGTAACACAAATTAATTATC	*Taq*I

Results

Patient characteristics

A total of 35 patients with CRPC were enrolled in the study between 2003 and 2009. Their pre-treatment characteristics are summarised in Table 2. The median age was 68 years (range 54–79). The Eastern Cooperative Oncology Group performance status (ECOG-PS) was 0–1 in 97.1% of patients. Sixteen (47.5%) patients suffered recurrence after local definitive treatments. Prior combined androgen blockade was performed in 33 (94.3%) patients, and 30 (85.7%) patients were previously administered EMP. All patients were docetaxel-naïve in this study. Under pathological examination, the grade of cancer in the majority (80.0%) of the patients was classified as 'poorly differentiated' according to the general rule for clinical and pathological studies on prostate cancer from the Japanese Urological Association and the Japanese Society of Pathology [9]. Gleason's score was 7–8 in 13 patients, 9–10 in 6 and unclassified in 16. Bone metastasis was present in 30 (85.7%) patients, while extra-osseous metastasis was present in 18 (51.4%). Median baseline PSA level at initiation of DEC regimen was 99.6 ng/mL (range 0.036–4900). Median duration from diagnosis of CRPC to initiation of DEC regimen was 14.9 months (range 1.0–109.1).

Clinical outcomes

A median of 3 cycles (range 1–9) was administered to each patient. Clinical responses to DEC therapy are summarised in Table 3. PSA levels were decreased by >30% in 65.7% and by >50% in 45.7% of patients as a maximum response. Measurable tumours were assessed in 34.3% (12/35) patients, the response rate being 66.7% (8/12). The median follow-up time was 11.1 months (range 2.6–48.2). At the time of final analysis, 19 (54.3%) patients had died due to disease progression. Median OS following the initiation of DEC regimen was 17.8 months (Fig. 1). Fourteen (40.0%) patients had a chemotherapy holiday after 2 consecutive DEC therapy cycles. Median total time of chemotherapy holidays from initial to final DEC therapies was 7.7 months (range 1.7–35.8). The 2-year survival rate following initiation of DEC therapy was 27.1%, while 5-year survival rates following CRPC and initial hormone treatment were 35.2 and 61.0%, respectively.

Adverse reactions

All ARs were reversible and most were moderate and grade 2 or less. ARs classified as grade 3 or 4 are listed in Table 4. The percentage of grade 3 or 4 ARs for the first cycle was 48.6% (Table 4). Thirteen (38.2%) patients developed grade 3 or 4 leukocytopenia that was managed successfully with granulocyte colony-stimulating factor administration. Red cell or platelet transfusions were given to patients who suffered from grade 4 anemia or thrombocytopenia. One patient died from a non-cancerous cause—aspiration pneumonia.

Survival analysis

Survival rates were compared between 2 groups divided as shown in Table 5. These parameters were previously described as being poorly prognostic in CRPC [6, 10, 11]. The median OS was significantly shorter in patients with LDH levels of >193 U/L than for those with lower levels (11.5 vs. 29.0 months, $p = 0.001$), and the median OS was significantly shorter for patients with platelet counts of $>25.5\times10^4/\mu L$ than for those with lower counts (13.8 vs. 19.4 months, $p = 0.004$). No significant association was found between other clinical parameters and outcomes. Multivariate analysis including 2 factors (platelet count and LDH level) demonstrated that the LDH level was an independent indicator of survival (odds ratio 6.084, 95% CI 1.650–22.438; $p = 0.007$) (Table 6; Fig. 2).

Table 2 Patient characteristics

	n (%)
Patient age (years)	
Median	68
Range	54–79
ECOG performance status	
0	28 (80.0)
1	6 (17.1)
2	1 (2.9)
Prior therapy	
Surgery	
Radical prostatectomy	9 (25.7)
Total cystoprostatectomy	3 (8.6)
Radiation	4 (11.4)
Hormone therapy	
Combined androgen blockade	33 (94.3)
Diethylstilbestrol	11 (31.4)
Dexamethazone	15 (42.9)
Chemotherapy	
Estramustine phosphate	30 (85.7)
Etoposide	2 (5.7)
Differentiation	
Well	0 (0.0)
Moderate	4 (11.4)
Poor	28 (80.0)
Unknown	3 (8.6)
Metastatic site	
Bone	30 (85.7)
Lymph nodes	12 (34.3)
Visceral	6 (17.1)
PSA at diagnosis (ng/mL)	
Median	95.3
Range	3–8010
Baseline PSA berore DEC	
Median	99.6
Range	0.036–4900
Laboratory data at baseline	
Hemoglobin (g/dL)	
Median	10.9
Range	7.2–13.7
Alkaline phosphatase (U/L)	
Median	483.5
Range	67–4455
Lactate dehydrogenase (U/L)	
Median	193
Range	103–2052
Platelet counts ($\times 10^4/\mu L$)	
Median	25.5
Range	9.4–79.4
Cancer pain	
Negative	24 (68.6)
Positive	11 (31.4)
Time from CRPC to DEC	
Median	14.9
Range	1.0–109.1

ECOG Eastern Cooperative Oncology Group, *PSA* prostate-specific antigen, *DEC* docetaxel, estramustine phosphate and carboplatine therapy, *CRPC* castration-resistant prostate cancer

Table 3 Clinical outcomes

	Effective no. of patients/total no. of patients (%)
PSA decrease	
30% or greater	23/35 (65.7)
50% or greater	16/35 (45.7)
75% or greater	10/35 (28.6)
Measurable disease	
PR	8/12 (66.7)
SD	3/12 (25.0)

PSA prostate-specific antigen, *PR* partial response, *SD* stable disease

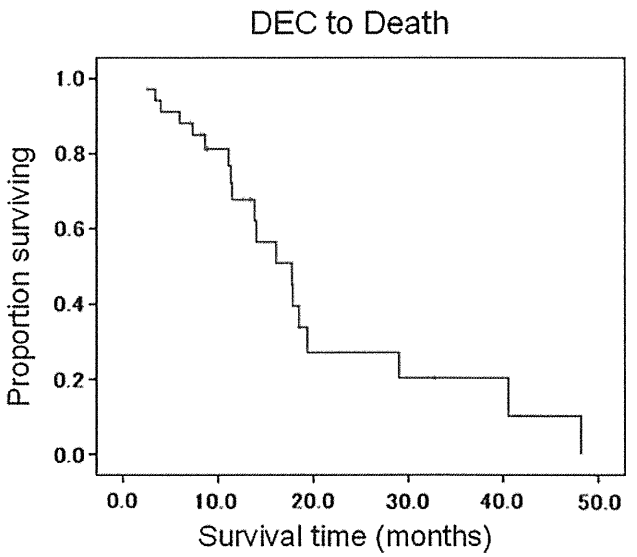

Fig. 1 Kaplan–Meier estimates of overall survival from initiation of DEC therapy

Genetic variation affecting adverse reaction

Next, we explored the association between each genotype and severe leukocytopenia. Two (6%) patients were excluded from the SNP study due to non-availability of

Table 4 Percentage of grade 3 and higher toxic effect at first cycle

	Grade 3	%	Grade 4	%	Total	%
Hematological						
Anemia	3	8.8	0	0.0	3	8.8
Leukopenia	10	29.4	3	8.8	13	38.2
Thrombocytopenia	1	2.9	1	2.9	2	5.9
Febrile neutropenia	1	2.9	0	0.0	1	2.9
Stomatitis	1	2.9	0	0.0	1	2.9
Anorexia	1	2.9	0	0.0	1	2.9
Pneumonitis	0	0.0	1	2.9	1	2.9
Diarrhea	1	2.9	0	0.0	1	2.9
Transamirase	2	5.9	0	0.0	2	5.9

Table 5 Univariate analysis of prognostic factors in patients with castration-resistant prostate cancer treated with DEC

Factor	Classification	*p*
Age (years)	>68 versus ≤68	0.647
Initial PSA (ng/mL)	>91 versus ≤91	0.212
Baseline PSA (ng/mL)	>115 versus ≤115	0.423
CRPC to DEC (months)	>15 versus ≤15	0.284
Pretreatment		
Dexamethazone	Positive versus negative	0.138
Estramustine	Positive versus negative	0.165
Initial stage	c versus d	0.569
PSA response (ng/mL)	Positive versus negative	0.158
	>30 versus ≤30	0.181
	>50 versus ≤50	0.447
	>75 versus ≤75	0.594
Laboratory data		
Hemoglobin (g/dL)	>11 versus ≤11	0.18
Alkaline phosphatase (U/L)	>484 versus ≤484	0.436
Lactate dehydrogenase (U/L)	>193 versus ≤193	0.001
Platelet counts ($\times 10^4/\mu L$)	>25.5 versus ≤25.5	0.004
Metastasis		
Skeletal only	Positive versus negative	0.461
Extra-osseous only	Positive versus negative	0.652
Skeletal plus extraosseous	Positive versus negative	0.744
ECOG-PS	0 versus >0	0.741
Time from initiation of hormonal therapy to CRPC (months)	>17.7 versus ≤17.7	0.489
Time from initiation of hormonal therapy to administration of DEC (months)	>36 versus ≤36	0.095
Pain	Positive versus negative	0.926

PSA prostate-specific antigen, *CRPC* castration-resistant prostate cancer, *DEC* docetaxel, estramustine phosphate and carboplatine therapy, *ECOG* Eastern Cooperative Oncology Group

DNA samples. Allelic distribution is listed in Table 7. On univariate analysis, patients carrying the TT genotype of the *ABCB1* C3435T polymorphism had significantly more severe leukocytopenia during the first cycle of DEC therapy ($p = 0.037$). In the multivariate model including all clinical and genetic variables used in the univariate analysis, the TT genotype of the *ABCB1* C3435T polymorphism was an independent predictor of severe leukocytopenia for the first cycle (odds ratio 14.537, 95% CI 1.253–824.316; $p = 0.036$) (Table 8). There was no significant association between any genotype of the 8 SNPs and OS.

Discussion

Regan et al. [4] reported on a pooled analysis that included 7 trials of TEC therapy. The pooled analysis showed that

Table 6 Multivariable model predicting overall survival duration

	Hazard ratio	95% CI	*p*
Lactate dehydrogenase (U/L)			
>193	6.084	1.650–22.438	0.007
≤193			
Platelet counts ($\times 10^4/\mu L$)			
>25.5	3.143	0.941–10.501	0.630
≤25.5			

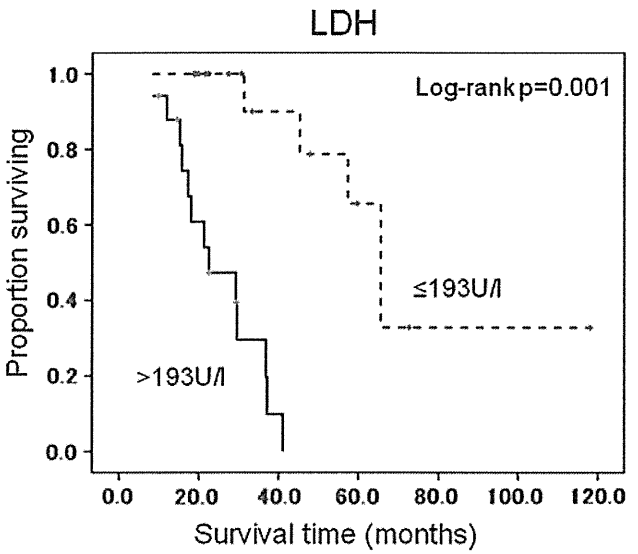

Fig. 2 Kaplan–Meier survival curves according to serum LDH level

the proportion of patients achieving a PSA response of >50% decrease from baseline was 69%, and that the estimated median survival was 18 months [4]. Kikuno et al. reported the results of a combination chemotherapy that consisted of a 4-week cycle of docetaxel (30 mg/m^2 weekly), EMP (10 mg/kg daily) and carboplatin (AUC 6). The outcome of their study was extremely positive, with 95% PSA response and median survival of 26.6 months [12], which appears to be much better than the results of our study. However, the length of the pre-treatment period and amount of medication given to patients in the study conducted by Kikuno et al. seem to have been shorter and lesser, respectively, than those in our study. For example, EMP was administered prior to DEC regimen in 15.0% patients in their study, but in 85.7% in our study. Therefore, it is difficult to assess the superiority of either regimen because of differences in patient characteristics and the timing of initiation of DEC regimen. Our results suggest that DEC may have a potential effect on patients with CRPC, even at the later more advanced stage, and on those who had been pre-treated with EMP.

Based on the concept of conservative treatment with minimum deterioration of QOL, intermittent chemotherapy

Table 7 Allelic distributions of 8 SNPs

	Grade 3 or 4 leukocytopenia, *n* (%)	
	−	+
Total	17	16
MAP4		
CC	11 (64.7)	11 (68.8)
CT + TT	5 (29.4)	4 (25.0)
MAPT		
CC	8 (47.1)	5 (31.3)
CA + AA	9 (52.9)	11 (68.8)
ABCG2		
AG + GG	15 (88.2)	14 (87.5)
AA	1 (5.9)	1 (6.3)
CYP3A5		
*3/*3	10 (58.8)	11 (68.8)
*1/*3 + *1/*1	6 (35.3)	4 (25.0)
XRCC1-A194G		
CC + CT	13 (76.5)	13 (81.3)
TT	4 (23.5)	3 (18.8)
XRCC1-C399T		
GG	11 (64.7)	8 (50.0)
AG + AA	6 (35.3)	8 (50.0)
ABCB1-intron		
GG	6 (35.3)	8 (50.0)
CG + CC	11 (64.7)	8 (50.0)
ABCB1-C3435T		
CC+CT	16 (94.1)	10 (62.5)
TT	1 (5.9)	6 (37.5)

is a promising option for patients with CRPC receiving chemotherapy. In a large multi-institutional trial to assess the efficacy of a combination chemotherapy with docetaxel and high-dose calcitriol, Beer et al. [13] reported that most patients took chemotherapeutic holidays and 45.5% patients showed a >50% PSA decline at the time of re-treatment. Because the DEC regimen appears to be associated with higher ARs, along with a higher response rate than the docetaxel regimen with or without EMP, the DEC regimen may not suitable as a continuous therapy. In this study, 40% patients took a chemotherapy holiday with a mean duration of 7.7 months. Further analysis is warranted to compare the QOL of patients having undergone intermittent versus continuous combination chemotherapy with DEC.

It is important to identify which categories of patient are most likely to benefit from docetaxel-based chemotherapy. In the study by Oh et al. [4], extra-skeletal metastases, ECOG-PS, hemoglobin, serum LDH and ALP levels were associated with poor patient survival rates on multivariate analysis. In addition to the LDH level, the univariate analysis indicates that platelet count is a potential marker in detecting poor survival rates in patients with CRPC