RESEARCH ARTICLE

Predictive Factors for Neutropenia after Docetaxel-Based Systemic Chemotherapy in Korean Patients with Castration-Resistant Prostate Cancer

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Abstract

The aim of this study was to determine predictive factors for neutropenia after docetaxel-based systemic chemotherapy in patients with castration-resistant prostate cancer (CRPC). The study included 40 Korean CRPC patients who were treated with several cycles of docetaxel plus prednisolone from May 2005 to May 2012. Patients were evaluated for neutropenia risk factors and for the incidence of neutropenia. In this study, nine out of forty patients (22.5%) developed neutropenia during the first cycle of docetaxel-based systemic chemotherapy. Four experienced grade 2, three grade 3, and one grade 4 neutropenia. Multivariate analysis showed that pretreatment white blood cell (WBC) count (p=0.042), pretreatment neutrophil count (p=0.015), pretreatment serum creatinine level (p=0.027), and pretreatment serum albumin level (p=0.017) were significant predictive factors for neutropenia. In conclusion, pretreatment WBC counts, neutrophil counts, serum creatinine levels, and serum albumin levels proved to be significant independent risk factors for the development of neutropenia induced by docetaxel-based systemic chemotherapy in patients with CRPC.

Keywords: Neutropenia - prostate cancer - docetaxel - predictive factor

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Introduction

Chemotherapy-induced neutropenia is the most common and often dose limiting toxicity of cytotoxic anticancer treatment (Crawford et al., 2004). In the urologic field, the incidences of docetaxel-induced neutropenia in patients with Castration-Resistant Prostate Cancer (CRPC) is about 25% in western (Italiano et al., 2009) and 17% in Korean study (Lee et al., 2010), respectively.

Docetaxel is a widely used anticancer agent that is active against breast, non-small cell lung, ovarian, head and neck, gastric, and prostate cancers (Sulkes et al., 1994; Dreyfuss et al., 1996; Sjostrom et al., 1999; Fossella et al., 2000; Tannock et al., 2004; Vasey, 2003). Patients with metastatic CRPC (mCRPC) who are treated with docetaxel (75 mg/m^2 taken once every 3 weeks) plus daily oral prednisone (PSL) (a regimen based on the TAX327 randomized phase III trial) show a significant survival advantage over those treated with mitoxantrone plus PSL (Tannock et al., 2004). Currently, docetaxel treatment is the standard frontline chemotherapy for mCRPC worldwide, including in Korea.

Docetaxel is cytotoxic to both cancer cells and normal cells. Cytotoxic chemotherapy predictably suppresses the hematopoietic system, thereby impairing host immune responses. Neutropenia (a condition characterized by an abnormally low number of neutrophils) is the most serious form of hematologic toxicity associated with cancer chemotherapy, often limiting the doses of chemopharmaceuticals that a patient can tolerate (Crawford et al., 2004).

Both the degree and duration of neutropenia determine the risk of infection in patients receiving chemotherapy (Bodey et al., 1966). Neutrophils are the first line of defense against infection, given that they are the initial cellular components of the inflammatory response and the key mediators of innate immunity. However, neutropenia blunts the inflammatory response to nascent infections, thereby allowing invading bacteria to multiply. Because neutropenia reduces the signs and symptoms of infection, patients with neutropenia often present with fever as the only sign of infection (Bodey et al., 1966).

The occurrence of neutropenia following the administration of cytotoxic anticancer drugs cannot be avoided. The probability of developing neutropenia varies for each individual regimen; currently, predictions are based on the treatment regimen used and the experience of the attending physician (Sato et al., 2012).

Numerous studies have reported factors predictive for the development of febrile neutropenia in patients receiving systemic chemotherapy with an assortment of

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anticancer drugs (Lyman and Delgado, 2003; Millward et al., 2003; Timmer-Bonte et al., 2005). By contrast, few investigations have examined the predictive factors for neutropenia after docetaxel-based systemic chemotherapy in patients with CRPC. Thus, the aim of this study was to identify factors that predict neutropenia in CRPC patients after docetaxel-based systemic chemotherapy.

Materials and Methods

Patients

The medical records of CRPC patients treated with docetaxel-based systemic chemotherapy at our institution (Wonkwang University Hospital, Iksan, Korea) between May 2005 and May 2012 were retrospectively reviewed. Forty patients fit the eligibility criteria for inclusion in the study. All had histologically confirmed adenocarcinoma of the prostate, evidence of metastasis, and progressive disease despite combined androgen blockade and withdrawal of anti-androgen therapy.

CRPC was defined as three consecutive increases in blood PSA content above the nadir (the absolute lowest level to which PSA levels drop after treatment), with a castrate level of serum testosterone, a continued increase in PSA after anti-androgen withdrawal, and/or the existence of clear clinical or radiologic evidence of progression. This retrospective study was approved by the Institutional Review Board of Wonkwang University School of Medicine and Hospital.

Treatment Protocol

The chemotherapy treatment protocol comprised several cycles (mean, 5.5) of prednisolone (5mg twice daily) and docetaxel (75 mg/m^2 once every 3 weeks), in consonance with the findings of the TAX327 trial. Blood samples were obtained at 2 and 8 days after the completion of each cycle of treatment and PSA levels were measured. None of patients received prophylactic granulocyte-colony stimulating factor (G-CSF) for chemotherapy-induced neutropenia.

According to the recommendations of the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, any grade of neutropenia is defined as a neutrophil count <1500/mm^3 . In the present study, neutropenia was graded based on the neutrophil count as follows: grade 1, <1500/mm^3 ; grade 2, <1500-1000/mm^3; grade 3, <1000-500/mm^3 ; and grade 4, <500/mm^3 .(National Cancer Institute, 2006).

The incidence of neutropenia and the potential risk factors for neutropenia were evaluated during the first cycle of chemotherapy.

Statistical analysis

The clinicopathological data were compared between two groups: patients who developed neutropenia during the first cycle of chemotherapy and those that did not. The Mann-Whitney U test and Fisher's exact test were used to compare continuous and categorical parameters, respectively, between groups. In addition, a multivariate logistic analysis was performed to determine predictive factors for neutropenia in patients with CRPC. The results were considered significant at a p-value of <0.05. All statistical analyses were performed using SPSS software, version 15.0 (SPSS Inc, Chicago, IL, USA).

Results

A total of 40 patients were included in the study. The mean age of the patients was 71.7 years (range, 58 to 85 years). The median Pre-treatment PSA level was 36.6 ng/ml (range, 4.5-1498.0 ng/ml). The mean number of docetaxel cycles was 5.5, and the median progression-free survival time was 6.5 months (range, 0-22 months). Median overall survival was 12 months (range, 2-30 months). The patients were classified into the "without neutropenia" group (n=31, 77.5% of patients) or the "with neutropenia" group (n=9, 22.5% of patients). The latter developed neutropenia during the first cycle of docetaxel-based systemic chemotherapy. Four patients experienced grade 2 neutropenia, four patients experienced grade 3 neutropenia, and one patient experienced grade 4 neutropenia.

Significant differences were observed between the two patient groups in terms of the pretreatment WBC count (7270±1934/mm^3 *vs* 5753±1741/mm^3, p=0.028), the pretreatment neutrophil count (4756±1741/mm3 *vs* 3260±1385/mm^3, p=0.019), the pretreatment serum albumin level (4.27±0.43g/dL *vs* 3.88±0.41g/dL, p=0.017), and prior chemotherapy regimens (2 *vs* 4,

Table 1. Characteristics and Pharmacokinetic Parameters of Docetaxel in Patients with or Without Neutropenia

Variables	Without neutropenia (n=31)	With neutropenia (n=9)	Total (n=40)	p-value
Mean age (years)	71.2±6.13	73.7±7.53	71.7±6.46	0.496
Body mass index (kg/m^2)	22.9±2.62	22.6±1.66	22.9±2.41	0.77
Mean serum Hg (g/dL)	11.8±1.52	10.9±2.02	11.6±1.66	0.315
Pretreatment WBC count (/mm^3)	7270.0±1934.80	5753.3±1741.95	6928.7±1978.24	0.028
Pretreatment neutrophil count (/mm^3)	4756.1±1741.69	3260.0±1385..23	4419.5±1768..44	0.019
Pretreatment serum albumin (g/dL)	4.27±0.43	3.88±0.411	4.18±0.45	0.017
Serum creatinine	1.21±0.44	0.84±0.18	1.12±0.42	0.007
Pretreatment PSA (ng/ml)	107.8±264.55	121.7±182.1	110.9±246.32	0.437
N stage				0.169
0	9	4	13	
1	21	4	25	
2	1	1	2	
Performance status (ECOG)				0.32
0	25	5	30	
1	4	3	7	
2	2	1	3	
Radiation therapy				
4	2	6	0.607	
Prior chemotherapy				
2	4	6	0.009	

*the Mann-Whitney U test and Fisher's exact test were used to compare continuous and categorical variables, respectively, between groups; ECOC, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; WBC, white blood cell

Table 2. Multivariate Analysis to Determine Predictive Factors for Neutropenia in Patients with CRPC

Variables	95% Confidence Interval (CI) for difference	p-value
Pretreatment WBC count	-2915.8 to -57.8	0.042
Pretreatment neutrophil count	-2603.5 to -305.4	0.015
Pretreatment albumin	-0.737 to -0.077	0.017
Serum creatinine	-0.663 to -0.043	0.027
Prior chemotherapy	-0.019 to 0.685	0.063

*CRPC, castration-resistant prostate cancer; WBC, white blood cell.

p=0.009) (Table 1).

Multivariate logistic analysis showed that the pretreatment WBC (p=0.042) and neutrophil counts (p=0.015),as well as pretreatment albumin (p=0.017) and serum creatinine levels (p=0.027), were significant predictive factors for neutropenia (Table 2). However, prior chemotherapy was not a significant predictive factor (p=0.063) (Table 2).

Discussion

In the study by (Park et al., 2013), men with prolonged docetaxel-based systemic chemotherapy have longer survival times than do men with discontinuation-protocol docetaxel-based systemic chemotherapy (13 compared with 6 months). Furthermore, men with prior systemic chemotherapy and a lower BMI (21.8 compared with 23.6 kg/m^2) tend to stop protocol docetaxel-based systemic chemotherapy. And Matsuyama H et al.(Matsuyama et al., 2013) reported that more than one-third of CRPC patients could safely receive over 10 cycles of docetaxel therapy with a 9% reduction in the risk of OS per cycle. And hematologic complication is one of the most crucial factor of docetaxel discontinuance. Therefore, determination of predictive factors for neutropenia after docetaxel-based systemic chemotherapy is of prime importance in the clinical treatment of the CRPC patients.

Other authors have suggested that the use of prophylactic G-CSF, antibiotics and pegfilgrastim for the secondary prevention of FN is extremely effective and allows the maintenance of chemotherapy dose intensity (Lalami et al., 2004; Jenkins et al., 2012). Based on these studies, We are cautiously considering using hematopoietic growth factors and advances in antibiotic therapy on docetaxel-Based Systemic Chemotherapy with CRPC in the next study.

An important challenge in the clinical management of CRPC chemotherapy is the accurate prediction and management of neutropenia. Chemotherapy-induced febrile neutropenia accompanied by infection and sepsis is a potentially fatal complication encountered by patients undergoing chemotherapy for prostate cancer, and is seen most often during the initial cycles of myelosuppressive therapy (Timmer-Bonte et al., 2005; Vogel et al., 2005 Crawford et al., 2008;Yasufuku et al., 2013) reported that both indwelling urinary catheter (OR=1.4×1010, p=0.01) and smaller Multinational Association for Supportive Care in Cancer score (MASCC) score (OR=0.46, p=0.05) significantly related to refractory febrile neutropenia (FN) by multivariate analysis.

In the present analysis, we found that pretreatment WBC and neutrophil counts, in addition to pretreatment serum albumin and creatinine levels, were significant independent risk factors for neutropenia induced by docetaxel-based systemic chemotherapy in Korean CRPC patients. These results are similar to those of other studies. Moreover, several studies identified additional patient-related factors that, although not identified in the present study, predisposed the afflicted individuals to either FN (Aapro et al., 2006; Smith et al., 2006) or excessive myelosuppression (Lyman et al., 2003). These included an age of >65 years, advanced disease, anemia, poor performance status, prior chemotherapy treatment, combined chemoradiotherapy, bone marrow infiltration, and medical comorbidities (particularly renal disease). However, many of these pretreatment risk factors were identified in reports that included patients with hematological malignancies and are thus of questionable relevance to the adjuvant treatment of prostate cancer. Other studies show that the first cycle absolute neutrophil count (ANC) nadir is a predictive factor for subsequent neutropenic events (Silber et al., 1998; Rivera et al., 2003; Savvides et al., 2003), however, we did not find similar results in the present study. There may be several reasons for the differences between our results and those of previous studies. First, the present work included only histologically confirmed adenocarcinomas of the prostate, whereas previous studies encompassed a variety of different tumor types (i.e., lymphomas, solid tumors, and breast cancer). Second, our cohort was very small (n=40) relative to the patient populations examined in previous studies, which is also one of the major limitations of this report.

Therapeutic strategies for cancer management continue to evolve, and chemotherapy regimens in turn continue to play important roles in cancer treatment. In the urological field, for example, chemotherapy regimens for metastatic prostate cancer have become more numerous and increasingly varied (George et al., 2011). Our future work will seek to evaluate the incidence of, and predisposing factors for, FN during urological chemotherapy, and to establish further guidelines for this purpose.

This study had several limitations, including its small size, as noted above. The lack of a large number of patients makes it difficult to draw definitive conclusions. In addition, the investigation was retrospective rather than prospective in nature. Furthermore, there are probably other factors that predict neutropenia induced by docetaxel-based systemic chemotherapy in patients with CRPC that may be identified in a larger study. Nonetheless, an advantage of the current study is that the patients were treated in a single institution by a limited number of attending physicians, and follow-up was also relatively long and complete.

In conclusion, the results of this study identified pretreatment WBC counts, neutrophil counts, serum creatinine levels, and serum albumin levels, but not prior chemotherapy, as significant independent risk factors for neutropenia induced by docetaxel-based systemic chemotherapy in patients with CRPC. To the best of our knowledge, this is the first study to show the prognostic ability of significant independent risk factors

for docetaxel-associated neutropenia in CRPC patients. However, a large cohort prospective study is required to confirm these results.

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