Clinical significance of a prostate-specific antigen flare phenomenon in patients with hormone-refractory prostate cancer receiving docetaxel

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Docetaxel has shown promise for the treatment of hormone-refractory prostate cancer and has become the standard of care. The flare phenomenon is a known entity in androgen-deprivation therapy of advanced prostate cancer and it has also been described in palliative chemotherapy of hormone-refractory prostate cancer. The aim of this study was to evaluate the clinical impact of a prostate-specific antigen flare phenomenon in docetaxel-treated hormone-refractory prostate cancer patients. From December 2002 to August 2005, we treated 44 patients with hormone-refractory prostate cancer applying docetaxel-based regimens. Prostate-specific antigen levels were determined before therapy and weekly thereafter. Patients were divided into three groups: response (group 1), progression (group 2) and flare (group 3). Flare was defined as initially rising prostate-specific antigen under therapy, dropping thereafter to values below baseline. The groups were compared for overall survival by Kaplan–Meier analysis. We observed a prostate-specific antigen flare phenomenon in eight (18%) of 44 evaluable patients; 24 (54.5%) patients were primary responders and 12 (27.3%) experienced progressive disease. In group 3, prostate-specific antigen levels rose to 107–180% from baseline and then dropped to 21–68%. Kaplan–Meier analysis showed significantly better overall median survival for groups 1 (18 months, $P=0.0005$) and 3 (19 months, $P=0.006$) than for group 2 (7 months). Survival in groups 1 and 3 was comparable. Grade 3 and 4 toxicity was below 5% and equally distributed between the 3 groups. In our limited patient cohort, prostate-specific antigen flare phenomenon does not seem to be a clinically relevant issue in terms of overall survival. Thus, an initial rise of prostate-specific antigen under docetaxel therapy in hormone-refractory prostate cancer does not indicate therapeutic failure and should not lead to early withdrawal from therapy in the absence of clinical signs of progression. *Anti-Cancer Drugs* **17:993–996 © 2006 Lippincott Williams & Wilkins.**

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Introduction

In 2005, it is estimated that there were more than 30 000 deaths from prostate cancer – the most prevalent male urogenital malignancy – in the US [1]. In Germany, there are more than 40 000 new cases of prostate cancer each year [2]. Having reached the terminal phase of their disease, almost all patients suffer from hormone-refractory prostate cancer (HRPCA). They experience advanced and progressive disease after complete androgen deprivation, antiandrogen withdrawal and perhaps secondary hormonal manipulation. HRPCA is a disabling and morbid disease with a median survival of 10–12 months; until recently, no treatment modality offered a survival benefit. Until 2004, mitoxantrone, combined with a corticosteroid was the standard of care, offering some palliation in terms of bone pain and quality of life [3,4]. Berry *et al.* [5] showed an advantage of mitoxantrone plus low-dose prednisone vs. prednisone alone in terms of recurrence-free survival. No phase III trial, however, was able to prove a positive effect on overall survival. Only recently, two independent phase III trials could provide evidence for docetaxel-based chemotherapy to prolong survival significantly in men with HRPCA [6,7]. Therefore, in 2004 docetaxel was approved by the US Food and Drug Administration for the treatment of HRPCA and has become the first-choice treatment. Docetaxel inhibits tumor growth by induction of microtubule stabilization [8] and inactivation of the antiapoptotic protein BCL-2, which has been shown to be overexpressed in metastatic cells from androgen-independent prostate tissue [9,10].

Prostate-specific antigen (PSA) has been validated to be the most useful marker to indicate treatment failure following local therapy and to control the effect of hormonal or cytotoxic therapy in advanced stages. Both the PSA level and relative PSA velocity correlate with

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tumor burden [11]. Initial PSA surges are well known in androgen deprivation therapy of advanced prostate cancer [12]. This flare phenomenon has also been observed in HRPCA patients treated with liposomal doxorubicin [13,14]. It has been described in 17 and 10% of patients, respectively. The temporary PSA surge exceeded baseline values by 37–400% and then decreased to below baseline values. This raises the question of when an initial PSA rise should result in early withdrawal from therapy in a palliative setting.

We have observed reversible PSA surges after initiation of docetaxel-based therapy of HRPCA, and analyzed patients treated at our institution to quantify this phenomenon and define its impact on clinical outcome in terms of overall survival.

Methods

From December 2002 to August 2005, we applied docetaxel-based chemotherapy as first-line regimen in 44 patients with HRPCA: docetaxel plus mitoxantrone was used in four patients (mitoxantrone 12 mg/m^2 and docetaxel 60 mg/m^2 on day 1 of a 21-day cycle), docetaxel plus estramustine in 20 patients (docetaxel 25 or 35 mg/m^2 on day 1 of a 7-day cycle and estramustine 3×280 mg orally on days 0–3) or docetaxel single agent in 20 patients (35 mg/m^2 on day 1 of a 7-day cycle; therapy was interrupted for 1 week after three cycles). PSA, alkaline phosphatase, hematologic, renal and hepatic toxicity as well as Eastern Cooperative Oncology Group performance status and clinical toxicity according to Common Toxicity Criteria were assessed before therapy and weekly thereafter. These parameters were documented every visit prospectively on a standardized toxicity questionnaire. Follow-up and survival data were acquired by a standardized telephone interview. All PSA values were determined in the central laboratory facility of the Marburg University Hospital. Patient records were analyzed for pretreatment and supportive treatment data in terms of primary therapy of prostate cancer after initial diagnosis, previous medical treatment after progression including secondary hormonal manipulation, concomitant bisphosphonate medication and erythropoietin medication.

Response (group 1) was defined as PSA decrease of at least 50% from baseline. Progression under therapy was defined as a continuous, irreversible rise of PSA or tumor growth at any metastatic site during treatment (group 2). Patients were considered to have a PSA flare phenomenon when PSA continued to rise after initiation of docetaxel-based therapy but dropped to values below baseline (50% or less of the maximal PSA value; group 3) thereafter. The three groups were compared with respect to the evaluated demographic and clinical parameters, and especially for overall survival. Therapy was discontinued in the case of grade 4 toxicity or if there was an increase of symptoms under therapy.

Statistical methods

Estimated overall survival was calculated for the three groups using Kaplan–Meier analysis. Log-rank analysis was used to compare equality of survival distributions for significant differences. Nonparametric test statistics (Kruskal–Wallis and Mann–Whitney *U*-test) was used to compare laboratory values of the groups at different time points. Descriptive statistics and test statistics including Kaplan–Meier analysis were performed using commercially available computer software (SPSS 12.0, Chicago, Illinois, USA).

Results

Mean patient age at first diagnosis of HRPCA was 66.3, 64.5 and 65.5 years in groups 1, 2 and 3, respectively. Median follow up was 14 months (16.5, 8.5 and 16.5 months for groups 1, 2 and 3, respectively). Patient characteristics concerning medical history and especially previous therapy are summarized in Table 1. The majority of patients in each group received two or more hormonal treatment modalities (87.5, 91.7 and 87.5% in groups 1, 2 and 3, respectively). Hemoglobin and alkaline phosphatase values before therapy were comparable. Toxicity according to Common Toxicity Criteria was usually grade 1–2. Four (9%) patients developed grade 3 or 4 nausea and vomiting, respectively. Two (4.5%) and one (2.3%) patient had grade 3 and 4 leucopenia, respectively, and one (2.3%) patient had to discontinue estramustine treatment due to progressive cardiac insufficiency and the patient received docetaxel monotherapy thereafter.

A PSA flare phenomenon was observed in eight (18%) patients. From baseline, PSA rose to a maximum of 107–180%, which was reached between weeks 1 and 7 from the beginning of therapy. Thereafter, we observed a PSA drop to 21–67% of the baseline value in weeks 7–14. Patient-specific data of group 3 are summarized in Table 2.

Kaplan–Meier curves are shown in Fig. 1. Log-rank survival analysis revealed a significantly longer overall median survival for patients in groups 1 (18 months; 95% confidence interval 8–28; $P = 0.0005$ vs. group 2) and 3 (19 months, 95% confidence interval 6–32; $P = 0.0064$ vs. group 2) than for patients who experienced progressive disease under therapy (group 2: 7 months, 95%

Table 1 Pretreatment data and supportive medical therapy

	Pretreatment and concomitant treatment data	
	All (%)	Flare (%)
Primary treatment		
Radical prostatectomy	14.3	0
Radiation	7.1	0
Androgen deprivation	78.6	100
Secondary hormonal manipulation	21.3	12.5
Bisphosphonates	63.8	62.5
Erythropoietin	19.1	25.0

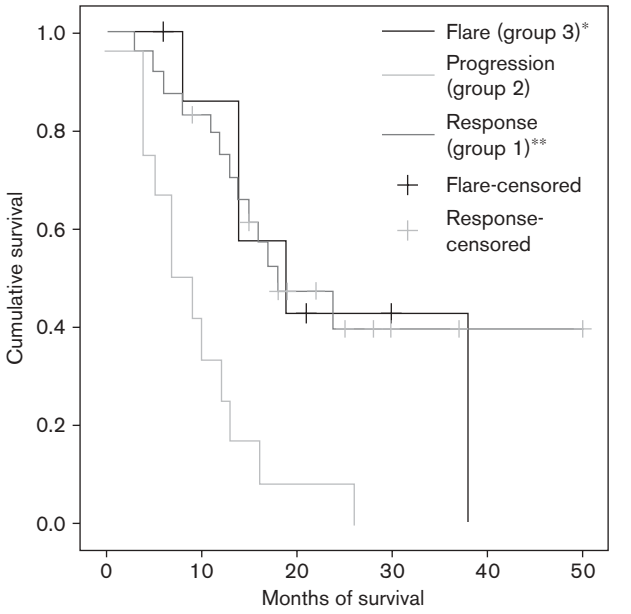
Table 2 **Patient-specific PSA courses of group 3 (flare up)**

Patient no.	PSA baseline (ng/ml)	PSA max (ng/ml)	PSA min (ng/ml)	Week of PSA max (after initiation of therapy)	Week of PSA min (after initiation of therapy)
1	220	249	113	1	12
2	26	30	11	2	7
3	465	534	148	4	10
4	245	263	105	1	14
5	49	84	33	7	12
6	198	246	52	4	13
7	40	72	9	2	12
8	183	196	39	2	14

PSA, prostate-specific antigen; PSA baseline, PSA before initiation of therapy; PSA max, maximal PSA value after initiation of therapy; PSA min, minimal PSA value after initiation of therapy.

confidence interval 2–12). Median overall survival of group 3 was not different from that of group 1 ($P = 0.9$) (Fig. 1).

Fig. 1



Kaplan–Meier curves. *P=0.0064 vs. progression; **P=0.0005 vs. progression.

Discussion

Today, serum PSA is accepted as a suitable follow-up tool after curative therapy of localized prostate cancer and during systemic treatment of advanced prostate cancer. In most cases, the PSA level correlates with tumor burden. A high PSA velocity predicts unfavorable outcome in HRPCA [11,15] and a 50% or greater PSA decrease during chemotherapy in these patients has been associated with prolonged survival [16]. Currently, docetaxel is the most effective cytostatic agent in the treatment of HRPCA with significant impact on overall survival and a high proportion of patients achieving an objective PSA response [6,7]. Cytotoxic therapy in HRPCA, however, is palliative and if it proves ineffective or causes intolerable toxicity, it should be stopped. The PSA flare phenomenon after initiation of medical androgen ablation in patients with advanced prostate cancer is well known [12,17]. Although the impact of a PSA flare-up at the beginning of luteinizing hormone-releasing hormone (LHRH) analogue treatment on survival is uncertain, cancer-associated symptoms may temporarily worsen. Therefore, concomitant antiandrogen treatment during the initial phase of LHRH analogue therapy is recommended in metastasized prostate cancer [18]. We and others have recently described a flare-like phenomenon for chemotherapy in HRPCA [13,14] under therapy with liposomal doxorubicin in 17 and 10% of patients. These studies, however, did not evaluate the impact of a PSA flare on prognosis.

The exact pathophysiologic basis for the flare phenomenon under cytotoxic therapy is most probably completely different from the 'classic' flare under hormonal therapy of prostate cancer and remains elusive. One explanation might be that HRPCA represents a malignant condition of immense cellular heterogeneity and diversity in terms of drug sensitivity, cell cycle kinetics and PSA expression [19,20]. This may partly explain why in some patients the PSA nadir is observed not before 1–3 months of treatment. The slow rate of PSA reduction could also be related to the relatively low proliferation rate of prostate cancer in general. Some subpopulations might be rapidly eradicated during the initial phase of chemotherapy, whereas others survive and continue to express PSA during the first cycles, but are destroyed later [19].

A totally different explanation of a PSA surge might be the release of PSA from lytic tumor cells and thus might reflect a certain sensitivity to cytotoxic therapy. This hypothesis, however, is highly speculative and the detailed molecular characterization of this phenomenon warrants further studies.

We can now confirm the existence of an initial PSA surge in a considerable portion of docetaxel-treated patients, too. Our retrospective study was conducted to evaluate whether this initial PSA surge in patients treated with docetaxel-based regimens might predict an unfavorable prognosis in terms of survival and should therefore lead to early discontinuation or change of therapeutic strategy. Moreover, the clinical impact of a temporary PSA rise that is misinterpreted as progression is considerable because progression under therapy has to result in discontinuation of treatment, especially in a palliative setting. In our cohort, the presence of a PSA flare did not negatively affect overall survival. Therefore, in the absence of

clinical signs of progression, an early increase of PSA under docetaxel-based therapy is not a reliable sign for progressive disease. At least 8 weeks of treatment have to be performed before withdrawing a patient from a docetaxel-based protocol. The knowledge of a PSA flare-like phenomenon under docetaxel in HRPCA might also have an impact on the design of clinical studies in terms of protocol discontinuation because of early rising PSA values.

References

1 National Cancer Institute. *Seer cancer statistics review 1975–2002*. Bethesda: National Cancer Institute; 2002. http://seer.cancer.gov.

2 Robert Koch Institut. *RKI Dachdokumentation Krebs*. Berlin: Robert Koch Institute; 2005. http://rki.de.

3 Tannock IF, Osoba D, Stockler MR, Ernst DS, Neville AJ, Moore MJ, *et al.* Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol* 1996; **14**:1756–1764.

4 Kantoff PW, Halabi S, Conaway M, Picus J, Kirshner J, Hars V, *et al.* Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. *J Clin Oncol* 1999; **17**:2506–2513.

5 Berry W, Dakhil S, Modiano M, Gregurich M, Asmar L. Phase III study of mitoxantrone plus low dose prednisone versus low dose prednisone alone in patients with asymptomatic hormone refractory prostate cancer. *J Urol* 2002; **168**:2439–2443.

6 Petrylak DP, Tangen CM, Hussain MH, Lara PN Jr, Jones JA, Taplin ME, *et al.* Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004; **351**:1513–1520.

7 Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, *et al.* Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; **351**:1502–1512.

8 Haldar S, Basu A, Croce CM. Bcl2 is the guardian of microtubule integrity. *Cancer Res* 1997; **57**:229–233.

9 Ringel I, Horwitz SB. Studies with RP 56976 (taxotere): a semisynthetic analogue of taxol. *J Natl Cancer Inst* 1991; **83**:288–291.

10 McDonnell TJ, Navone NM, Troncoso P, Pisters LL, Conti C, von Eschenbach AC, *et al.* Expression of bcl-2 oncoprotein and p53 protein accumulation in bone marrow metastases of androgen independent prostate cancer. *J Urol* 1997; **157**:569–574.

11 Vollmer RT, Dawson NA, Vogelzang NJ. The dynamics of prostate specific antigen in hormone refractory prostate carcinoma: an analysis of cancer and leukemia group B study 9181 of megestrol acetate. *Cancer* 1998; **83**:1989–1994.

12 Noguchi K, Uemura H, Harada M, Miura T, Moriyama M, Fukuoka H, *et al.* Inhibition of PSA flare in prostate cancer patients by administration of flutamide for 2 weeks before initiation of treatment with slow-releasing LH-RH agonist. *Int J Clin Oncol* 2001; **6**:29–33.

13 Fossa SD, Vaage S, Letocha H, Iversen J, Risberg T, Johannessen DC, *et al.* Liposomal doxorubicin (Caelyx) in symptomatic androgen-independent prostate cancer (AIPC): delayed response and flare phenomenon should be considered. *Scand J Urol Nephrol* 2002; **36**:34–39.

14 Heidenreich A, Sommer F, Ohlmann CH, Schrader AJ, Olbert P, Goecke J, *et al.* Prospective randomized phase II trial of pegylated doxorubicin in the management of symptomatic hormone-refractory prostate carcinoma. *Cancer* 2004; **101**:948–956.

15 D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, Chen MH. Surrogate end point for prostate cancer specific mortality in patients with nonmetastatic hormone refractory prostate cancer. *J Urol* 2005; **173**:1572–1576.

16 Smith DC, Dunn RL, Strawderman MS, Pienta KJ. Change in serum prostate-specific antigen as a marker of response to cytotoxic therapy for hormone-refractory prostate cancer. *J Clin Oncol* 1998; **16**:1835–1843.

17 Kahan A, Delrieu F, Amor B, Chiche R, Steg A. Disease flare induced by D-Trp6-LHRH analogue in patients with metastatic prostatic cancer. *Lancet* 1984; **1**:971–972.

18 Bubley GJ. Is the flare phenomenon clinically significant? *Urology* 2001; **58** (**Suppl 1**):5–9.

19 Liu AY, True LD, LaTray L, Ellis WJ, Vessella RL, Lange PH, *et al.* Analysis and sorting of prostate cancer cell types by flow cytometry. *Prostate* 1999; **40**:192–199.

20 van der Poel HG, Oosterhof GO, Schaafsma HE, Debruyne FM, Schalken JA. Intratumoral nuclear morphologic heterogeneity in prostate cancer. *Urology* 1997; **49**:652–657.