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Docetaxel, Estramustine and Prednisone for Hormone-refractory Prostate Cancer: A Single-center Experience

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Abstract. *Background: The results of chemotherapy in patients with advanced, hormone-refractory prostate cancer (HRPC) have been disappointing. Mitoxantrone has been used in the past for palliation, but it does not prolong survival. It was recently demonstrated that docetaxel is able to improve median survival as compared to mitoxantrone. We, therefore, wanted to evaluate a docetaxel-based regimen, with regard to efficacy and tolerability, in men with HRPC at our institution. Patients and Methods: Patients with progressive HRPC (new metastatic lesions or PSA progression) and no prior cytotoxic chemotherapy received the following treatment administered in 21-day cycles: 280 mg estramustine three times daily on days 1 to 5 and 7 to 11, 70 mg docetaxel per square meter of body surface area on day 2, and 10 mg prednisone once daily throughout the course. After four cycles, the patients were re-evaluated via PSA, blood counts, CT and bone scans. If no progression had occurred, two more cycles were given. Objective response rates, post-treatment declines in serum PSA levels, as well as side-effects, were recorded. Results: Thirty-nine patients with HRPC (age range 43-79 years, average 65 years) were enrolled after informed consent. The median PSA in this cohort was 144 (1.5-3030) ng/ml. The percentage of patients with bone and lymph node metastases was 82% and 61.5%, respectively. During an average follow-up period of 11 months, 20 patients (64.5%) showed a response to therapy, including a complete (CR), partial (PR) or mixed (MR) response, stable disease (SD) of metastatic lesions, or a PSA response. A post-therapeutic decrease of serum PSA levels of >25%, >50% and >75% occurred in 26.1%, 21.7% and 26.1% of patients, respectively. Lymph node metastases responded better to therapy (73%) than bone metastases (42%). Regarding toxicity, the regimen was generally well tolerated. Only three patients showed adverse events (one grade 4 neutropenia, one dermatological and one as a result of pain), which led to therapy withdrawal. Minor adverse events included nausea, alopecia and fatigue. No cardiovascular events were reported. Conclusion: Although the patients included in the present study had advanced disease, responses were promising and toxicity was tolerable. These preliminary data support the findings of recently published studies and suggest that docetaxel-based chemotherapy is going to play an important role as a regimen for patients with HRPC.*

Prostate cancer is the most common cancer among men in industrialized countries (1). Although, as a result of increased PSA-testing, most men are diagnosed with organ-confined disease, about 10 to 20% of patients still present with metastases at the time of first diagnosis (2). For decades, androgen ablation has been the standard treatment for these patients. Medical or surgical castration leads to a rapid improvement of clinical symptoms, a reduction of metastatic tumor burden and a decline of serum prostate-specific antigen (PSA) levels; however, this treatment remains palliative and patients will develop hormone-refractory disease after a median of 18 to 24 months after castration (3). Once patients become refractory to androgen blockade, their prognosis is dismal, with a median survival time of 9 to 12 months (4).

Chemotherapeutic agents have been shown to be palliative in the state of hormone-refractory prostate cancer (HRPC), but, until recently, no single-agent or combination therapy has proved able to prolong survival. In a review of 26 chemotherapy trials performed between 1988 and 1991 in men with HRPC, a disappointing overall response rate of 8.7% (6.4-9.0%) was demonstrated in 1001 treated patients (5). The situation changed in October 2004, when two phase

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III studies, namely the SWOG 99-16 and the TAX 327 studies, were able to demonstrate an improvement in median survival of patients treated with docetaxel and estramustine, as compared with the standard treatment of mitoxantrone and prednisone (2, 6). Preliminary data presented at meetings earlier in 2004 had already suggested an advantage of this combination therapy.

Metastatic cells from androgen-independent prostate tissues overexpress Bcl-2, an anti-apoptotic protein, as demonstrated by immunohistochemical studies (7). Docetaxel, an extract from *Taxus baccata*, is able to inactivate Bcl-2 through phosphorylation, leading to eventual cell death by apoptosis (8). In addition, docetaxel inhibits microtubular function, and is involved in p53-associated apoptosis, leading to arrest of the G1- and G2-phases of the cell cycle (9).

As a urological oncology center with a special interest in prostate cancer, we performed a phase II study in patients with hormone-refractory prostate cancer who lacked any other therapeutic options; using the drug off-label, *i.e.* before its official approval, we administered four to six cycles of docetaxel-based chemotherapy in a uniform therapeutic regimen.

Patients and Methods

Enrolled patients had to have histopathologically confirmed adenocarcinoma of the prostate and progressive metastatic disease despite prior hormonal ablative treatment. Disease progression was defined by increasing serum PSA levels in at least two consecutive samples obtained 1 week apart, or findings from imaging investigations (computed tomography or bone scan). The patients had had no prior treatment with cytotoxic drugs (except estramustine) or radioisotopes, no history of pulmonary embolism or another malignancy and no other current serious medical condition, including active thrombophlebitis or clinically significant neuropathy. The Karnofsky performance status had to be at least 60%, and informed consent was obtained from all patients. The baseline characteristics of the patients are shown in Table I.

Prior to treatment, the patients were evaluated by means of a physical examination, blood counts, liver and kidney laboratory studies, PSA serum levels, a chest X-ray (followed by a CT of the thorax if suspicious lesions were found), a CT of the abdomen and pelvis, and a bone scan. The following treatment was administered in 21-day cycles: 280 mg estramustine orally three times daily on days 1 to 5 and 7 to 11, 70 mg docetaxel per square meter of body surface area intravenously on day 2, and 10 mg prednisone orally once daily throughout the course. The treatment was continued until disease progression, until unacceptable adverse effects were reported or until a maximum of six cycles had been administered. Serum PSA levels were determined before therapy and before each cycle. Restaging was performed after four cycles and, in the case of a therapeutic response, two more cycles were administered. The combination treatment of docetaxel and estramustine was chosen, as recommended by Petrylak (4), and prednisone was added in accordance with a phase II study by Oudard *et al.* (10). A therapeutic response was defined as complete/partial remission (CR/PR), a mixed response (MR) or a stable disease (SD) of metastatic lesions in CT or bone scan as well as a PSA response (see Results).

Table I. *Patients' baseline characteristics (n=39).*

Demographics	No. (%)
Age, years	
Average	65
Range	43-79
Racial group	
Caucasian	39 (100)
PSA, ng/ml	
Median	144
Average	631
Range	1.57-3030
Site of metastases*	
Bone	32 (82)
Lymph nodes	24 (61.5)
Lung	2 (5.1)
Liver	3 (7.7)
Prior therapy†	
Medical/surgical castration (incl. complete androgen blockade)	39 (100)
Radiotherapy	18 (46.2)

*Patient may have had more than one site of metastasis.
†Patient may have had more than one type of prior therapy.

Results

At the time of evaluation, 31 patients had completed their treatment (Table II). Therapeutic responses according to the above-mentioned criteria were observed in 20 patients (64.5%). Five patients (16.1%) progressed during treatment. Two patients (6.5%), with initially diagnosed hepatic metastasis, died during therapy. One patient discontinued therapy at his own request after four cycles in spite of tumor response, and one patient was lost to follow-up.

The results of the objective, measurable response according to CT or bone scintigraphy are shown in Table III. Lymphatic metastases showed the best response to the therapeutic regimen. In 11 out of 15 cases (73.3%), therapy led to either inhibition of tumor progression and stable disease (SD), partial remission (PR) and in 2 cases even complete remission (CR). In contrast, bone metastases were less sensitive with stable disease being achieved in 9 out of 24 cases (37.5%) and only a mixed response (MR). Due to the small number of cases, the response of hepatic and pulmonary metastases could not be properly evaluated.

Table II. *Therapeutic response and toxicity (n=31).*

	N	%
Response to therapy	20	64.5
Progression/death during therapy	5/2	16.1/6.5
Toxicity		
- Grade 4 neutropenia	1	3.2
- Grade 2 erythema/grade 1 stomatitis	1	3.2
- Abdominal pain without clinical correlate or laboratory changes	1	3.2
		Total: 9.7
Lost to follow-up or consent withdrawal	2	6.5

Table III. *Objective therapeutic response, measurable lesions*.*

Localization	Lymph nodes (n=15)	Bone (n=24)	Lung (n=2)	Liver (n=1)
CR	2 (13.3 %)	-	1	-
PR	2 (13.3 %)	-	-	-
SD	7 (46.7 %)	9 (37.5 %)	-	-
MR	-	1 (4.2 %)	-	-
Progression	4 (26.7 %)	14 (58.3 %)	1	1

CR: complete response; PR: partial response; SD: stable disease; MR: mixed response.
*Patient may have had more than one site of metastasis.

PSA levels of 23 patients were available after completion of four cycles of chemotherapy (Figure 1). One patient was PSA-negative even before treatment. PSA normalization (defined as a level < 4 ng/ml) was achieved in 6/23 cases (26.1%); PSA decreases of >75%, >50% and >25% were noted in 5/23 cases (21.7%), 6/23 cases (26.1%) and 1/23 cases (4.3%), respectively. Three out of 23 patients (13%) showed stable PSA levels and one patient (4.3%) had PSA progression. The PSA decrease was not dependent on the baseline PSA. The remaining patients did not complete four cycles of chemotherapy because of side-effects, toxicity, early study drop-out or death (see Table II). In relation to the total of 31 patients who completed the therapy, a cumulative PSA decrease or at least stable PSA was achieved in 70.1%.

The majority of patients had only minor side-effects. The most common side-effects mentioned were alopecia, nausea and fatigue. Three patients (9.7%) suffered adverse events, which led to treatment discontinuation (Table II). No fever, infection, diarrhea, thrombo-embolic or cardiovascular events were reported.

The follow-up period for patients who completed the therapy of six cycles ranged from 4 to 20 months (average 11 months). PSA levels after completion of therapy were available for 15 out of 19 patients. Only one patient continued to show a PSA response (PSA 7-8 ng/ml after an initial PSA of 24.1 ng/ml) 14 months after completion of the therapy. The remaining patients showed a PSA relapse within the first 6 months after completion of six courses, although it is important to note that most of them were without clinical symptoms.

Discussion

Taxanes have been used successfully for the treatment of different tumor entities, including breast, ovarian and lung cancer, since the 1990s. The first substance introduced was paclitaxel, which, similar to docetaxel, is produced semi-synthetically (11). The mechanism of action of both substances is inhibition of microtubular function, which results in an interruption of mitosis and, consequently, of cell division (9). In addition, the taxanes are able to phosphorylate and inhibit the anti-apoptotic protein Bcl-2, an effect that results in increased apoptosis. Docetaxel seems to be more potent than paclitaxel with regard to Bcl-2 inhibition, an effect that is partly due to a slower efflux out of the cell (8). The taxanes also lead to an increase of serum cytokine levels, such as IL-2, IL-6 or IFNγ, but the exact reason for these immunological phenomena and their relevance in terms of their antineoplastic mechanisms have not been fully explained (11).

In the early nineties, paclitaxel was evaluated as a monotherapeutic agent for prostate cancer in a phase II study by Roth *et al.* (12). It was administered every 3 weeks at a dosage of 135-170 mg per square meter in 23 patients. With only partial remissions observed and a PSA decrease in only 16-24% of the patients, the results were disappointing. In addition, toxicity, especially grade 4 neutropenia in 63% and neutropenic fever in 26% of the patients, was significant. In 2000, Trivedi *et al.* used a weekly mode of administration for paclitaxel in 18 patients (13). The dosage was 150 mg per square meter, and the duration was 6 weeks. A PSA decrease of more than 50% was achieved in 39% of the patients, the median progression-free survival was 2.5 months and the median overall survival was 13.5 months. Compared with the previous study, toxicity was less frequent, although peripheral neuropathy was reported in 35% of the patients.

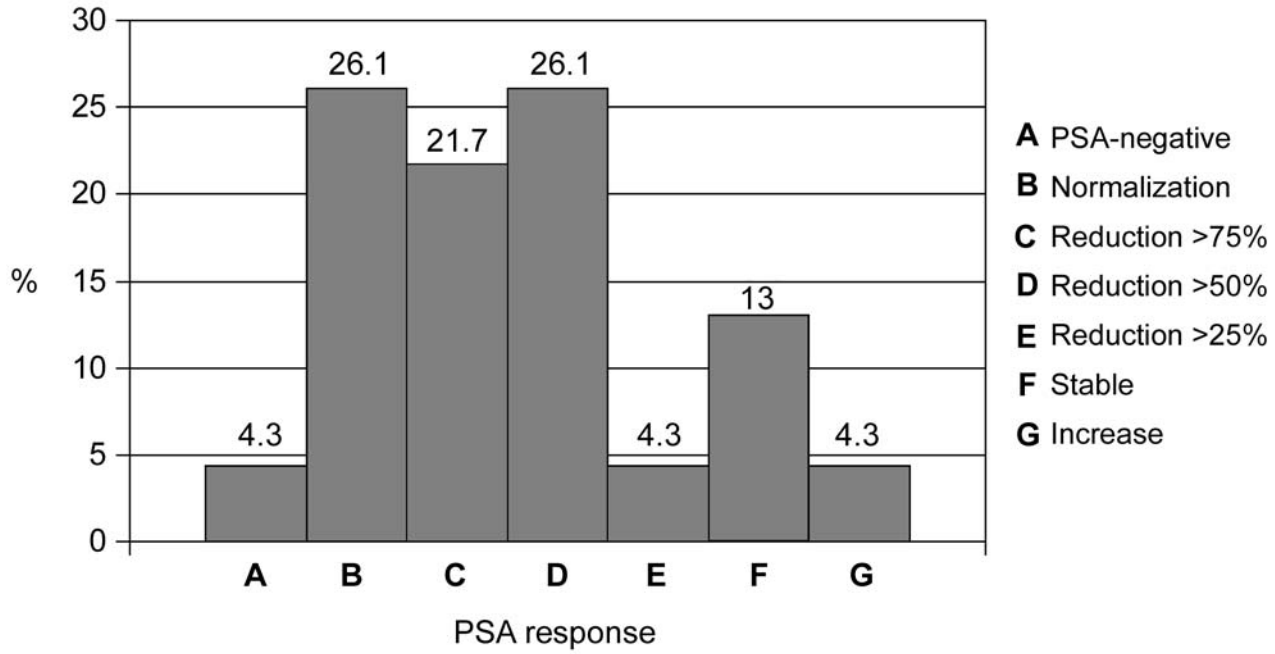

Figure 1. *Post-therapeutic decrease of serum PSA levels in 23 patients after completion of four cycles of the described docetaxel-based regimen.*

In the late nineties, docetaxel was introduced in trials with three-weekly as well as weekly treatment intervals. In studies using three-weekly administration, the most commonly used dosage was 75 mg per square meter. Thirty-eight to 80% of the patients showed PSA responses, 25 to 50% showed objective responses, the median survival of the responding patients was up to 27 months, and grade 3 to 4 neutropenia was reported in 43 to 71% (14, 15).

Until very recently, results of trials comparing docetaxel-based chemotherapeutic regimens with mitoxantrone in the treatment of hormone-refractory prostate cancer were only available as published abstracts. We used the work by Oudard *et al.* as our reference study, and adopted their therapeutic regimen (10). In the meantime, the results of the largest phase III multicenter trials comparing docetaxel with mitoxantrone, namely the SWOG 99-16 study and the TAX 327 study, have been published and will therefore be used for comparison and discussion (2, 6). In the TAX 327 study, the median overall survival was higher (18.9 months) for the group that received docetaxel every 3 weeks than for the mitoxantrone group (16.5), but not for the group that received weekly docetaxel (17.4 months). In addition, the docetaxel groups had better pain control and more PSA responses at the expense of more adverse effects (2). Petrylak *et al.,* in the SWOG study 99-16, also reported significantly longer median survival in comparison with the mitoxantrone group (17.5 *vs.* 15.6 months), although the effect on pain was similar in both arms (6).

Differences in administration patterns and intervals of docetaxel-based regimens make comparisons between different reports problematic: Petrylak *et al.* administered docetaxel [D] 60-70 mg/m^2 whole body surface area on day 2 and estramustine [E] 3 x 280 mg on days 1-5 and dexamethasone [Dex] 60 mg in three divided doses before docetaxel administration in a 21-day cycle (6); Savarese *et al.* administered identical doses of D+E 10 mg/kg/body weight days 1-5 + hydrocortisone [HC] 40 mg/day; Sinibaldi *et al.* used identical doses of D + 5 x 280 mg single doses [SD] 6-hourly (qid) (16, 17). Differing docetaxel doses were used by Kosty *et al.*: D 43 mg/m^2/week 2, E 4 x 140 mg/day days 1-5, Dex 3 x 8 mg for 3 out of 4 weeks; Copur *et al.* used D 35 mg/m^2/week + E 4 x 420 mg ED + 5 x 280 mg ED for 2 out of 3 weeks (18, 19). In the TAX 327 study, dosing was D 75 mg/m^2 3-weekly + prednisone [P] 2 x 5 mg/day + Dex 12, 3 and 1 h before docetaxel administration (2). The dosage used in the present study was similar to the dosage in the SWOG trial and, in retrospect, the choice of the 21-day interval has been shown to be superior to weekly administration (6).

Our own patient population was not randomized but was preselected, having been admitted by our colleagues in private practice. Compared with other studies, the patient population was younger, with an average age of 65 years at onset of therapy (SWOG study: 70 years, TAX 327 study: 68 years). The serum PSA level at entry, however, was

Table IV. *Results of combination therapies of docetaxel and estramustine.*

Study/Author	Year	No.	Clinical response (%)	PSA response (%) (total)
Bagliella *et al.* (23)[1,2]	2000	37	57	68
Sinibaldi *et al.* (17)[1]	2000	32	23	45
Sitki Copur *et al.* (19)	2000	20	50	76
Savarese *et al.* (16)[1,2]	2001	47	50	68
Kosty *et al.* (18)[2]	2001	21	11	71
Oudard *et al.* (10)[1,2]	2002	43	-	67
SWOG 99-16 (6)[2]	2004	386	17	50
TAX 327 (2)[2,3]	2004	335	46	45
Present study[1,2]		31	64	70

[1]docetaxel 70 mg/ kg, 21-day cycle
[2]+ prednisone derivative
[3]without estramustine

higher with a median of 144 ng/ml (average 631 ng/ml) compared with 97 ng/ml in the SWOG study and 123 ng/ml in the TAX 327 study, reflecting high tumor burden and short life expectancy (2, 6). The evaluation of patient characteristics showed a similar percentage of pre-existing bone metastases and a higher percentage of (frequently synchronous) lymph node metastases compared with the study by Oudard *et al.* The results of the other quoted studies are listed in Table IV.

The results of the present study show a better therapeutic response for lymph node than for bone metastases (73.3% *vs.* 41.7%) after docetaxel-based chemotherapy. In the patient population of this study, the PSA response was 70.1%, with an average PSA decrease to about 1/3 of baseline values. The course was not dependent on the baseline PSA. The fraction with PSA normalization and >75% decrease accounted for 47.8%, nearly twice the number published by Oudard *et al.* (28%). In the SWOG study, 50% of the patients had a PSA decrease >50%, which is comparable to the present population. In contrast, the time to PSA relapse in our patients was markedly shorter than reported by Oudard *et al.* at 2.7 *vs.* 9.1 months. This may be explained by the notably higher baseline PSA, suggesting a higher tumor burden and advanced disease. Toxic side-effects were remarkably low in our patients. Only one patient had to discontinue therapy because of neutropenia, generally occurring in 19-37% (grade 4) of patients on docetaxel therapy (15, 16, 19-23). The majority of our patients, in contrast, developed leukocytosis, which might have been a consequence of the concomitant prednisone treatment.

Conclusion

The initial results of the docetaxel-based chemotherapeutic regimen in our patients with hormone-refractory prostate cancer were encouraging. The PSA responses were impressive, albeit of limited duration, and the adverse effects were only mild in nature and tolerable for most of the patients. We currently suggest the combination of docetaxel and estramustine for patients with metastatic, androgen-independent prostate cancer. However, these individuals present with progressive disease, high tumor burden and limited life expectancy. Therefore, despite the observation that docetaxel prolongs survival in comparison with mitoxantrone, the effect remains palliative at this time. Further trials are necessary to determine the role of docetaxel, not only in the metastatic patient, but also in an earlier adjuvant setting.

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