Rational indication for docetaxel rechallenge in metastatic castration-resistant prostate cancer

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Study Type – Therapy (case series)
Level of Evidence 4

What's known on the subject? and What does the study add?
Docetaxel rechallenge has shown preserved anti-tumour activity and has therefore been proposed as an option for further treatment in patients with metastatic castration-resistant prostate cancer, who have shown a good response to first-line chemotherapy with docetaxel.

The present study provides evidence of docetaxel activity in patients who were treated with full-dose (75 mg/m^2) 3-weekly docetaxel at first-line chemotherapy and rechallenge. It shows that PSA response to first-line chemotherapy may provide a rational indication for docetaxel rechallenge.

OBJECTIVE

- To determine whether prostate-specific antigen (PSA) response at first-line chemotherapy with docetaxel correlates with PSA response and survival at docetaxel rechallenge in patients with metastatic castration-resistant prostate cancer (mCRPC).

PATIENTS AND METHODS

- We retrospectively evaluated the oncological outcomes of patients with mCRPC, who were treated with full-dose (75 mg/m^2), 3-weekly docetaxel plus prednisone/prednisolone at first-line chemotherapy and rechallenge, between 1999 and 2011, at our institution.
- The endpoints were PSA-progression-free survival (PSA-PFS) and overall survival (OS) at docetaxel rechallenge.
- Statistical analyses included Kaplan–Meier curves and log-rank tests to evaluate the effect of PSA response at first-line chemotherapy on PSA-PFS and OS at rechallenge.

RESULTS

- Fourty-four patients were included in the analysis.
- At a median (range) follow-up of 26.4 (9.8–89.8) months after the first administration of docetaxel, 24 (55%) patients had died. At first-line chemotherapy, 36 (82%) patients achieved a reduction in PSA level of ≥50%. At rechallenge, 10 (28%) patients responded with a reduction of ≥50% for a second time.
- The median (95% confidence interval [CI]) PSA-PFS was 5.9 (95% CI 3.5–6.8) months and the median OS was 21.8 (95% CI 19.9–23.7) months at docetaxel rechallenge.
- Of the PSA response variables evaluated, only a PSA level reduction of ≥50% at first-line chemotherapy correlated significantly with prolonged PSA-PFS (5.8 vs. 4.5 months; $P = 0.01$) and OS (22.1 vs. 7.2 months; $P = 0.03$) at rechallenge.

CONCLUSION

- In the present single-institution study, a reduction in PSA level of ≥50% at first-line chemotherapy with docetaxel correlated with superior PSA-PFS and OS in the rechallenge setting and might, therefore, present a rational indication for docetaxel rechallenge.

KEYWORDS

castration-resistant prostate cancer, chemotherapy, docetaxel rechallenge

INTRODUCTION

Chemotherapy with docetaxel is currently the standard first-line cytotoxic treatment in metastatic castration-resistant prostate cancer (mCRPC). The clinical efficacy of a 3-weekly docetaxel-based chemotherapy in chemo-naïve patients with mCRPC has been demonstrated by two randomized phase III trials (TAX-327 study; SWOG 99-16 study), resulting in a median survival benefit of 2–3 months compared with mitoxantrone and prednisone [1–4]. In patients with tumour progression after docetaxel first-line chemotherapy, docetaxel rechallenge has shown preserved anti-tumour activity and has therefore been proposed as an option for further treatment [5–12]; therefore, tumour response at first-line chemotherapy with docetaxel has been suggested as an indicator for activity of docetaxel rechallenge [5–12]. Nevertheless, the criteria defining an indication for docetaxel rechallenge in

mCRPC patients have not yet been determined.

In the present study, we sought to determine whether PSA response, as a surrogate marker of tumour response, at docetaxel first-line chemotherapy correlated with PSA response and survival at docetaxel rechallenge in patients with mCRPC.

PATIENTS AND METHODS

We retrospectively analysed data from patients with mCRPC, who were treated with docetaxel chemotherapy or with a subsequent systemic therapy regimen at the Department of Urology, of the Technical University of Munich, between 1999 and 2011. We included patients who met the following criteria: (i) histopathology of prostatic adenocarcinoma; (ii) treatment of mCRPC with docetaxel first-line chemotherapy at a dose regimen of 75 mg/m^2 in a 3-week interval in combination with prednisone or prednisolone 10 mg daily; (iii) confirmation of tumour progression by clinical, biochemical or radiographic assay; and (iv) docetaxel rechallenge at a dose regimen of 75 mg/m^2 in a 3-week interval in combination with prednisone or prednisolone 10 mg daily. PSA levels were measured before initiation of docetaxel chemotherapy and then at every clinical visit before docetaxel infusion at a 3-week interval.

The relevant endpoints included PSA-progression-free survival (PSA-PFS) and overall survival (OS) after initiation of docetaxel rechallenge. PSA-PFS was determined according to the guidelines of the Prostate Cancer Trials Clinical Working Group 2 [13]. Follow-up data were obtained from medical records and the Munich Cancer Registry.

SPSS Version 19.0 was used for statistical analysis. The median PSA-PFS and OS were determined using Kaplan–Meier curves. The effect of PSA response at first-line chemotherapy on PSA-PFS and OS was analysed using univariate analysis and log-rank tests. Determinants for PSA response at first-line chemotherapy included the best response, with PSA normalization defined as a reduction in PSA level of <1 ng/mL or a reduction of <4 ng/mL, reductions of ≥30% and ≥50%, PSA progression while on therapy as well as PSA progression >3 months after the last cycle of first-line chemotherapy with docetaxel. A baseline PSA level at docetaxel rechallenge <50 ng/mL or <100 ng/mL was also included in the analysis. A *P* value of 0.05 was considered to indicate statistical significance.

TABLE 1 Patient characteristics

	Median (range)
Age, years	68 (46–77)
Gleason score	8 (6–9)
No. of cycles	
First-line docetaxel	9.5 (3–9)
Docetaxel rechallenge	
1 line	5.5 (2–12)
2 lines	4 (2–10)
3 lines	5.5 (4–7)
No. of patients with docetaxel rechallenge	
≥1 line	44
≥2 lines	19
≥3 lines	2
PSA at baseline, ng/mL	
First-line docetaxel	56.0 (0.9–9317.9)
Docetaxel rechallenge	80.4 (0.3–6292.5)
PSA nadir, ng/mL	
First-line docetaxel	12.5 (0.4–5954.9)
Docetaxel rechallenge	46.9 (0.3–6292.5)
Haemoglobin at baseline, g/dL	
First-line docetaxel	12.7 (8.7–16.1)
Docetaxel rechallenge	11.9 (9.5–15.8)
Lactate dehydrogenase at baseline, U/L	
First-line docetaxel	255 (31–573)
Docetaxel rechallenge	311 (199–620)
Symptomatic disease at baseline, *n* (%)	
First-line docetaxel	16 (64)
Docetaxel rechallenge	21 (75)
ECOG performance status	
First-line docetaxel	0 (0–1)
Docetaxel rechallenge	0 (0–2)
Liver metastases at baseline, *n* (%)	
First-line docetaxel	2 (5.9)
Docetaxel rechallenge	2 (6.3)
Time since diagnosis, years	
First-line docetaxel	3.6 (0.2–11.7)
Docetaxel rechallenge	4.8 (1.4–12.5)
Docetaxel-free time between first-line and rechallenge, months	5.0 (1.4–24.6)

ECOG, Eastern Cooperative Oncology Group.

RESULTS

Fourty-four patients with mCRPC received 3-weekly docetaxel at first-line chemotherapy and rechallenge. Seven (16%) patients who received first-line docetaxel chemotherapy participated in the prospective TAX 327 study [2]. In 36 (82%) patients, docetaxel first-line chemotherapy was initiated in 2004 or later. The median patient age at rechallenge was 68 years. The median (range) number of docetaxel cycles was 9.5 (3–19) at first-line chemotherapy and 5.5 (2–12) at rechallenge. The median (range) docetaxel-free interval between both chemotherapy lines was 5 (1.4–24.6) months. Docetaxel rechallenge was performed more than once in 19 patients and more than twice in two patients. Patient characteristics are shown in Table 1.

TABLE 2 Influence of PSA response at first-line chemotherapy on PSA-PFS and OS at docetaxel rechallenge

	No. patients (%)	Median PSA-PFS, months (95% CI)	*P*	Median OS, months (95% CI)	*P*
PSA level normalization at first-line docetaxel					
≥1 ng/mL	37 (86.0)	5.2 (3.3–6.8)		21.8 (20.1–23.5)	
<1 ng/mL	6 (14.0)	9.9 (N/A)	0.53	18.0 (0.0–38.0)	0.76
≥4 ng/mL	32 (74.4)	5.1 (4.2–6.1)		21.8 (20.1–23.5)	
<4 ng/mL	11 (25.6)	6.3 (3.7–8.9)	0.71	22.8 (13.3–32.3)	0.81
PSA level reduction at first-line docetaxel					
≥30% PSA reduction	38 (88.4)	5.8 (4.3–7.2)		21.8 (20.1–23.5)	
<30% PSA reduction	5 (11.6)	3.3 (1.9–4.7)	0.03	5.1 (3.9–6.4)	0.13
≥50% PSA reduction	35 (83.3)	5.8 (4.6–7.0)		22.1 (19.5–24.6)	
<50% PSA reduction	7 (16.7)	4.5 (3.0–6.1)	0.01	7.2 (1.9–12.4)	0.03
PSA progression at first-line docetaxel					
Progression while on therapy	5 (12.2)	3.5 (1.2–5.7)		7.2 (1.2–13.1)	
No progression while on therapy	36 (87.8)	5.8 (4.8–6.7)	0.03	22.1 (20.1–24.0)	0.11
≥3 months after last cycle	14 (34.1)	4.1 (3.5–4.8)		21.4 (13.2–29.6)	
<3 months after last cycle	27 (65.9)	5.3 (3.6–7.0)	0.34	22.8 (17.4–28.2)	0.36
Baseline PSA level at docetaxel rechallenge					
≥50 ng/mL	28 (65.1)	5.1 (4.0–6.2)		21.8 (8.8–34.8)	
<50 ng/mL	15 (34.9)	5.7 (3.2–8.3)	0.65	22.1 (20.3–23.9)	0.92
≥100 ng/mL	22 (51.2)	5.8 (3.6–6.8)		17.1 (2.5–31.6)	
<100 ng/mL	21 (48.8)	5.2 (5.2–7.2)	0.29	22.1 (20.1–24.1)	0.72

FIG. 1. PSA-PFS at docetaxel rechallenge in patients with a PSA reduction of ≥ or <50% at first-line docetaxel chemotherapy. PSA reduction ≥50% at first-line chemotherapy correlated with superior PSA-PFS at docetaxel rechallenge (P = 0.01).

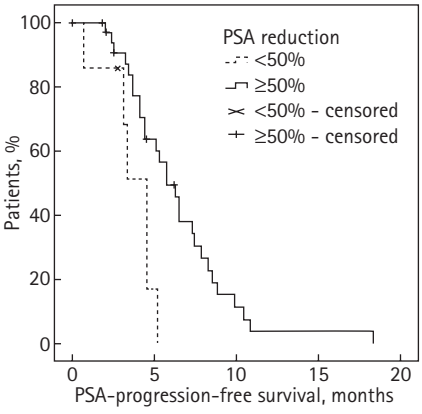
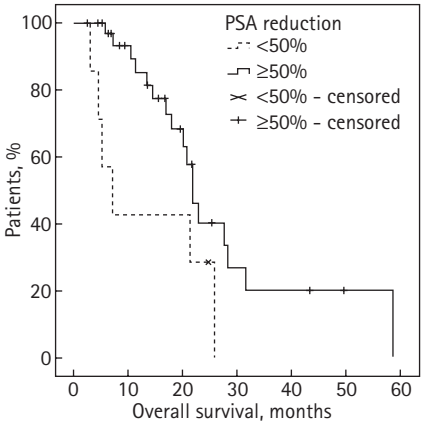


FIG. 2. OS at docetaxel rechallenge in patients with a PSA reduction of ≥ or <50% at first-line docetaxel chemotherapy. PSA reduction ≥50% at first-line chemotherapy correlated with superior OS at docetaxel rechallenge (P = 0.03).



At a median (range) follow-up of 26.4 (9.8–89.8) months after the first administration of docetaxel, 24 out of 44 (55%) patients had died. The median (95% CI) OS was 32.2 (26.0–38.5) months after initiation of first-line chemotherapy and 21.8 (19.9–23.7) months after initiation of docetaxel rechallenge. The median (95% CI) PSA-PFS was 5.9 (3.5–6.8) months at docetaxel rechallenge. At first-line docetaxel chemotherapy, 36 out of 44 (82%) patients achieved a reduction in PSA level of ≥50%. At docetaxel rechallenge, 10 out of 36 (28%) patients responded with a reduction of ≥50% for a second time.

Analysing the influence of PSA response at first-line chemotherapy on oncological outcome at docetaxel rechallenge, only a reduction in PSA level ≥50% correlated significantly with prolonged PSA-PFS and OS (Table 2). PSA-PFS at docetaxel rechallenge was 5.8 months in patients with a reduction in PSA level of ≥50% at first-line chemotherapy vs 4.5 months in patients with a PSA level reduction of <50% ($P = 0.01$). The corresponding Kaplan–Meier curves are shown in Fig. 1.

Patients with a reduction in PSA level of ≥50% at first-line chemotherapy achieved a median OS time of 22.1 months after initiation of docetaxel rechallenge compared with 7.2 months in patients with a reduction of <50% ($P = 0.03$). The corresponding Kaplan–Meier curves are shown in Fig. 2.

A reduction in PSA level of ≥30% at first-line chemotherapy as well as PSA progression during first-line chemotherapy correlated with PSA-PFS ($P = 0.03$; respectively) but not with OS after initiation of docetaxel rechallenge ($P = 0.13$ and $P = 0.11$, respectively).

DISCUSSION

Several treatment options are currently available for patients with tumour

progression after first-line chemotherapy with docetaxel. The approval of abiraterone acetate and cabazitaxel in 2011 by the US Food and Drug Administration and the European Medical Agency, has meant that two new treatment options in addition to docetaxel rechallenge are now available. Abiraterone is a selective inhibitor of androgen biosynthesis that potently blocks cytochrome P450 c17 (CYP17), a critical enzyme in testosterone synthesis, thereby inhibiting androgen synthesis in the adrenal glands, testes and within the prostate tumour. In a double-blinded randomized phase III trial (COU-AA-301) treatment with abiraterone acetate, a prodrug of abiraterone, plus prednisone improved median OS by 3.9 months compared with placebo plus prednisone [14]. Cabazitaxel is a novel tubulin-binding taxane with anti-tumour activity in docetaxel-resistant cells. In an open-label randomized phase III trial (the TROPIC trial) treatment with cabazitaxel plus prednisone showed a median OS benefit of 2.4 months compared with treatment with mitoxantrone plus prednisone [15].

As a third treatment option, docetaxel rechallenge has been proposed by several authors [5–12] for patients with mCRPC who have experienced disease progression after first-line chemotherapy with docetaxel. In 2010, Di Lorenzo *et al.* [6] published a prospective phase II trial with 45 patients who were treated with 3-weekly docetaxel rechallenge after first-line chemotherapy with docetaxel. The authors defined the initial PSA response at first-line chemotherapy as the main eligibility criterion for docetaxel rechallenge. Patients who responded with a reduction in PSA level of <1 ng/mL or ≥50% at first-line chemotherapy in combination with disease progression after a chemotherapy-free interval of at least 5 months were included in the study. Consistent with the present results, 24.5% of patients with mCRPC treated with docetaxel rechallenge responded with a reduction in PSA level of ≥50% for a second time and the median PSA-PFS was 5 months. Notably, Di Lorenzo *et al.* [6] reported a median OS rate of 13 months, which is 9 months shorter compared with our results. Side effects were moderate, with the main haematological grade 3–4 toxicities being neutropenia in 24.5%, thrombocytopenia in 11.1% and anemia in 6.7% of patients. The main non-haematological grade 3–4 toxicities were nausea/vomiting and hypertension in 6.6% of patients, respectively. The authors concluded that docetaxel rechallenge preserved anti-tumour activity and was well tolerated in a selected population of pretreated patients with mCRPC.

The activity of docetaxel rechallenge has also been demonstrated in a controlled trial, which was presented at the annual congress of the European Society of Medical Oncology in 2011. Oudard *et al.* [12] reported the results of a retrospective study comparing docetaxel rechallenge with a non-taxane based regimen. Out of 270 patients with mCRPC who responded well to first-line docetaxel chemotherapy (with a decrease in PSA level of ≥50% and/ or objective clinical response), 223 patients were treated with rechallenge and 47 patients were treated with a non-taxane based regimen (mainly mitoxantrone, 40%). In their study, the median OS was 18.2 months with docetaxel rechallenge vs 16.8 months with a non-taxane based therapy, which was statistically nonsignificant. However, a reduction in PSA level of ≥50% was more frequent with rechallenge (40.4%) than with a non-taxane based regimen (10.6%, $P < 0.001$). Clinical improvement (i.e. improved performance status and/or pain relief and/or reduced analgesic consumption) and stable disease were more frequently reported with rechallenge than with non-taxane based therapy.

Initial tumour response at first-line chemotherapy with docetaxel has frequently been suggested as an eligibility criterion for docetaxel rechallenge [5–10]. Nevertheless, specific criteria for docetaxel rechallenge have not yet been defined. In the present study, we analysed the activity of docetaxel rechallenge according to PSA response at first-line chemotherapy. As a result, we confirmed that anti-tumour activity was preserved at docetaxel rechallenge with one quarter of all patients responding for a second time with a reduction in PSA level of ≥50% in the rechallenge setting. On analysis of different PSA response criteria, only a relative reduction in PSA level of ≥50% at first-line chemotherapy correlated significantly with prolonged PSA-PFS (5.8 vs. 4.5 months; $P = 0.01$) and OS (22.1 vs. 7.2 months; $P = 0.03$) at rechallenge. An absolute reduction in PSA level of <1 ng/mL at first-line chemotherapy, which was suggested by Di Lorenzo *et al.* [6] as an eligibility criterion for rechallenge, neither correlated with PSA-PFS ($P = 0.53$) nor with OS ($P = 0.94$) at docetaxel rechallenge in the present cohort. An absolute PSA reduction <4 ng/mL at first-line chemotherapy, which was listed under inclusion criteria for subsequent docetaxel therapy in a study by Beer *et al.* [9], also did not correlate with efficacy at rechallenge (PSA-PFS $P = 0.71$; OS $P = 0.81$). In summary, relative PSA-reduction in contrast to absolute PSA-reduction at first-line of docetaxel rechallenge chemotherapy correlated with activity in the present study.

Similarly to the present study, Loriot *et al.* [8] reported retrospective results of a single center experience with docetaxel rechallenge. In a cohort of 39 patients with mCRPC, they identified an interval from the last cycle of docetaxel-based chemotherapy to progression as a clinical variable associated with the efficacy of docetaxel rechallenge. If PSA levels progressed <3 months after the last cycle of first-line docetaxel, patients treated with docetaxel rechallenge had significantly worse PSA-PFS ($P = 0.04$) and OS ($P = 0.04$). In the present study, we could not confirm the association of time to progression after first-line chemotherapy and efficacy at rechallenge. Nevertheless, we observed an association of PSA progression during first-line chemotherapy with worse PSA-PFS at rechallenge ($P = 0.03$) indicating the presence or development of docetaxel resistance. Discrepancies may result from differences of applied chemotherapy regimens in both study populations. The trial by Loriot *et al.* [8] comprised a mixed population of patients who were treated with a combination therapy of docetaxel and estramustine (26% at first-line chemotherapy and 40% at rechallenge) or with docetaxel alone, whereas in the present study, docetaxel was the only cytotoxic agent applied in both lines of chemotherapy. Furthermore, the exact dose regimen of docetaxel was not reported in their trial and may have further contributed to different results.

Caffo *et al.* [11] retrospectively reported on 46 patients with mCPRC undergoing multiple lines (92 rechallenges, in total) of docetaxel rechallenge. Of these, 27 patients underwent at least a second rechallenge. Similarly to the present results, median OS

was 32 months from the start of first-line therapy. On multivariate analysis, slope-log PSA during the previous treatment holiday, the time from the previous docetaxel line and the biochemical response at the previous line correlated with the response at rechallenge. These factors were used to obtain a predictive score by assigning one point to each when it was present before the start of the rechallenge. The rechallenges with baseline scores of 3, 2 and 0–1 led to biochemical response rates of 100%, 86% and 32.3%, respectively. A major limitation of the study by Caffo *et al.* is that their results were based on a mixed patient population, with mCRPC patients receiving weekly docetaxel, 3-weekly docetaxel monotherapy or 3-weekly docetaxel in combination with estramustine at first-line and subsequent rechallenges.

Currently, a standard practice of first-line docetaxel chemotherapy is continuous application until tumour progression or unacceptible toxicity. According to the TAX-327-study, continuous application often is further limited to a predefined dose, e.g. 10 cycles of 3-weekly docetaxel, so as to avoid accumulating toxicity [2,16]. In this concept, a reduction in PSA level of ≥50% might present a rational indication for docetaxel rechallenge, indicating preserved anti-tumour activity and favourable outcome in patients who achieve a pre-defined chemotherapy dose without developing tumour progression or unacceptable toxicity.

In contrast to continuous chemotherapy, intermittent chemotherapy is a systematic approach to providing breaks in treatment schedules for patients who experience an initial response to chemotherapy to avoid or delay the development of progressive toxicity [16]. In patients with mCRPC treated with intermittent chemotherapy, a PSA level reduction of ≥50% has been used as a response criterion indicating a break of chemotherapy and simultaneousliy qualifying for a subsequent line of docetaxel chemotherapy. Mountzios *et al.* [5] published a study evaluating intermittent docetaxel chemotherapy in 35 chemo-naïve patients with mCRPC . All patients were treated with a reduced dose regimen of 45 mg/m^2 docetaxel chemotherapy every 2 weeks until they had reached a reduction in PSA level of ≥50% from baseline. Chemotherapy was resumed at a 25% increase in PSA level from the nadir level or in cases of documented disease progression. Out of 35 patients, 18 (51.42%) patients entered a first chemotherapy-free interval after a median (range) of 6 (2–12) infusions. The median (range) interval ‚off chemotherapy' was 4.5 (1–16) months between the first two lines of docetaxel. The median (95% CI) lengths of time before treatment failure were 8.1 (5.1–12.2) months for the entire cohort and 12.2 (8.3–25) months for patients who had entered the first chemotherapy-free interval.

The question of whether continuous therapy offers an advantage over intermittent therapy in terms of balancing disease control and OS with treatment-related toxicities remains unanswered in mCRPC [16]. Nevertheless, in both regimens a reduction in PSA level of ≥50% may be a useful marker qualifying for a subsequent line of docetaxel chemotherapy.

With new emerging second-line therapy regimens with a survival benefit, such as abiraterone acetate and cabazitaxel, the question remains whether docetaxel rechallenge will play a role in the treatment of mCRPC. In the absence of a prospective randomized controlled trial, a survival benefit in patients with mCRPC treated with docetaxel rechallenge has not yet been demonstrated. Nevertheless, docetaxel rechallenge has shown preserved anti-tumour activity in one prospective and several retrospective trials [6–9,11,12] and, therefore, presents a rational treatment option in patients with good response and tolerability to first-line chemotherapy with docetaxel. Rather than being a competitive alternative, docetaxel rechallenge may be seen as an additional option complementing a treatment sequence with abiraterone acetate and cabazitaxel in selected patients. A PSA reduction of ≥50% at first-line chemotherapy may be of help to select patients who eventually benefit from docetaxel rechallenge before switching to another chemotherapy with cabazitaxel.

One limitation of the present study is its retrospective design. Furthermore, the small sample size and the long accrual time limit the significance of the presented data. With a sample size of 44 patients, the power of the study may have been too low to detect statistically significant results for other biomarkers such as a reduction in PSA level of ≥30% or PSA progression at first-line chemotherapy, which both showed a trend for a correlation with OS after docetaxel rechallenge ($P = 0.13$ and $P = 0.11$, respectively). PSA response criteria at first-line chemotherapy as an indication for docetaxel rechallenge should, therefore, be validated prospectively in a larger cohort.

Nevertheless, the present study is the first to analyse systematically the activity of docetaxel rechallenge according to PSA response at first-line chemotherapy in patients with mCRPC who were all treated with the same 3-weekly docetaxel regimen at both first-line and rechallenge which is, with the exception of docetaxel chemotherapy in combination with estramustine, the only dose regimen of docetaxel with a proven survival benefit [1,2,4]. Previous studies on docetaxel rechallenge were based on mixed cohorts of patients with mCRPC that included patients who were treated with a reduced 3-weekly docetaxel dosage at first-line chemotherapy [6], with a weekly regimen at both docetaxel lines [7,11], with an unspecified docetaxel dose regimen in combination with other agents at both lines [8] or a combination with other active agents [7,11,12].

In conclusion, the present results confirm the general hypothesis that patients with good tumour response at first-line chemotherapy with docetaxel show preserved anti-tumour activity at rechallenge. In this single institution experience, a reduction in PSA level of ≥50% at first-line chemotherapy with docetaxel correlated with superior PSA-PFS and OS in the rechallenge setting and might, therefore, present a rational indication for docetaxel rechallenge. Nevertheless, these retrospective data need prospective confirmation.

CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Petrylak DP, Tangen CM, Hussain MHA *et al*.** Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004; **351**: 1513–20

2 **Tannock IF, de Wit R, Berry WR *et al*.**

Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; **351**: 1502–12

3 **Berthold DR, Pond GR, Roessner M *et al*.** Treatment of hormone-refractory prostate cancer with docetaxel or mitoxantrone: relationships between prostate-specific antigen, pain, and quality of life response and survival in the TAX-327 study. *Clin Cancer Res* 2008; **14**: 2763–7

4 **Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF.** Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol* 2008; **26**: 242–5

5 **Mountzios I, Bournakis E, Efstathiou E *et al*.** Intermittent docetaxel chemotherapy in patients with castrate-resistant prostate cancer. *Urology* 2011; **77**: 682–7

6 **Di Lorenzo G, Buonerba C, Faiella A *et al*.** Phase II study of docetaxel re-treatment in docetaxel-pretreated castration-resistant prostate cancer. *BJU Int* 2011; **107**: 234–9

7 **Eymard J-C, Oudard S, Gravis G *et al*.** Docetaxel reintroduction in patients with metastatic castration-resistant docetaxel-sensitive prostate cancer: a retrospective multicentre study. *BJU Int* 2010; **106**: 974–8

8 **Loriot Y, Massard C, Gross-Goupil M *et al*.** The interval from the last cycle of docetaxel-based chemotherapy to progression is associated with the efficacy of subsequent docetaxel in patients with prostate cancer. *Eur J Cancer* 2010; **46**: 1770–2

9 **Beer TM, Garzotto M, Henner WD, Eilers KM, Wersinger EM.** Intermittent chemotherapy in metastatic androgen-independent prostate cancer. *Br J Cancer* 2003; **89**: 968–70

10 **Schallier D, Decoster L, Braeckman J, Fontaine C, Degrève J.** Docetaxel in the Treatment of Metastatic Castration-resistant Prostate Cancer (mCRPC): an Observational Study in a Single Institution. *Anticancer Res* 2012; **32**: 633–41

11 **Caffo O, Pappagallo G, Brugnara S *et al*.** Multiple rechallenges for castration-resistant prostate cancer patients responding to first-line docetaxel: assessment of clinical outcomes and predictive factors. *Urology* 2012; **79**: 644–9

12 **Oudard S, Kramer G, Creppy L *et al*.** Management of metastatic castration-resistant prostate cancer (mCRPC) After an initial good response to first-line docetaxel (D) – a retrospective study on 270 patients (pts). *Eur J Cancer* 2011; **47** (Suppl. 1): S499–S500. 7049 [abstract]

13 **Scher HI, Halabi S, Tannock I *et al*.** Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008; **1**: 1148–59

14 **de Bono JS, Logothetis CJ, Molina A *et al*.** Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011; **26**: 1995–2005

15 **de Bono JS, Oudard S, Ozguroglu M *et al*.** Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010; **376**: 1147–54

16 **Lin AM, Ryan CJ, Small EJ.** Intermittent chemotherapy for metastatic hormone refractory prostate cancer. *Crit Rev Oncol Hematol* 2007; **61**: 243–54

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Abbreviations: **mCRPC**, metastatic castration-resistant prostate cancer; **PSA-PFS**, PSA-progression-free survival; **OS**, overall survival.