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Docetaxel rechallenge after an initial good response in patients with metastatic castration-resistant prostate cancer

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Objective

To evaluate the benefit of docetaxel rechallenge in patients with metastatic castration-resistant prostate cancer (mCRPC) relapsing after an initial good response to first-line docetaxel.

Patients and Methods

We retrospectively reviewed the records of consecutive patients with mCRPC with a good response to first-line docetaxel [serum prostate specific antigen (PSA) decrease ≥50%; no clinical/radiological progression]. We analysed the impact of management at relapse (docetaxel rechallenge or non-taxane-based therapy) on PSA response, symptomatic response (performance status/pain/analgesic consumption), and overall survival (OS). We used multivariate stepwise logistic regression to analyse potential predictors of a favourable outcome.

Results

We identified 270 good responders to first-line docetaxel. The median progression-free interval (PFI) was 6 months from the last docetaxel dose. At relapse, 223 patients were rechallenged with docetaxel (82.5%) and 47 received non-taxane-based therapy. There was no significant difference in median OS {18.2 [95% confidence interval (CI) 16.1–22.00] and 16.8 [95%CI 13.4–21.5] months, respectively, $P = 0.35$}. However, good PSA response and symptom relief/stable disease were more frequent on docetaxel rechallenge (40.4% vs 10.6%, $P < 0.001$ for PSA). A PFI of >6 months and added estramustine predicted a good PSA response and symptomatic response on docetaxel rechallenge but only a PFI of >6 months predicted longer OS. Haemoglobin (<13 g/dL) and pain were associated with reduced OS. Docetaxel rechallenge increased the incidence of grade ≥3 sensory neuropathy, nail disorders and asthenia/fatigue.

Conclusions

Docetaxel rechallenge is a management option for responders to docetaxel with a PFI of >6 months, but did not prolong survival. Potential benefits should be weighed against the risk of cumulative toxicity.

Keywords

prostate cancer, castration-resistant, chemotherapy, docetaxel

Introduction

Docetaxel was the first cytotoxic agent to show a survival benefit, as well as pain alleviation and improved quality of life, in patients with metastatic castration-resistant prostate cancer (mCRPC) [1–3]. In the pivotal TAX 327 phase III trial in 1006 patients with mCRPC, the 3-year survival rate was 18.6% for docetaxel (75 mg/m^2 every 3 weeks) plus prednisone compared with 13.5% for mitoxantrone plus prednisone, despite one in five patients crossing over to docetaxel at progression [3,4]. In a phase II prospective randomised study evaluating the impact of cross-over on outcomes, patients crossing over from mitoxantrone to a 3-weekly docetaxel regimen had considerably longer overall survival (OS) than those receiving no further or a non-docetaxel-based chemotherapy [31.7 months (95% CI 26.4–36.9) vs 7.5 months

 | doi:10.1111/bju.12845
Published by John Wiley & Sons Ltd. www.bjui.org

(95% CI 4.9–10.1)] [5]. Considering these results, a 3-weekly docetaxel regimen became the standard of care for symptomatic patients with mCRPC and asymptomatic patients with progressive disease [6–8].

A variety of new therapeutic agents have recently been shown to increase OS in patients with mCRPC. They include the cytotoxic agent cabazitaxel, the hormone-blocking agents, enzalutamide and abiraterone acetate, a radionucleotide (radium-223), and sipuleucel-T immunotherapy [9–13]. However, until 2010, patients with mCRPC in the post-docetaxel setting could only benefit from palliative mitoxantrone plus prednisone therapy [14], although several small retrospective studies had reported PSA response rates ranging from 25% to 77% on docetaxel rechallenge after an initial good response to first-line therapy with the drug [15–25]. The aim of the present large-scale retrospective European study was: (i) to evaluate the potential benefit of reintroducing a taxane-based rather than a non-taxane based chemotherapy in patients with mCRPC relapsing after an initial good response to first-line docetaxel, (ii) to identify potential predictors of favourable outcomes (biochemical and clinical responses, OS) on docetaxel rechallenge.

Patients and Methods

The records of consecutive patients with mCRPC with a good PSA response to first-line docetaxel were collated in 17 centres in seven European countries (September 2009 to January 2011). A good response was defined as a ≥50% decline in PSA according to the guidelines of the Prostate Cancer Working Group 2 (PCWG2) [26] with no signs of radiological or clinical progression. For inclusion in this retrospective study, patients must not have had progressive disease at any time during docetaxel therapy. We collected data on patient demographics, prostate cancer history and management at progression after first-line docetaxel (number and type of therapy lines). The study was approved by the Institutional Review Boards of the participating centres.

Outcome measures included PSA response, clinical outcome, progression-free interval (PFI) since the last docetaxel dose (progression being defined as per PCWG2 guidelines [26]), OS (calculated from first day of rechallenge to death), and grade 3–4 toxicities. Clinical outcome categories were: symptom relief [improved Eastern Cooperative Oncology Group (ECOG) performance status (PS) and/or pain relief and/or reduced analgesic consumption], stable disease (stable PS and/or stable pain/analgesic consumption) or no response (worse PS and/or worse pain/higher analgesic consumption).

Continuous variables were expressed as medians (ranges) and categorical variables as frequencies (percentages). OS data were censored at the last date the patient was known to be alive at the study end date. OS data were analysed by the Kaplan–Meier method and compared using the log-rank test.

Potential predictors of biochemical and clinical outcomes after the first docetaxel rechallenge were analysed by a multivariate stepwise logistic regression procedure in patients in whom all selected variables were documented. The variables comprised patient characteristics [age at initial diagnosis, prior curative therapy, metastatic sites (bone, lymph node, visceral)], type of progression (PSA, clinical, bone scan), pain, ECOG PS, number of prior hormonal manipulations, number of docetaxel cycles before rechallenge, added estramustine, haemoglobin (<13 or ≥13 g/dL), alkaline phosphatase, Gleason score, PSA value (Log10), PSA doubling time, and PFI from last first-line docetaxel dose. Variables with a $P \leq 0.05$ were kept in the final multivariate model. A Cox proportional hazard analysis was performed to identify potential predictors of OS. Odds ratios (ORs) or hazard ratios (HRs) with 95% CIs were calculated. SAS® (version 9.2) software was used.

Results

Patient Characteristics

Overall, 270 consecutive patients showed a good PSA response to first-line docetaxel therapy. Throughout their PFI, they received maintenance LHRH agonist therapy only. At progression, 223 patients (82.6%) were rechallenged with docetaxel. The remaining 47 patients (17.4%) received non-taxane based second-line therapy [mitoxantrone/prednisone (alone, 18; combined with estramustine, one), vinorelbine (alone, six, combined with estramustine, two), platinum-based therapy (eight), diethylstilboestrol (seven), cyclophosphamide (four), capecitabine (one)]. Patients' clinical characteristics at progression were relatively well balanced between the two regimens with the exception of clinical progression/presence of pain at treatment initiation and combination with estramustine during first-line docetaxel therapy, which were more common within the non-taxane arm (Table 1).

Activity of Therapies Prescribed after First-line Docetaxel

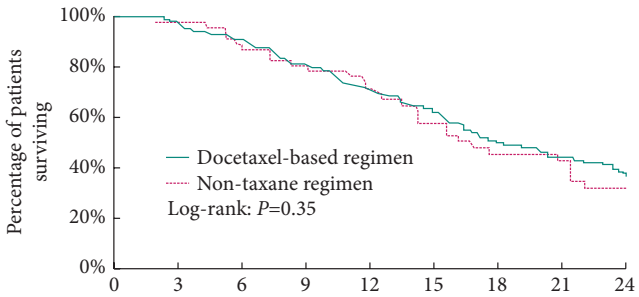
The median OS (calculated from the first day of treatment for relapse) was not significantly different between docetaxel rechallenge (18.2 months, 95% CI 16.1–22.0) and second-line non-taxane therapy (16.8 months, 95% CI 13.4–21.5; $P = 0.35$) (Fig. 1). However, a good PSA response (≥50% decrease from baseline) was significantly more common in docetaxel-rechallenged patients than patients receiving second-line non-taxane therapy (40.0% vs 11.0%, $P < 0.001$). Similarly, there was a higher rate of stable disease (66% vs 49%) and a lower rate of non-responders (18% vs 32%) in patients rechallenged with docetaxel (Fig. 2).

The 223 patients rechallenged with docetaxel had received a median of eight cycles of first-line docetaxel therapy. The

Table 1 Clinical characteristics of patients with mCRPC progressing after a good PSA response to first-line docetaxel.

	Overall	Docetaxel rechallenge	Second-line non-taxane therapy	P
Patients, *N*	270	223	47	
Characteristics at diagnosis				
Median (range) age, years	62 (44–88)	63 (44–88)	62 (51–83)	0.50
Gleason score, %				
8–10	54.2	54.7	52.3	0.87
≤7	45.8	45.3	47.7	
Clinical stage, %				
T1/T2, N0, M0	11.5	9.7	11.2	0.41
T3/T4, N0, M0	36.3	38.5	25.8	
All T, N1, M0	13.5	22.6	15.1	
M1	37.4	36.5	41.9	
Prior curative local therapy, %	55.9	54.3	63.8	0.26
Characteristics at first-line docetaxel				
Median (range) age, years	68 (49–90)	68 (49–90)	66 (52–87)	0.36
Aged ≥70 years, %	43.7	44.4	40.4	0.63
Pain, %	37.4	34.5	51.1	0.05
ECOG PS, %				
0–1	96.5	96.7	95.5	0.65
≥2	3.5	3.3	4.5	
Median (range) PSA, ng/mL	78.8 (1–6120)	78.8 (1–6120)	81.3 (5–1930)	0.63
Metastatic site, %				
Lymph node only	24.1	20.6	40.4	
Bone (without visceral)	79.6	78	87.2	0.22
Visceral	5.2	5.4	4.3	
First-line docetaxel therapy				
Median (range) number of cycles	8 (3–28)	8 (3–28)	8 (3–10)	0.89
Type of administration %				
Monotherapy	76.7	80.3	59.6	
Combined with estramustine	17.4	14.8	29.8	<0.05
Other combination	5.6	4.9	10.6	
Characteristics at progression				
Median (range) PFI, months	6.0 (1–54)	6.0 (1–54)	5.7 (2–39)	0.47
Type of progression, %				
PSA	90.0	88.8	95.7	0.19
Clinical	27.4	23.3	46.8	<0.05
Bone scan	24.4	23.3	29.8	0.35
Measurable disease	11.9	10.3	19.1	0.13
Pain, %	48.5	45.7	61.7	0.054
ECOG PS 0–1, %	92.7	92.7	93.0	1.00
Median (range) PSA level, ng/mL	84.0 (1–3261)	82.4 (1–3261)	99.7 (5–3039)	0.56
Median (range) follow-up since start of first docetaxel cycle, months	26.1 (5–82)	25.7 (5–82)	26.8 (11–82)	0.31

Fig. 1 OS after a docetaxel rechallenge and after second-line non-taxane based therapy (calculated from first day of treatment after relapse).



Number at risk:

Docetaxel-based	223	207	179	150	120	94	72	57	43
Non-taxane	47	46	41	37	32	25	18	16	11

number of prior docetaxel cycles received (>8 vs <8 cycles) did not influence outcomes with subsequent docetaxel rechallenge, either in terms of PSA response (no decline vs decline; 33.8% vs 34.8%, $P = 0.886$), symptom relief (no vs yes; 34.8% vs 31.6%, $P = 0.851$) or OS (HR 0.856, 95% CI 0.588–1.245, $P = 0.416$).

Impact of PFI on Response to First Docetaxel Rechallenge

The median (range) PFI from the last first-line docetaxel dose was 6 (1–54) months. There was a strong relationship between PFI and outcome on docetaxel rechallenge. Patients progressing at >6 months after the last docetaxel dose had greater PSA response rates (54.9%) and symptom relief (25.7%), and the longest median OS (20.4 months) (Table 2).

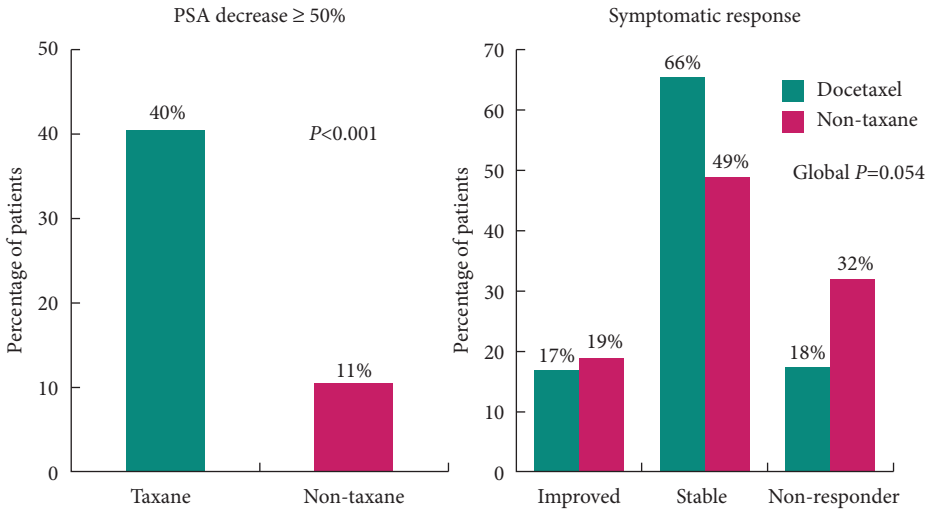


Fig. 2 Good PSA response rates and symptomatic response rates after one to three consecutive docetaxel rechallenges and after second-line non-taxane based therapy (improved = improved performance status and/or pain relief and/or reduced analgesic consumption).

Table 2 Efficacy of first docetaxel rechallenge as a function of PFI since last docetaxel dose.

	PFI from last docetaxel dose		
	≤3 months (*n* = 38)	3–6 months (*n* = 72)	>6 months (*n* = 113)
Good PSA responders, %	10.5	33.3	54.9
Clinical outcome, %			
Symptom relief	5.3	9.7	25.7
Stable disease	60.5	72.2	62.8
Non responders	34.2	18.1	11.5
Median (95% CI) OS from first docetaxel rechallenge, months	15.7 (11.8–20.3)	17.1 (13.3–24.6)	20.4 (16.8–25.7)

Good PSA responder: ≥ 50% decrease from baseline.

Activity and Safety of Multiple Docetaxel Rechallenges

Of the initial 270 good responders to docetaxel, 223 (82.6%) were rechallenged at least once with docetaxel and, of these 223 patients, 87 were rechallenged at least twice and 38 three times. Of the 47 patients on non-taxane second-line therapy, most received non-taxane third-line (17 patients) and fourth-line (seven) therapy. Patient characteristics at each challenge, as well as the type, activity and safety of docetaxel rechallenge are given in Table 3. The PFI since the last docetaxel dose, as well as PSA response rates and symptom relief, tended to decrease with each challenge, whereas the incidence of grade ≥3 sensory neuropathy, nail disorders and asthenia/fatigue tended to increase.

Predictors of PSA Response, Symptomatic Response and OS

Potential predictors of a good PSA response, and longer OS on a first docetaxel rechallenge were analysed by multivariate analysis (Table 4). A PFI of >6 months and added estramustine tripled the chances of a good PSA response (OR 3.82 and 2.85, respectively) and were also strong predictors of symptom relief (OR 4.17 and 4.21, respectively). Clinical progression (OR 5.01) and pain (OR 3.53) at treatment initiation, lack of prior local curative therapy (OR 3.05) and, to a lesser extent, high baseline serum PSA values (OR 1.82) also decreased the chances of symptom relief with docetaxel rechallenge. The area under the receiver operating characteristic curve was 0.68 for the PSA response model and 0.889 for the symptomatic response model (Fig. 3A,B). A PFI of >6 months was associated with significantly longer survival (HR 0.55), whereas pain (HR 1.90), haemoglobin <13 g/dL (HR 1.79) and high pre-challenge serum PSA values (HR 1.87) predicted poorer OS.

Discussion

In this retrospective study of 270 patients with mCRPC progressing at >6 months after the last first-line docetaxel dose, docetaxel rechallenge was associated with a higher frequency of good PSA responses and symptomatic responses than observed on second-line non-taxane therapy. However, there was no significant impact on OS.

PFI duration after the last first-line docetaxel dose predicted response to docetaxel rechallenge. Benefits in terms of PSA

Table 3 Patient characteristics at rechallenge and docetaxel efficacy and toxicity.

	First-line docetaxel	Rechallenge with docetaxel		
		First	Second	Third
Patients, *N*	270	223	87	38
Characteristics at first-line docetaxel				
Median (range) PFI, months	NR	6 (1–54)	5 (1–32)	4 (0–12)
Pain, %	37.4	45.7	44.2	39.5
ECOG PS 0–1, %	96.5	92.7	92.8	80.6
Median (range) PSA level, ng/mL	79 (1–6120)	82 (1–3261)	107 (1–3630)	166 (10–1012)
Types of docetaxel therapy				
Median (range) number of cycles	8 [3–28]	6 [1–24]	6 [1–16]	6 [3–16]
Docetaxel alone, %	77.1	83.4	72.1	65.8
Added estramustine, %	17.4	15.2	27.9	31.6
Other combination, %	5.6	1.3	0	2.6
3-weekly schedule, %	65.2	60.8	65.5	68.4
Weekly schedule, %	34.8	39.2	34.5	31.6
Activity of docetaxel therapy, %				
PSA level decrease of ≥50%*	96	40	39	26
Symptom relief	28	17	9	16
Stable disease	70	66	64	61
Non responder	3	18	26	24
Grade ≥3 toxicity, %				
Asthenia/fatigue	6.7	4.9	4.6	10.5
Nail disorders	6.3	3.1	4.6	7.9
Sensory neuropathy	0.4	2.2	9.2	7.9
Febrile neutropenia	4.8	3.6	5.7	0
Neutropenia	4.1	2.2	2.3	0
Anaemia	3.3	4.5	11.5	0
Thrombocytopenia	0	1.3	0	0
Dyspnoea	0	3.1	5.7	2.6
Nausea/vomiting	1.5	0.4	1.1	0
Diarrhoea	1.5	0	0	0
Anorexia	0.7	1.8	1.1	0
Thrombosis	1.5	0	0	0
Peripheral oedema	0	0.4	0	0
Rash/desquamation	0	0.4	0	0
Prophylactic G-CSF, %	0.9	1.8	2.3	2.6

**Good PSA responder: ≥ 50% decrease from baseline; NR: not relevant.*

response, clinical outcomes and OS were greater for a PFI of >6 months than of 3–6 months. For a PFI of <3 months, there was no benefit at all, thereby confirming results from two earlier studies: (i) In a study of 39 patients with mCRPC rechallenged with docetaxel, those progressing at ≥3 months after the last docetaxel cycle had a longer median progression-free survival (PFS, 6.3 vs 3.4 months, $P = 0.04$) and median OS (19.4 vs 12.8 months) than those progressing within 3 months [21], (ii) In another study of 46 patients with mCRPC rechallenged with docetaxel, the time slope of the log PSA decline and the interval from and PSA response to the previous cycle were predictors of response, with good responders having a median PFI of 6 months [23]. A positive response to rechallenge in patients with a PFI of >6 months suggests that the tumour cells are still docetaxel-sensitive whereas patients relapsing earlier have probably developed resistance mechanisms due to mutations (e.g. β-tubulin), altered protein expression (membrane-bound efflux proteins, microtubule-associated protein, βIII-tubulin), defective apoptotic pathways, or hypoxia [27].

Longer PFIs have been linked with better responses to rechallenge with the same drug in many cancers (e.g. breast cancer, colorectal cancer, advanced-stage gastrointestinal stromal tumours, chronic myelocytic leukaemia) [28,29], with a PFI of 6 months being a common threshold for predicting response to rechallenge. Patients with ovarian cancer with a PFI of >6 months after first-line platinum-based therapy ('platinum-sensitive') were given paclitaxel plus platinum, whereas patients relapsing ≤6 months ('platinum-resistant') received other cytotoxic therapy [30]. Patients with metastatic RCC progressing after treatment with the tyrosine kinase inhibitor sunitinib had a significantly longer median PFS if their PFI exceeded 6 months (16.5 vs 6 months, $P = 0.03$) [31].

The benefits of a docetaxel rechallenge have to be weighed against the risk of cumulative toxicity and impaired quality of life. In the present study, there was an increased incidence of grade ≥3 sensory neuropathy (up to 9.2%), nail disorders (up to 7.9%) and asthenia/fatigue (up to 10.5%) on docetaxel rechallenge. However, multiple docetaxel rechallenges did not

Table 4 Potential predictors of outcome after first docetaxel rechallenge.

	n/N (%)	OR or HR (95% CI)	*P*
Good PSA response			
PFI (months)			
≤6	28/110 (25.4)	1 (reference)	
>6	62/113 (54.9)	3.82 (2.13–6.84)	<0.001
Added estramustine			
no	70/189 (37.0)	1 (reference)	
yes	20/34 (58.8)	2.85 (1.29–6.30)	0.009
Symptomatic response			
PFI (months)			
≤6	9/110 (8.2)	1 (reference)	
>6	29/113 (25.7)	4.17 (1.64–10.59)	<0.001
Added estramustine			
no	28/189 (14.8)	1 (reference)	
yes	10/34 (29.4)	4.21 (1.43–12.36)	<0.001
Clinical progression at therapy initiation			
no	15/171 (8.8)	1 (reference)	
yes	23/52 (44.2)	5.01 (2.04–12.3)	<0.001
Pain at treatment initiation			
no	7/121 (5.8)	1 (reference)	
yes	31/102 (30.4)	3.53 (1.28–9.73)	0.014
Prior local curative therapy			
yes	12/133 (9.0)	1 (reference)	
no	27/102 (26.5)	3.05 (1.21–7.65)	0.018
High PSA level at treatment initiation (Log 10)	–	1.82 (0.93–3.53)	0.079
Overall survival			
PFI (months)			
≤6		1 (reference)	
>6		0.55 (0.37–0.81)	0.002
Pain at treatment initiation			
No		1 (reference)	
Yes		1.90 (1.29–2.79)	0.001
Haemoglobin (g/dL)			
>13		1 (reference)	
≤13		1.79 (1.16–2.75)	0.009
High PSA level at treatment initiation (Log 10)		1.87 (1.39–2.52)	<0.001

OR, odds ratio for good PSA response (≥50% decrease from baseline) and for clinical improvement; HR, hazard ratio for overall survival; PFI, progression-free interval from last docetaxel dose.

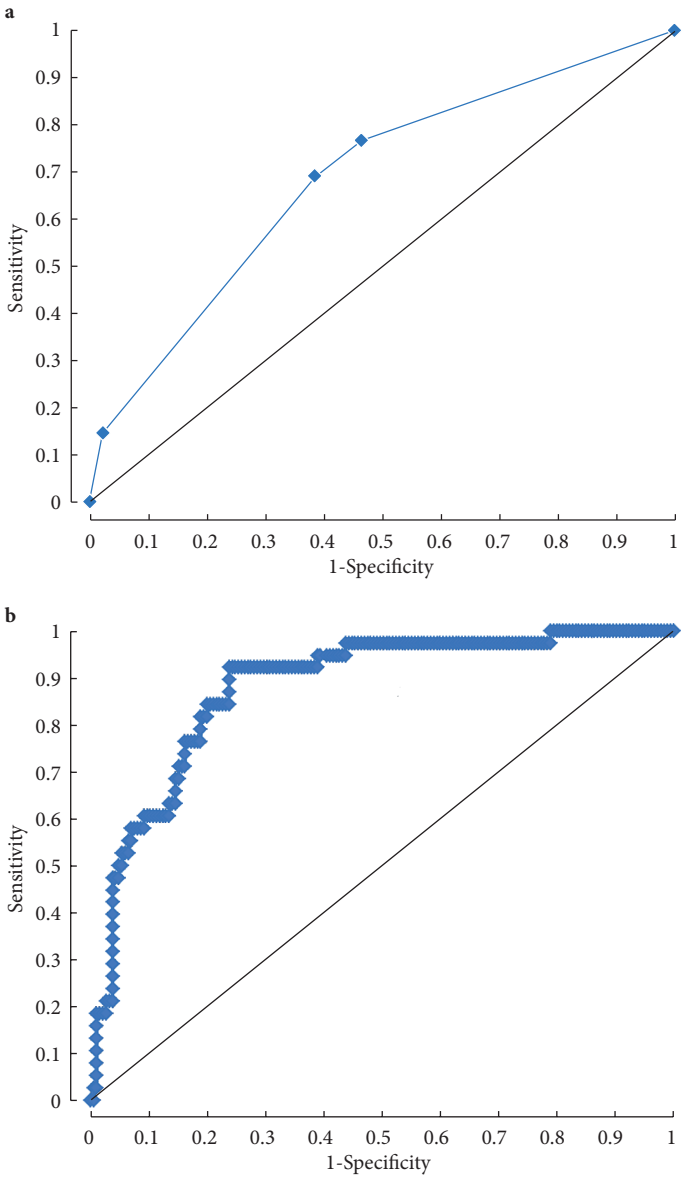
increase the risk of febrile neutropenia (0–5.7%), despite infrequent prophylactic granulocyte colony-stimulating factor (G-CSF) use (1.8–2.6%).

In patients in whom docetaxel reintroduction is unadvisable because of a PFI of <6 months or because of toxicity, the newly available treatments showing a survival benefit over placebo in patients with mCRPC progressing during or after docetaxel therapy (e.g. abiraterone, enzalutamide, and radium-223 [10–12]) may be considered. In taxane-sensitive patients with unacceptable docetaxel toxicity, a switch to the new generation taxane cabazitaxel may be an option, as this drug is associated with a low incidence of grade ≥3 sensory neuropathy and nail disorders (<1%) [9]. Cabazitaxel nevertheless carries an increased risk of febrile neutropenia (7.5%) and grade ≥3 diarrhoea (6%), although a compassionate-use programme involving 746 patients (aged ≥75 years, $N = 145$) has indicated that these side-effects can be considerably reduced by training staff in side-effect management and G-CSF use [32]. Cabazitaxel has shown a survival benefit over mitoxantrone in a post-docetaxel setting [9].

The present study, which is the largest to date to evaluate the usefulness of docetaxel rechallenge in patients with mCRPC, has some limitations. First, it is hypothesis generating only because of the biases inherent in chart reviews. Second, it was not powered to compare treatments; the taxane/non-taxane comparison is thus indicative only. Third, we excluded patients without a PSA decline but who had symptomatic improvement and who might have benefited from docetaxel rechallenge. Taxanes decrease androgen receptor (AR) nuclear translocation [33,34] and inhibit AR-transcriptional activity by inducing nuclear accumulation of the AR suppressive nuclear factor FOXO1 [33], but their beneficial effects on symptoms are not always associated with a PSA response, especially in the more advanced stages of the disease [35,36].

In conclusion, docetaxel rechallenge, although it has no survival benefit, may be a treatment option in good responders

Fig. 3 Receiver operating characteristic (ROC) curve for (**A**) PSA response model and (**B**) symptomatic response model. The area under the ROC curve was 0.68 for the PSA response model and 0.889 for the symptomatic response model.



to first-line docetaxel who relapse more than 6 months after the last docetaxel cycle. However, its benefit on symptoms has to be weighed against the increased incidence of grade ≥3 sensory neuropathy, nail disorders and asthenia. Docetaxel rechallenge reflects real-life practice in many European centres but its place in the rapidly evolving mCRPC landscape needs to be defined. With the recent results of the large randomised Chemohormonal Therapy vs Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) trial showing a median survival benefit of 13.6 months with docetaxel plus androgen-deprivation therapy (ADT) vs ADT alone in hormone-naïve metastatic prostate cancer, docetaxel is likely to be prescribed earlier, especially in case of high disease burden [37]. The place of new powerful AR-targeted agents (abiraterone, enzalutamide) also prolonging survival but to a much less extent (≈2 months) in the pre-docetaxel setting needs to be reconsidered [38,39]. Their possibly negative impact on the activity of docetaxel remains a concern. Indeed, several small retrospective studies suggest that patients progressing with these new AR-targeted agents have a reduced PSA response and OS with docetaxel [40], which does not seem to be the case with cabazitaxel, a next generation taxane developed to overcome docetaxel resistance [41,42]. In such a context, benefits of docetaxel rechallenge may not be valid anymore. The ongoing UK randomised phase II study CANTATA comparing docetaxel rechallenge vs cabazitaxel in patients with mCRPC previously treated with docetaxel might help to solve the issue.

Acknowledgements

We would like to thank Florence Mercier (Statprocess, France) for performing the statistical analyses.

Conflicts of Interest

O.C. reports grants and other from Sanofi-Aventis, grants and other from Janssen, during the conduct of the study; S.H. reports personal fees from Amgen, Sanofi, Janssen, Roche, Astellas, Bayer, outside the submitted work; G.K. reports personal fees from Association Artic, during the conduct of the study; S.O. reports grants and personal fees from Sanofi, personal fees from Bayer, Janssen, Takeda, Astellas, outside the submitted work; F.R. reports personal fees from Association Artic, during the conduct of the study; Y.L. reports grants, personal fees and non-financial support from Sanofi, during the conduct of the study; grants and personal fees from Astellas and Janssen, other from Celgene, grants from Roche, outside the submitted work; All other authors report no conflicts of interest.

References

1 **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

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

3 **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

4 **Berthold DR, Pond GR, de Wit R, Eisenberger M, Tannock IF, TAX 327 Investigators.** Survival and PSA response of patients in TAX327 study who crossed over to receive docetaxel after mitoxantrone or vice versa. *Ann Oncol* 2008; 19: 1749–53

5 **Oudard S, Banu E, Beuzeboc P et al.** Multicenter randomized phase II study of two schedules of docetaxel, estramustine and prednisone versus

mitoxantrone plus prednisone in patients with metastatic hormone-refractory prostate cancer. *J Clin Oncol* 2005; 23: 3343–51

6 **Horwich A, Hugosson J, de Reijke T et al.** Prostate cancer: ESMO Consensus Conference Guidelines 2012. *Ann Oncol* 2013; 24: 1141–62

7 **Heidenreich A, Bastian PJ, Bellmunt J et al.** EAU Guidelines on Prostate Cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol* 2014; 65: 467–79

8 **Cookson MS, Roth BJ, Dahm P et al.** Castration-resistant prostate cancer: AUA guideline 2013. *J Urol* 2013; 190: 429–38

9 **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 randomized open-label trial. *Lancet* 2010; 376: 1147–54

10 **Scher H, Fizazi K, Saad F et al.** Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012; 367: 1187–97

11 **Fizazi K, Scher H, Molina A et al.** Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomized, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2012; 13: 983–92

12 **Parker C, Nilsson S, Heinrich D et al.** Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013; 369: 213–23

13 **Kantoff PW, Higano CS, Shore ND et al.** Sipuleucel-T Immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010; 363: 411–22

14 **Tannock IF, Osoba D, Stockler MR 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: 1756–64

15 **Beer TM, Garzotto M, Henner WD, Eilers KM, Wersinger EM.** Multiple cycles of intermittent chemotherapy in metastatic androgen independent prostate cancer. *Br J Cancer* 2004; 91: 1425–7

16 **Beer TM, Ryan CW, Venner PM et al.** Intermittent chemotherapy in patients with metastatic androgen independent prostate cancer: results from ASCENT, a double-blinded, randomized comparison of high-dose calcitriol plus docetaxel with placebo plus docetaxel. *Cancer* 2008; 112: 326–30

17 **Ansari J, Hussain SA, Zarkar A, Tanguay JS, Bliss J, Glaholm J.** Docetaxel chemotherapy for metastatic hormone refractory prostate cancer as first-line palliative chemotherapy and subsequent re-treatment: Birmingham experience. *Oncol Rep* 2008; 20: 891–6

18 **Soga N, Kato M, Nishikawa K et al.** Intermittent docetaxel therapy with estramustine for hormone-refractory prostate cancer in Japanese patients. *Int J Clin Oncol* 2009; 14: 130–5

19 **Eymard JC, 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

20 **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

21 **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

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

23 **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

24 **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

25 **Heck M, Thalgott M, Retz M et al.** Rational indication for docetaxel rechallenge in metastatic castration-resistant prostate cancer. *BJU Int* 2012; 110: E630–40

26 **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; 26: 1148–59

27 **Seruga B, Ocana A, Tannock IF.** Drug resistance in metastatic castration resistant prostate cancer. *Nat Rev Clin Oncol* 2011; 8: 12–23

28 **Kuczynski EA, Sargent DJ, Grothey A, Kerbel RS.** Drug rechallenge and treatment beyond progression – implications for drug resistance. *Nat Rev Clin Oncol* 2013; 10: 571–87

29 **Toulmonde M, Madranges N, Brouste V et al.** Docetaxel rechallenge after a first response in non-resistant metastatic breast cancer: significant activity with manageable toxicity. *Breast Cancer Res Treat* 2012; 134: 325–32

30 **Parmar MK, Ledermann JA, Colombo N et al.** Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet* 2003; 361: 2099–106

31 **Zama IN, Hutson TE, Elson P et al.** Sunitinib rechallenge in metastatic renal cell carcinoma patients. *Cancer* 2010; 116: 5400–6

32 **Heidenreich A, Bracarda S, Mason M et al.** Safety of cabazitaxel in senior adults with metastatic castration-resistant prostate cancer (mCRPC): results of the European compassionate-use programme. *Eur J Cancer* 2014; 50: 1090–9

33 **Gan L, Chen S, Wang Y et al.** Inhibition of the androgen receptor as a novel mechanism of taxol chemotherapy in prostate cancer. *Cancer Res* 2009; 69: 8386–94

34 **Zhu ML, Horbinski CM, Garzotto M, Qian DZ, Beer TM, Kyprianou N.** Tubulin-targeting chemotherapy impairs receptor activity in prostate cancer. *Cancer Res* 2010; 70: 7992–8002

35 **Halabi S, Armstrong AJ, Sartor O et al.** Prostate-specific antigen changes as surrogate for overall survival in men with metastatic castration-resistant prostate cancer treated with second-line chemotherapy. *J Clin Oncol* 2013; 31: 3944–50

36 **Halabi S, Lin CY, Small EJ et al.** Prognostic model predicting metastatic castration-resistant prostate cancer survival in men treated with second-line chemotherapy. *J Natl Cancer Inst* 2013; 105: 1729–37

37 **Sweeney C, Chen YH, Carducci MA et al.** Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone sensitive newly metastatic prostate cancer (mPrCa): an ECOG led phase III randomized trial. *J Clin Oncol* 2014; 32 (Suppl.): LBA2

38 **Ryan CJ, Smith MR, de Bono JS et al.** Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013; 368: 138–48

39 **Beer TM, Armstrong AJ, Rathkopf DE et al.** Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014; 371: 424–33

40 **Mezynski J, Pezaro C, Bianchini D et al.** Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? *Ann Oncol* 2012; 23: 2943–7

41 **Pezaro CJ, Omlin AG, Altavilla A et al.** Activity of cabazitaxel in castration-resistant prostate cancer progressing after docetaxel and next-generation endocrine agents. *Eur Urol* 2014; 66: 459–65

42 **Al Nakouzi N, Le Moulec S, Albiges L et al.** Cabazitaxel remains active in patients progressing after docetaxel followed by novel androgen receptor pathway targeted therapies. *Eur Urol* 2014 pii: S0302-2838(14)00396-0. [Epub ahead of print]. doi:10.1016/j.eururo.2014.04.015

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Abbreviations: ADT, androgen-deprivation therapy; AR, androgen receptor; ECOG (PS), Eastern Cooperative Oncology Group (performance status); G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; OR, odds ratio; OS, overall survival; PCWG2, Prostate Cancer Working Group 2; PFI, progression-free interval; PFS, progression-free survival.