Prostate-specific antigen flare induced by cabazitaxel-based chemotherapy in patients with metastatic castration-resistant prostate cancer

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Survival rate

Abstract Background: A prostate-specific antigen (PSA) flare occurs in about 15% of metastatic castration-resistant prostate cancer (mCRPC) patients receiving docetaxel. This flare has no standard definition. Its impact on treatment efficacy is unclear. We sought to evaluate the incidence and characteristics of PSA flare on cabazitaxel, and its impact on survival.
Methods: Multicentre retrospective review of consecutive patients treated with cabazitaxel second-line chemotherapy for mCRPC. Collection of baseline characteristics, disease history and PSA levels before and during cabazitaxel therapy. Overall survival (OS) and radiological/clinical progression-free survival (PFS) for patient groups corresponding to different definitions of PSA flare estimated by the Kaplan–Meier method and compared using the log-rank test.

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Results: Overall, 125 patients were included. Median PFS and OS were 6.5 and 13.3 months, respectively. Depending upon the definition used, flare incidence ranged from 8.3% to 30.6%. The flare lasted <2.6 months. A PSA flare followed by a $\geq 50\%$ decrease was associated with a median PFS and OS of 11.2 and 25.2 months, respectively. Median PFS and OS for a $\geq 30\%$ rather than $\geq 50\%$ decrease were 10.4 and 16.5 months. These outcomes were not significantly different from those in patients with immediate PSA decreases of $\geq 50\%$ or $\geq 30\%$ from baseline, but were significantly better than in patients experiencing no PSA decrease ($p = 0.006$ and 0.015, respectively, for OS).

Conclusion: The PSA response to cabazitaxel, with or without initial flare, was associated with a strong survival benefit. The taxane-induced flare during the first 12 weeks of therapy can be ignored when evaluating PSA response.

1. Introduction

Over the last 10 years or so, major advances have been made in the treatment of metastatic castration-resistant prostate cancer (mCRPC) [1]. Cabazitaxel is a newly available taxane which has shown survival benefit in mCRPC patients progressing during or after docetaxel therapy [2–6]. As for any other drug, clinicians need to learn to use the drug properly to optimise patient outcomes. A specific issue that needs to be addressed with taxanes is the early PSA flare. This is an isolated PSA rise that occurs after initiation of taxane therapy. It is uncertain whether it should lead to treatment discontinuation or not.

An early PSA flare (aka ‘PSA surge’) followed by a decrease in PSA was first reported in 2004 [7] and has been documented in up to 20% of mCRPC patients treated with first-line docetaxel chemotherapy but its impact on treatment outcome and patient management is unclear. Four retrospective studies have concluded that such a flare is not associated with adverse outcomes and can therefore be disregarded ([8–11], see [12] for review). However, these studies involved small patient numbers and did not use a standard definition for the PSA flare. Any initial rise, whether relative or absolute, in PSA is considered to signal a flare. On the other hand, there is no consensus on the extent of the subsequent PSA decline for the phenomenon to be a flare. It may be a $\geq 50\%$ decline of the peak or baseline PSA value, a stable PSA of no given threshold, or even an undefined PSA response [8–11]. In addition, available studies do not indicate clearly whether the observed lack of impact of the flare on treatment outcomes applies to just docetaxel, to just first-line taxane chemotherapy, or can be generalised to various chemotherapy regimens.

The aim of our study was to determine whether the flare should or should not prompt treatment discontinuation in clinical practice.

2. Patients and methods

Data on consecutive mCRPC patients treated with cabazitaxel for progression during or after docetaxel therapy were collected from French cancer centres participating in the CRF trial [13].

Table 1

<table>
<thead>
<tr>
<th>Clinical characteristics of cabazitaxel-treated mCRPC patients ($N = 125$).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate cancer at diagnosis</strong></td>
</tr>
<tr>
<td>Gleason score</td>
</tr>
<tr>
<td>8–10</td>
</tr>
<tr>
<td>$\leq 7$</td>
</tr>
<tr>
<td>Missing data</td>
</tr>
<tr>
<td><strong>Clinical stage</strong></td>
</tr>
<tr>
<td>T3/T4, M0</td>
</tr>
<tr>
<td>M1</td>
</tr>
<tr>
<td>Prior curative local therapy</td>
</tr>
<tr>
<td><strong>Site of metastases</strong></td>
</tr>
<tr>
<td>Bone</td>
</tr>
<tr>
<td>Lymph nodes</td>
</tr>
<tr>
<td>Visceral</td>
</tr>
<tr>
<td><strong>Type of progression</strong></td>
</tr>
<tr>
<td>PSA only</td>
</tr>
<tr>
<td>Radiological</td>
</tr>
<tr>
<td>Clinical but not radiological</td>
</tr>
<tr>
<td><strong>Median duration of response to first androgen deprivation therapy (range), months</strong></td>
</tr>
<tr>
<td>Docetaxel lines before cabazitaxel</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2 or more</td>
</tr>
<tr>
<td>Median number of docetaxel cycles before cabazitaxel [range]</td>
</tr>
<tr>
<td>3–34</td>
</tr>
</tbody>
</table>

mCRPC, metastatic castration-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; PSA, prostate specific antigen.

*Unless otherwise specified.
were collected retrospectively in nine centres (eight in France and one in Turkey) using an electronic case report form. Patients had received cabazitaxel between January 2007 and May 2012 either in the TROPIC phase III trial (NCT00417079) or in the cabazitaxel compassionate use programme implemented before the availability of the drug on the market. Cabazitaxel was administered as recommended, i.e. 25 mg/m² (or exceptionally 20 mg/m² at the physician’s discretion) every 3 weeks in association with 10 mg daily prednisone or equivalent, with proper anti-allergic/anti-emetic premedication and granular colony-stimulating factor support. Treatment was pursued until disease progression, unacceptable toxicity, or a maximum of 10 cycles in the clinical trial.

For inclusion in the present study, patients had to have received at least two cycles of cabazitaxel treatment and, if alive, had to have undergone at least 6 months follow-up. Patients’ baseline characteristics, detailed disease history (including prior therapies), and all PSA measurements performed before and during cabazitaxel therapy were collected in 2012 for pooled analysis in December 2012. PSA was measured at each treatment cycle in TROPIC trial participants and in nearly all patients of the compassionate use programme. Imaging (bone scan with or without computerized tomography (CT)-scan for patients with measurable disease) was performed every two or three cycles at the physician’s discretion.

We determined the incidence, amplitude and time to peak for six different definitions of PSA flare. A flare was defined as any rise in PSA followed by a decrease which could be: (1) any decrease, (2) any decrease below baseline, (3) a ≥30% decrease from the peak PSA value, (4) a ≥50% decrease from baseline, (5) a ≥30% decrease from the peak value, and (6) a ≥30% decrease from baseline. In each instance, we determined OS from the first day of cabazitaxel therapy to death and radiological and/or clinical PFS according to the recommendations of Prostate Cancer Working Group 2 (PCWG2) [13].

On statistical testing, a two-sided p value of 0.05 was considered significant. OS and PFS were estimated by the Kaplan Meier method and were compared between groups using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with a Cox proportional hazards model. A landmark analysis was performed at 3 months from the first cabazitaxel cycle to remove guarantee-time bias. We used SAS® software (SAS Institute, NC, Cary, United States of America [USA]).

This retrospective non-interventional observational study was approved by the Ethics Committee. Only confidentiality approval was required and was obtained from the Commission nationale de l'informatique et des libertés (CNIL). Informed consent was not required as data were anonymised.

3. Results

3.1. Population characteristics and outcomes of cabazitaxel therapy

At the time of data collection, 170 mCRPC patients had been treated with cabazitaxel in the participating centres. Twelve patients were excluded because they had received only one cycle of cabazitaxel and 33 patients because of insufficient follow-up. This left 125 patients for inclusion in the present study (46 from the TROPIC trial; 79 from the compassionate use programme). Their characteristics, including data on prior treatments, are given in Table 1. Median age at the first cycle of cabazitaxel treatment was 67 years. Median follow-up of the patients who were still alive at the time of data collection was 14.3 months (range, 6–59). All deceased patients had undergone complete follow-up until death. The median number of cabazitaxel treatment cycles was 6 (range, 2–14). No patient discontinued cabazitaxel for an isolated PSA rise before the fourth cycle of therapy. Details on treatment and outcomes are given in Table 2. A PSA decrease of ≥50% and ≥30% was achieved in 41.3% and 48.8% of patients, respectively. Median OS and clinical or radiological PFS were 13.3 and 6.5 months, respectively.

3.2. Outcomes according to definition of PSA flare

The incidence of the PSA flare, its relative amplitude and the time to PSA peak, as well as subsequent survival (PFS and OS), varied according to the definition used for flare (definitions 1–6) (Table 3). Flare incidence

\begin{table}[h]
\centering
\caption{Cabazitaxel treatment and outcomes (N = 125).}
\begin{tabular}{|l|l|}
\hline
\textbf{Treatment} & \textbf{Number of patients} (% of available data) \\
\hline
Median number of cycles [range] & 6 [2–14] \\
Initial 25 mg/m² dosage & 114/125 (91.2) \\
Dose reduction & 5/99 (5.0) \\
Dose delay & 15/99 (15.2) \\
Comedications & \\
Prednisone or equivalent & 113/113 (100) \\
G-CSF & 93/125 (74.4) \\
Bisphosphonate & 40/125 (32.0) \\
\hline
\textbf{Outcomes} & \\
PSA response ≥50% & 50/121 (41.3) \\
PSA response ≥30% & 59/121 (48.8) \\
Median OS [95% CI], mos & 13.3 [11.2–16.4] \\
Median radiological or clinical & 6.5 [5.1–8.0] \\
PFS [95% CI], mos & \\
\hline
\end{tabular}
\end{table}

G-CSF, granulocyte colony-stimulating factor; PSA, prostate specific antigen; CI, confidence interval; OS, overall survival; PFS, progression-free survival.

* Unless otherwise specified.
ranged from 8.3% to 30.6%, the lowest incidence being recorded for the most stringent definition (definition 4: flare followed by a $\geq 50\%$ decrease from the baseline value). The median PSA peak (percentage rise from baseline) was lowest (19.8%) and median time to peak was shortest (0.6 months, range 0.2–1.4 months) for this stringent definition. However, sample size was smallest. Median time to reach the nadir for definition 4 was 4.2 months (range, 2.0–7.4 months). A flare could last for up to 2.6 months with the least stringent definitions (definitions 1 and 2).

Patients experiencing a flare with a $\geq 50\%$ decline from baseline (definition 4) had an estimated median OS and PFS that did not differ significantly from those of immediate responders (OS: 25.2 versus 20.1 months, $p = 0.46$; PFS: 11.2 versus 8.8 months, $p = 0.96$). However, their median OS and PFS were significantly better than those of non-responders (OS: 25.2 versus 10.5 months, $p = 0.006$; PFS: 11.2 versus 3.0 months, $p = 0.003$) (Table 4, Figs. 1A and 2A). Survival results for patients experiencing a flare with a $\geq 30\%$ decline from baseline (definition 6) were similar (Table 4, Figs. 4B and 2B). These results on survival were confirmed in a landmark analysis at 3 months from the first cabazitaxel cycle (see Supplementary Table S1).

### 4. Discussion

Our study analysed the early PSA flare occurring on second-line chemotherapy of mCRPC patients with the recently available taxane, cabazitaxel. Two-thirds of the 125 patients had been treated outside a clinical trial in a real-life setting. The incidence of a PSA flare ranged from 8.3% to 30.6% depending upon the definition used for flare and was roughly similar to that recorded for first-line docetaxel chemotherapy (11–18%) [8–11]. The time to peak of the cabazitaxel-induced PSA flare was also similar to that reported for a docetaxel-induced flare (0.2–2.6 months versus 0.2–2 months [12]).

### Table 3

<table>
<thead>
<tr>
<th>PSA response</th>
<th>Reference for definition</th>
<th>Patients N (%)</th>
<th>Median PSA rise from baseline (%)</th>
<th>Median time to peak PSA [range] (mos)</th>
<th>Median PFS (mos)</th>
<th>Median OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 50%$ decline</td>
<td>1 Any decline from peak [11]</td>
<td>37 (30.6)</td>
<td>38.7</td>
<td>1.2 [0.2–2.6]</td>
<td>6.9</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>2 Any decline below baseline –</td>
<td>25 (20.7)</td>
<td>26.6</td>
<td>0.8 [0.2–2.6]</td>
<td>8.0</td>
<td>16.5</td>
</tr>
<tr>
<td></td>
<td>3 $\geq 50%$ decline from peak and below baseline [8,10]</td>
<td>16 (13.2)</td>
<td>39.8</td>
<td>0.8 [0.2–1.9]</td>
<td>10.1</td>
<td>16.5</td>
</tr>
<tr>
<td></td>
<td>4 $\geq 50%$ decline from baseline [9]</td>
<td>10 (8.3)</td>
<td>19.8</td>
<td>0.6 [0–2–1.4]</td>
<td>11.2</td>
<td>25.2</td>
</tr>
<tr>
<td></td>
<td>5 $\geq 30%$ decline from peak, and below baseline –</td>
<td>22 (18.2)</td>
<td>38.7</td>
<td>0.8 [0–2–1.1]</td>
<td>8.0</td>
<td>16.5</td>
</tr>
<tr>
<td></td>
<td>6 $\geq 30%$ decline from baseline –</td>
<td>14 (11.6)</td>
<td>32.6</td>
<td>0.7 [0–2–1.4]</td>
<td>10.4</td>
<td>16.5</td>
</tr>
</tbody>
</table>

**Immediate decline from baseline**

| $\geq 50\%$ decline | 40 (33.1) | NA | NA | 8.8 | 20.1 |
| $\geq 30\%$ decline | 45 (37.2) | NA | NA | 9.0 | 20.1 |
| None | 31 (25.6) | NA | NA | 3.0 | 10.5 |

PSA, prostate specific antigen; CI, confidence interval; PFS, progression-free survival; OS, overall survival; NA, not applicable.

Four patients were not properly evaluable for PSA response.

### Table 4

Impact of PSA response on overall and progression-free survival.

<table>
<thead>
<tr>
<th>Definition (threshold)</th>
<th>PSA response</th>
<th>Overall survival</th>
<th>Progression-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>N° 4 $\geq 50%$</td>
<td>Immediate</td>
<td>20.1 [12.7–34.1]</td>
<td>0.46</td>
</tr>
<tr>
<td>Flare</td>
<td>25.2 [9.1–32.1]</td>
<td>0.006</td>
<td>11.2 [0.1–25.2]</td>
</tr>
<tr>
<td>None</td>
<td>10.5 [7.5–13.4]</td>
<td></td>
<td>3.0 [2.4–4.9]</td>
</tr>
<tr>
<td>N° 6 $\geq 30%$</td>
<td>Immediate</td>
<td>20.1 [12.7–34.2]</td>
<td>0.097</td>
</tr>
<tr>
<td>Flare</td>
<td>16.5 [8.0–31.6]</td>
<td>0.015</td>
<td>10.4 [4.3–20.7]</td>
</tr>
<tr>
<td>None</td>
<td>10.5 [7.5–13.4]</td>
<td></td>
<td>3.0 [2.4–4.9]</td>
</tr>
</tbody>
</table>

PSA, prostate specific antigen; HR, hazard ratio; CI, confidence interval.

* $p$ values with respect to flare.
When defined as a rise followed by a decrease of at least 50% or 30% from baseline (definitions 4 and 6), a cabazitaxel-induced PSA flare was associated with a median PFS and OS that were not significantly different from the OS and PFS recorded in patients experiencing an immediate PSA response. Absence of a significant difference had already been observed with first-line docetaxel. On the other hand, survival (whether OS or PFS) of patients with no PSA decrease during cabazitaxel therapy was significantly worse.

Although our study has explored the association between the definition for a PSA flare and survival, it has not definitively resolved the debate on the choice of definition. We consider that, for an accurate comparison with immediate responders, it is preferable to calculate PSA response from the baseline and not peak PSA value. However, whether a decrease of $\geq 50\%$ or $\geq 30\%$ from baseline is preferable remains a moot point. A PSA decrease of $\geq 30\%$ within 3 months of treatment provided the highest degree of surrogacy for survival in the TAX327 trial [14] whereas the stricter criterion of a $\geq 50\%$ decrease is easier and faster to calculate mentally in daily clinical practice.

Our overall PSA response rates and survival times (median OS and clinical or radiological PFS of 13.3 and 6.5 months, respectively) support published out-

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**Fig. 1.** (A and B) Overall survival (OS) in patients with initial PSA flare followed by a $\geq 50\%$, response (A) or a $\geq 30\%$ response (B) compared to OS in immediate responders, patients with progression and patients with stable disease.

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comes for second-line cabazitaxel therapy in mCRPC patients [4]. They also support a broad relationship between survival and the magnitude of the PSA decline, as suggested by an ancillary study of a large-scale phase III trial on docetaxel [14,15]. The PSA decline may be due to inhibition of androgen receptor (AR) nuclear translocation. Growing evidence shows that taxanes impair cell trafficking and inhibit AR nuclear translocation by stabilizing spindle microtubules [16–18]. They inhibit both ligand-dependent and ligand-independent transcriptional activities; inhibition might also be mediated by the nuclear accumulation of forkhead box protein O1 (FOXO1), a potent AR-suppressive nuclear factor [19]. In the case of the well-known luteinizing-hormone-releasing hormone (LH–RH) analogue-induced PSA and clinical flare, initial pituitary hyper-stimulation by the analogue leads to transient hypertestosteronaemia and increased transcription of AR target genes, such as the PSA gene (KLK3) [20]. Possible mechanisms for the taxane-induced flare may be PSA release from lytic tumour cells, heterogeneous tumour sensitivity to taxanes, or transactivation of a ‘promiscuous’ AR by corticosteroid premedication [9,21–23].

Our findings on PSA flare and survival have important implications for routine clinical practice because they confirm that cabazitaxel should not be withdrawn in mCRPC patients experiencing an early isolated PSA flare. The survival benefit of cabazitaxel over mitoxantrone is demonstrated in patients experiencing an early isolated PSA flare.
rise. This is especially relevant in a second-line chemotherapy setting where physicians need to take quick decisions because the disease is progressing rapidly, patient anxiety is growing and treatment costs need to be considered. However, even if an early isolated rise should not be a reason for discontinuing taxane therapy, we recommend not foregoing PSA monitoring during the first cycles of therapy because any early response that may occur might be a useful criterion in evaluating the risk–benefit ratio of therapy. Monitoring PSA is a useful inexpensive means of predicting response even if PSA response probably explains only part of the efficacy of taxanes. New monitoring tools are currently being developed (e.g. circulating tumour cell or circulating DNA counts and analysis) [24–27] and new therapies such as bone metastasis-directed cabozantinib seem to be effective in mCRPC without inducing any PSA response [28].

The main limitation of this study conducted in consecutive patients in a multicenter setting was its retrospective design. Other limitations are some lack of standardization in patient follow-up between the clinical trial and real-life settings. The combination of the two patient populations, however, allowed us to reach a critical population size which, to our knowledge, is the largest so far in a study addressing taxane-induced PSA flare in mCRPC patients.

5. Conclusions

In conclusion, the initial PSA flare during second-line cabazitaxel therapy was not associated with a worse outcome if followed by a PSA decrease of \( \geq 30\% \) or \( \geq 50\% \) from baseline. This finding provides additional support to the PCWG2 recommendation that an early PSA rise (prior to 12 weeks) on administration of a cytotoxic agent should be ignored in evaluating PSA response and should not be interpreted by clinicians as immediate disease progression necessitating treatment discontinuation [13]. Moreover, our study highlights the need for consensual definitions and thresholds for PSA-related issues to ensure consistency among studies. A standard definition for PSA flare, from the PCWG for instance, would be welcome.

Conflict of interest statement

MO: Consultant or Advisory Role, Entity: Sanofi-Aventis, Janssen, Astellas, Relationship: Myself, Compensation: Compensated.
FM: Consultant or Advisory Role, Entity: Sanofi-Aventis, GlaxoSmithKline, Bristol Myers Squibb, Celgene, Boston Scientific, Relationship: Myself, Compensation: Compensated.
GG: Consultant or Advisory Role, Entity: Sanofi-Aventis, Relationship: Myself, Compensation: Uncompensated.
PB: Honoraria, Consultant or Advisory Role, Entity: Sanofi-Aventis, Janssen, Astellas, Ipsen, Relationship: Myself.
SO: Consultant or Advisory Role; Entity: Sanofi, Novartis, Roche, Bayer, Keo cyt, Amgen, Relationship: Myself, compensation: Compensated, Honoraria, Entity: Sanofi, Novartis, Roche, Bayer, Keyocyt, Amgen, Pfizer, Relationship: Myself.
All remaining authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2014.03.015.

References


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