Severe neutropenia during cabazitaxel treatment is associated with survival benefit in men with metastatic castration-resistant prostate cancer (mCRPC): A post-hoc analysis of the TROPIC phase III trial

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Abstract  Background: Cabazitaxel significantly improves overall survival (OS) in men with metastatic castration-resistant prostate cancer (mCRPC) progressing during or after docetaxel, but is associated with a higher rate of grade ≥3 neutropenia compared with docetaxel. We thus examined the relationship between cabazitaxel-induced grade ≥3 neutropenia, baseline neutrophil-lymphocyte ratio (NLR) and treatment outcomes.  Methods: Data from the experimental arm of the TROPIC phase 3 trial which randomly assigned men with mCRPC to cabazitaxel or mitoxantrone every 3 weeks, both combined with daily prednisone, were analysed. The influence on OS (primary end-point) and progression-free survival (PFS) of at least one episode of grade ≥3 neutropenia during cabazitaxel therapy was investigated using Cox regression models, adjusted for pain at baseline. The relationships with prostate-specific antigen (PSA) responses during cabazitaxel therapy and baseline NLR were also analysed.
1. Introduction

Cabazitaxel was the first agent demonstrating a survival benefit in men with metastatic castration-resistant prostate cancer (mCRPC) progressing during or after docetaxel [1]. Although cabazitaxel is associated with less peripheral neuropathy, nail disorders, alopecia and dysgeusia than docetaxel [2], it induces a high rate of grade ≥3 neutropenia which needs to be proactively managed to avoid potential neutropenic complications [3]. This contributes to limit its use compared with new androgen receptor (AR)-targeted agents such as abiraterone acetate [4] or enzalutamide [5] which are given orally with less adverse events. Nevertheless, the increasing evidence that prostate cancer is a highly heterogeneous disease [6,7], that some patients exhibit primary resistance to AR-targeted agents [8,9] and that respondents to AR-targeted agents will ultimately progress through various mechanisms such as splice variants [10] or aggressive histological subtypes which are not driven by AR [11], accords cabazitaxel an important role in such a setting.

In many solid tumour types and haematological malignancies, it has been reported that chemotherapy-induced neutropenia is associated with a prolonged overall survival (OS), both in adjuvant and metastatic settings [12–20]. In mCRPC, in a retrospective review of 221 patients treated with docetaxel, Pond et al [21] concluded that development of a grade ≥3 neutropenia on day 8 of cycle 1 was associated with a better outcome. Since a particularly high incidence of grade ≥3 neutropenia (82%) was reported with cabazitaxel, administered at a dose of 25 mg/m² every 3 weeks, in the TROPIC trial [1], we examined whether this was associated with improved OS and PFS. We also investigated grade ≥3 neutropenia in relation to the neutrophil-lymphocyte ratio (NLR). The NLR is the quotient of baseline absolute peripheral neutrophils (cells/mm³) and baseline absolute lymphocytes (cells/mm³) and has been shown to have prognostic value in mCRPC [22–24] as in many other tumour types [25]. Lorente et al. have demonstrated an association of a high NLR with decreased survival, PSA and Response Evaluation Criteria in Solid Tumours responses in patients treated with cabazitaxel [22]. A decrease of the NLR from high (≥3) to low (<3) resulted in improved survival (hazard ratio [HR] 0.66; 95% confidence interval [CI] 0.51–0.85; p = 0.001) and better PSA response rates (66.4% versus 33.6%; p = 0.000) [22]. Finally, we investigated the relationship between grade ≥3 neutropenia, granulocyte colony-stimulating factor (G-CSF) usage and OS.

2. Methods

2.1. Patients

We conducted a post-hoc analysis of the randomised phase III trial TROPIC which compared the efficacy of cabazitaxel (25 mg/m² every 3 weeks) versus mitoxantrone (12 mg/m² every 3 weeks), both in combination with prednisone 10 mg daily, in 755 patients with mCRPC progressing during or after docetaxel. Full details of patient eligibility and trial results have been
published [1]. The study was approved by the local ethic committee (EKNZ UBE 15/105).

Patient characteristics collected at enrolment, included number and duration of prior lines of treatment, sites of metastases, age, Eastern Cooperative Group performance status, pain score, testosterone and PSA concentrations, steroid use, full blood count (including absolute neutrophil and lymphocyte counts) and biochemistry. Full blood counts were carried out on a weekly basis (day 1, 8 and 15 of each 21-day cycle). Imaging studies (computed tomography and bone scintigraphy) were carried out every 12 weeks. Treatment was planned for a maximum of 10 cycles. Prophylactic G-CSF was not allowed during the first cycle, but was allowed (at physicians’ discretion) after first occurrence of either a grade ≥3 neutropenia lasting 7 d or more or a grade ≥3 neutropenia complicated by fever or infection.

2.2. Statistical analyses

All analyses reported below were performed in those 371 patients who received cabazitaxel in the TROPIC trial.

The primary objective of this study was to explore the prognostic role of grade ≥3 neutropenia during cabazitaxel therapy on OS, calculated from date of randomisation to death. Secondary objectives were to evaluate the effect of grade ≥3 neutropenia on progression-free survival (PFS), defined as the time between randomisation and the first date of progression (either PSA progression or tumour progression or pain progression or death) and PSA response, defined by a confirmed PSA decrease ≥50% from baseline.

OS and PFS were estimated by Kaplan-Meier method and comparisons were made by the log rank test. We investigated using Cox proportional-hazards survival models whether (A) the occurrence of at least one grade ≥3 neutropenia at any time during treatment, (B) the frequency of grade ≥3 neutropenia during therapy (i.e. number of cycles with grade ≥3 neutropenia divided by the total number of cycles received), (C) the relative change in absolute neutrophil count (ANC) during treatment cycle 1 compared to baseline and (D) the time to first grade ≥3 neutropenia (as continuous variable) had an influence on OS and PFS with cabazitaxel. The variable ‘measurable pain at baseline’ (1 = yes, 0 = no) was included in the model. For analyses related to variables (A) and (B), only patients who completed at least three treatment cycles without missing covariates were included (n = 259). The Wilcoxon signed rank sum test was employed to test whether the occurrence of grade ≥3 neutropenia (A) and the relative change in ANC during treatment cycle 1 (C) were associated with a confirmed PSA decrease ≥50%. Waterfall plots of maximum PSA changes from baseline during therapy in patients experiencing or not at least one grade ≥3 neutropenia were also provided.

The NLR was calculated by dividing the ANC at baseline by the absolute lymphocytes count (cells/mm³). This continuous variable was further stratified into high NLR (≥3.0) and low NLR (<3.0) according to the suggestion of Lorente et al [22]. Based on this, we defined four groups of patients: (1) grade ≥3 neutropenia and high NLR, (2) grade ≥3 neutropenia and low NLR, (3) no grade ≥3 neutropenia and high NLR, and (4) no grade ≥3 neutropenia and low NLR. We tested the two groups ‘high NLR’ and ‘low NLR’ for a difference in proportions of patients with and without grade ≥3 neutropenia, using a two-sample test for equality of proportions with continuity correction. OS in each of these subgroups was analysed using a Cox proportional-hazards survival model, adjusted for measurable pain at baseline. We also tested the association between NLR (as a continuous variable) and OS.

Primary prophylaxis with G-CSF was not permitted at cycle 1; however, as per protocol, G-CSF use was permitted for primary prophylaxis in case of first occurrence of either a grade ≥3 neutropenia lasting 7 d or more or a grade ≥3 neutropenia complicated by fever or infection. We further grouped patients with grade ≥3 neutropenia according to G-CSF use (none, after first grade ≥3 neutropenia, before first grade ≥3 neutropenia), and compared their OS to those patients without grade ≥3 neutropenia, using Cox proportional-hazards survival model, adjusted for measurable pain at baseline.

3. Results

3.1. Primary end-point: OS

Patients developing grade ≥3 neutropenia during cabazitaxel therapy had a significantly prolonged OS compared to those without grade ≥3 neutropenia (16.3 versus 14.0 months; HR = 0.65 [95% CI, 0.43–0.97], p = 0.035) (Fig. 1A).

There was also a trend for improved OS in patients experiencing a high frequency of grade ≥3 neutropenia during therapy (HR = 0.61 [0.36–1.04], p = 0.067).

OS was not affected by the relative change in ANC from baseline during the first cycle (HR = 0.97 [0.57–1.66], p = 0.908) and by the time to first grade ≥3 neutropenia (HR = 0.99 [0.97–1.01], p = 0.404).

Of the total of 303 patients that experienced at least grade 3 neutropenia during treatment 242 (79.9%) had neutropenia in their first cycle. A total of 274 patients (90.5%) had neutropenia within the first two cycles and 288 (95.1%) patients had neutropenia within their first three cycles of cabazitaxel.

3.2. Secondary end-point: PFS

Patients with grade ≥3 neutropenia during cabazitaxel therapy had a longer PFS compared to those with a
lower grade neutropenia (5.3 versus 2.6 months; HR = 0.56 [0.40–0.79], p = 0.001) (Fig. 1B).

PFS also significantly increased with the frequency of grade ≥3 neutropenia during therapy (HR = 0.63 [0.42–0.95], p = 0.029). A beneficial effect on PFS was already apparent after one single episode of grade ≥3 neutropenia.

Lastly, patients with small relative changes from baseline in ANC during cycle 1 tended to have a reduced PFS (HR = 1.49 [0.98–2.25], p = 0.061).

### 3.3. Secondary end-point: PSA response

Patients with grade ≥3 neutropenia during cabazitaxel therapy had a greater fall in PSA from baseline compared with cases of milder neutropenia (median −48.4 versus −4.6, p < 0.001). Only 10/41 patients (24.4%) who did not experience grade ≥3 neutropenia had a confirmed PSA decline ≥50% compared to 104/209 patients (49.8%) with grade ≥3 neutropenia (p = 0.005) (Fig. 2 and Supplementary Fig. 1).

### 3.4. Analysis of the NLR in combination with grade ≥3 neutropenia

Of the 371 patients exposed to cabazitaxel, 198 had a NLR ≥3 (high NLR), 169 had an NLR <3 (low NLR), and four patients had missing NLR values. The occurrence of grade ≥3 neutropenia during cabazitaxel therapy was significantly lower in patients with a high NLR (149/198, 75.3%) compared with patients with a low NLR (150/169, 88.8%, p = 0.002).

It was previously reported that patients with high NLR had a worse OS compared to those with low NLR (12.6 versus 15.9 months, p < 0.001) [22]. Combined evaluation of the occurrence of grade ≥3 neutropenia and NLR, showed that patients with a low baseline NLR who developed grade ≥3 neutropenia during therapy had the longest OS (19.2 months), while those with a high NLR and no grade ≥3 neutropenia during therapy had the worst OS (12.9 months, HR 0.46 [95% CI 0.28–0.76], p = 0.002)

### 3.5. A risk model based on NLR and occurrence of grade ≥3 neutropenia

Since high NLR at baseline and absence of grade ≥3 neutropenia during therapy were associated with a poor outcome, we developed a risk model integrating these two factors. Patients were classified into three groups: a low-risk group (low NLR at baseline, grade ≥3 neutropenia during cabazitaxel therapy), a high-risk group (high NLR at baseline, no grade ≥3 neutropenia during therapy) and an intermediate-risk group (only one risk factor, either high NLR or no grade ≥3 neutropenia). The median OS in the low-risk group (n = 130) was 19.2 months and significantly longer when compared with 12.9 months in the high-risk (n = 35), (p = 0.0024) and 14.2 months in the intermediate-risk group (n = 132), (p = 0.0024) (Fig. 3).

### 3.6. G-CSF use

Of the 371 patients analysed, 303 (82%) experienced at least one episode of grade ≥3 neutropenia during cabazitaxel therapy and 77/303 (21%) received G-CSF prophylaxis, either after a prior grade ≥3 neutropenia (n = 59) or not (n = 18). Of those 77 patients treated
with G-CSF, 76 (99%) subsequently developed at least one episode of grade ≥3 neutropenia versus 266/294 (77%) who did not receive G-CSF. Median OS was 19.7 months in patients treated with prophylactic G-CSF after a first episode of neutropenia grade ≥3 (n = 59), 17.3 months in those treated with G-CSF without prior grade ≥3 neutropenia and 16.0 months in those who never received G-CSF (Fig. 4 and Supplementary Table 2).

4. Discussion

This post-hoc analysis of TROPIC suggests that the occurrence of grade ≥3 neutropenia with cabazitaxel is associated with improved OS but also greater PFS and PSA responses. Patients with a low NLR at baseline were more likely to develop grade ≥3 neutropenia with cabazitaxel therapy and showed the longest OS (median 19.2 months). Conversely, high NLR at baseline and no grade ≥3 neutropenia during therapy was associated with a poor outcome (median OS of 12.9 months). Importantly, all patients had a full blood count on day 8, 15 and 21 enabling the capture of the neutrophil nadir during therapy. The majority (90.5%) of neutropenic events occurred early, within the first two cycles of therapy, making a cumulative effect unlikely.

Chemotherapy-induced neutropenia is associated with an improved OS in many solid tumours such as breast cancer [19], colorectal cancer [23,25], non-small-cell lung cancer [17], gastric cancer [16], cervical cancer [15], nasopharyngeal cancer [13] and haematological malignancies [12,26]. In the context of mCRPC, one retrospective analysis in 221 patients treated with docetaxel (75 mg/m2 every 3 weeks) also suggests that the occurrence of grade ≥3 neutropenia on day 8 of cycle 1 is associated with an improved OS and a greater PSA response compared with those without grade ≥3 neutropenia [21]. Our results further support these findings as cabazitaxel-induced grade ≥3 neutropenia in the TROPIC study is also associated with a better outcome.

The large scale TAX327 study, demonstrated a survival advantage (median 2.4 months) for docetaxel plus prednisone versus mitoxantrone plus prednisone in mCRPC [27]. The incidence of grade ≥3 neutropenia and febrile neutropenia were 32% and 3%, respectively. Several clinical studies were then initiated at the same dose in earlier stages of the disease (i.e. in hormone-naive patients) and showed a higher incidence of grade ≥3 neutropenia (61–88%) [28]. The lower rate of grade ≥3 neutropenia in mCRPC was attributed to a dramatic

Fig. 2. PSA response according to the occurrence of grade ≥3 neutropenia with cabazitaxel. Waterfall plot showing maximum PSA change from baseline according to whether patients developed at least one episode of grade ≥3 neutropenia during cabazitaxel therapy (blue bars, n = 259) or not (red bars, n = 57). PSA response was defined as a confirmed ≥50% decrease from baseline (dotted line). The y-axis is capped at +100% for better representation (maximum PSA rise was 377%). Patients who experienced at least one grade ≥3 neutropenia had greater PSA declines than those without grade ≥3 neutropenia.

Fig. 3. Overall survival (OS) according to risk groups (based on neutrophil-to-lymphocyte ratio [NLR] and occurrence of grade ≥3 neutropenia). The curves show the probability of survival (in months) by number of risk groups: 0 (at least one grade ≥3 neutropenia during cabazitaxel therapy and low NLR), 1 (high NLR or no grade ≥3 neutropenia during cabazitaxel therapy) 2 (high NLR and no grade ≥3 neutropenia during cabazitaxel therapy). Vertical lines indicate median OS. Only patients who completed at least three treatment cycles were included. Comparison of outcome between the risk groups is depicted in Table 1.
In the TROPIC study, conducted in mCRPC patients progressing during or after docetaxel, the incidence of grade $\geq 3$ neutropenia and febrile neutropenia with cabazitaxel (25 mg/m$^2$ every 3 weeks) was much higher (82% and 8%, respectively) than with docetaxel in the TAX327 study (32% and 3%, respectively), although the OS benefit versus mitoxantrone plus prednisone was similar (median 2.4 months) [1]. A large compassionate use program providing access to cabazitaxel at a dose of 25 mg/m$^2$ to 746 mCRPC patients progressing during or after docetaxel reported 17% of grade $\geq 3$ neutropenia and 5.5% of febrile neutropenia [32]. In comparison with TROPIC, the improved tolerability was interpreted to be due to better monitoring of patients and proactive management of adverse events, including use of prophylactic G-CSF in 52% of patients. Indeed, a multivariate analysis concluded that age $\geq$75 years, treatment cycle 1, and neutrophil count $<$4000/mm$^3$ before cabazitaxel injection were associated with increased risk of developing grade $\geq 3$ neutropenia and/or neutropenic complications but in the presence of these factors, prophylactic G-CSF at a given cycle significantly reduced this risk by 30% (odds ratio 0.70 [0.49–0.99], p = 0.04) [32]. Two phase III studies (NCT01308580 – PROSELICA in post-docetaxel setting and NCT01308567 – FIRSTANA in chemo-naive patients) are ongoing and should unambiguously determine if a dose of 20 mg/m$^2$ provides a greater benefit/risk ratio than 25 mg/m$^2$. Pharmacokinetic (PK) guided dose individualisation of cabazitaxel is currently tested versus the standard regimen (25 mg/m$^2$ every 3 weeks) in the prospective randomised phase II study CAINTA (EudraCT number: 2013-005504-34).

Thus, if validated prospectively, a practical implication of our results might be to tailor cabazitaxel dosing on the basis of its haematological effects. Indeed, the absence of grade $\geq 3$ neutropenia, especially in patients with a high NLR, could suggest insufficient drug exposure or limited impact on the tumour-associated immune response. Our data indicate that G-CSF use after successful dose calibration could further positively impact patient survival. A risk stratification according to our model could be helpful in selecting patients who would eventually benefit from dose escalation, provided all safety measures are considered.

In conclusion, this post-hoc analysis of the TROPIC trial suggests that the occurrence of grade $\geq 3$ neutropenia with cabazitaxel is associated with a prolonged OS and doubles the PFS. Patients with a low NLR at baseline were more likely to develop grade $\geq 3$ neutropenia during cabazitaxel therapy and showed the longest OS. High NLRs at baseline and no grade $\geq 3$ neutropenia during therapy was associated with a poor outcome which may suggest under dosing. These results, if prospectively confirmed, would justify

Fig. 4. Outcome (OS) of patients with and without secondary prophylactic G-CSF use. Kaplan-Meier estimates of the probability of overall survival stratified for neutropenia grade $\geq 3$ and G-CSF use after a first episode of neutropenia grade $\geq 3$. Vertical lines indicate median overall survival in months. Patients without neutropenia grade $\geq 3$ were not allowed G-CSF according to the protocol. One patient who received G-CSF without preceding neutropenia grade $\geq 3$ was excluded from the analysis. All patients who completed at least three treatment cycles and who did not receive G-CSF before first episode of neutropenia grade $\geq 3$ were included (n = 204). Eighteen patients who received G-CSF prophylaxis before their first neutropenic episode had a median OS of 17.3 months and are not displayed in this figure. G-CSF, granulocyte colony-stimulating factor.

Table 1

| OS stratified according to risk groups | HR   | 95% CI      | z   | p (>|z|) |
|---------------------------------------|------|------------|-----|-------|
| Risk group 1 versus 0                 | 1.72 | [1.21; 2.44]| -3.03 | 0.00241|
| Risk group 2 versus 0                 | 2.18 | [1.32; 3.61]| -3.03 | 0.00241|
| Pain at baseline                      | 2.40 | [1.71; 3.36]| 5.09 | <0.001|

OS, overall survival; HR, hazard ratio; CI, confidence interval.

increase in docetaxel clearance (by approximately 100%) due to increased hepatic uptake compared to hormone-naive men, resulting in a two-fold reduction in the area under the curve [28]. Results of two large phase III trials, CHAARTED (n = 790) and STAMPEDE (n = 1776), have been reported [29,30]. These trials compared docetaxel (six cycles) plus androgen deprivation therapy (ADT) versus ADT alone in metastatic hormone-naive patients. A third trial GETUG 15 which included only 385 hormone-naive metastatic patients showed a significant PFS improvement with the combination of ADT and docetaxel but only a trend in OS [31]. Interestingly, a much higher rate of febrile neutropenia was reported in these three studies (ranging from 6% to 12%) compared with TAX327 (3%) reflecting possibly a greater incidence of grade $\geq 3$ neutropenia than effectively reported.

In the TROPIC study, conducted in mCRPC patients progressing during or after docetaxel, the incidence of grade $\geq 3$ neutropenia and febrile neutropenia with cabazitaxel (25 mg/m$^2$ every 3 weeks) was much higher (82% and 8%, respectively) than with docetaxel in the TAX327 study (32% and 3%, respectively), although the OS benefit versus mitoxantrone plus prednisone was similar (median 2.4 months) [1]. A large compassionate use program providing access to cabazitaxel at a dose of 25 mg/m$^2$ to 746 mCRPC patients progressing during or after docetaxel reported 17% of grade $\geq 3$ neutropenia and 5.5% of febrile neutropenia [32]. In comparison with TROPIC, the improved tolerability was interpreted to be due to better monitoring of patients and proactive management of adverse events, including use of prophylactic G-CSF in 52% of patients. Indeed, a multivariate analysis concluded that age $\geq$75 years, treatment cycle 1, and neutrophil count $<$4000/mm$^3$ before cabazitaxel injection were associated with increased risk of developing grade $\geq 3$ neutropenia and/or neutropenic complications but in the presence of these factors, prophylactic G-CSF at a given cycle significantly reduced this risk by 30% (odds ratio 0.70 [0.49–0.99], p = 0.04) [32]. Two phase III studies (NCT01308580 – PROSELICA in post-docetaxel setting and NCT01308567 – FIRSTANA in chemo-naive patients) are ongoing and should unambiguously determine if a dose of 20 mg/m$^2$ provides a greater benefit/risk ratio than 25 mg/m$^2$. Pharmacokinetic (PK) guided dose individualisation of cabazitaxel is currently tested versus the standard regimen (25 mg/m$^2$ every 3 weeks) in the prospective randomised phase II study CAINTA (EudraCT number: 2013-005504-34).

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keeping the cabazitaxel dose at 25 mg/m² whenever possible.

Conflict of interest statement

AM and FS have served as consultants for Sanofi and have received funds for travelling from Sanofi. SvF, DV and HL have declared to have no conflict of interests.

RdW, OS and JdB have served as investigator and consultant for Sanofi.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2015.12.009.

References


