Multidisciplinary treatment of metastatic prostate cancer

Bouman, E.W.

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A randomized phase II trial of docetaxel versus docetaxel plus carboplatin in patients with castration resistant prostate cancer who have progressed after response to prior docetaxel chemotherapy: the Recardo trial

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Abstract

Background

Docetaxel is standard first-line chemotherapy for patients with metastatic castration resistant prostate carcinoma (mCRPC). Docetaxel re-challenge has never been tested in a prospective RCT. As some studies support the addition of carboplatin to docetaxel, we performed a phase II trial investigating the combination of docetaxel plus carboplatin versus docetaxel re-treatment in docetaxel pre-treated mCRPC patients.

Patients and methods

Patients with mCRPC with a progression-free interval (PFI) of ≥3 months after initial docetaxel treatment were randomized between docetaxel 75mg/m^2 or docetaxel 60mg/m^2 plus carboplatin AUC4. The primary endpoint was progression-free survival (PFS) (PSA/RECIST).

Results

Due to insufficient recruitment, the study was discontinued early after inclusion of 75 patients (targeted 150).
PFS and OS were comparable between both groups (median PFS 12.7 months (95% CI 9.9-17.5 months) with docetaxel monotherapy and 11.7 months (95% CI 8.5-21.0months) with combination therapy (p=0.98); OS 18.5 months (95% CI 11.8-24.5 months) versus 18.9 months (95% CI 16.0-23.7 months) (p=0.79). An interim analysis (SEQTEST) showed that the null hypothesis could already be excepted and no significant difference between both study arms was expected if inclusion would be completed. The incidence of grade 3-4 infections and gastro-intestinal (GI) side effects was numerical higher in the carboplatin arm (p=0.056).

Conclusion

This early terminated study suggests no benefit from the addition of carboplatin to docetaxel retreatment in patients with mCRPC, while the combination resulted in more toxicity. Retreatment with docetaxel monotherapy appears to be feasible, save and effective for patients with mCRPC and an initial good response to docetaxel.

Introduction

Docetaxel is the standard first-line chemotherapeutic treatment for patients with symptomatic metastatic castration resistant prostate carcinoma (mCRPC) or asymptomatic patients with progressive disease[1]. In 2004, two randomized phase III trials showed a survival benefit for docetaxel as first-line treatment for these patients, as well as pain relief and improvement in quality of life[2, 3].

After response to docetaxel, at some point, progression will occur. At the start of this study in 2010, mitoxantrone was the only approved second-line chemotherapeutic agent . Two different studies showed better pain palliation and quality of life for the combination of mitoxantrone with steroids compared to steroids alone. Nevertheless, there was no survival benefit for the combined therapy and the PSA response rates of 10-20% after second line treatment with mitoxantrone were modest[4-7].

Nowadays, there are several different treatment options with cabazitaxel as a second-line cytotoxic agent, enzalutamide and abiraterone as hormone-blocking agents, radiopharmaceuticals as radium-233 and sipuleucel-T immunotherapy[8-12]. Although all these agents have a proven survival benefit and are all registered for treatment in the post-docetaxel setting, they all have their own limitations and side effects, and effects on survival are still modest.

Previous phase II studies supported the use of platinum chemotherapy in the management of mCRPC and suggested a synergistic effect when carboplatin is combined with docetaxel[13, 14]. In mCRPC patients refractory to docetaxel, a median PFS of 3-6.5 months with an OS of 12.4-15.8 months has been described with combination therapy of carboplatin and docetaxel[15, 16]. Recently, molecular profiling has shown a role for DNA repair defects (in BRCA 1/2 germline variants) in advanced prostate cancer. This makes these tumors more sensitive for treatment with platinum compounds which exert their antitumor effect through covalent adducts with cellular DNA resulting in DNA damage[17]. Moreover, treatment of docetaxel naïve patients with clinical features of an anaplastic prostate carcinoma with docetaxel plus carboplatin resulted in stable disease in 65% of the patients after 12 weeks and an median OS of 16 months[18].

There is also evidence from retrospective data and small cohorts of patients that patients with an initial good response to docetaxel might benefit from a re-challenge with single agent docetaxel. In these patients, docetaxel was mostly discontinued after receiving the planned number of treatment cycles, without severe side effects[19-21]. In the trial of

Bracarda *et al*. 98 patients were re-treated after an initial response to docetaxel (median interval between treatments 8.3 months), with a median PFS of 16.4 months[21]. In the prospective cohort study of Di Lorenzo *et al*., 45 patients with an initial biochemical remission of at least 5 months were re-treated with docetaxel[22]. The median PFS was 5 months (range 2-8 months) with an overall survival of 13 months.
The progression free interval after first-line docetaxel seems to be associated with the response rate and PFS after re-challenge[20].

Since both docetaxel re-treatment as well as docetaxel combined with carboplatin seem to be appealing second-line treatment options for a selected patient group, we performed this phase II study comparing both treatment regimens.
This study is the first phase II randomized study prospectively assessing the activity of docetaxel plus carboplatin relative to that of re-treatment with docetaxel monotherapy in mCRPC patients with an initial response but progression on prior docetaxel-based treatment.

Patients and methods

We performed a randomized multi-center phase II study in patients with histologically proven metastatic castration resistant prostate cancer (mCRPC).

Patients

Patients with an initial PSA and/or clinical response to first-line docetaxel containing treatment were eligible if disease progression (defined as 50% increase in PSA over nadir and/or according to RECIST criteria) occurred after a progression free interval (PFI) of at least 3 months.
Supplemental inclusion criteria were age ≥ 18 years, ECOG performance status ≤2, Gleason score ≥7, PSA ≥5ng/ml, castration by orchiectomy or LHRH agonist, and adequate hematological, liver and kidney function. Patients were excluded if they had had more than 1 line of chemotherapy, used prior platinum containing treatment, underwent radiotherapy within 2 weeks prior to treatment start or had evidence of symptomatic brain or leptomeningeal metastasis.
This study was approved by the institutional review board or medical ethics committee for each site, and all patients gave written informed consent.

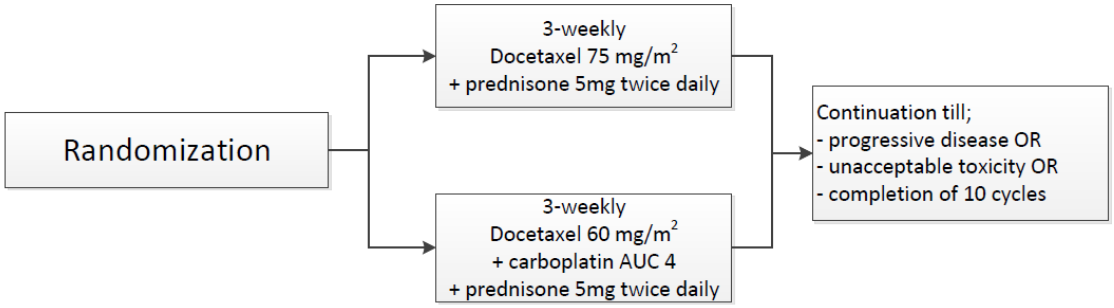

Figure 1 Randomization and treatment schedule

Study design and treatment plan

Patients were randomized between two study arms (Figure 1). Arm A consisted of 3-weekly docetaxel 75mg/m^2. Patients in arm B were treated with 3-weekly docetaxel 60mg/m^2, combined with 3-weekly carboplatin at a dose corresponding to AUC4; both drugs administered on day 1 of the 3-weekly cycle. Docetaxel was administered as a 1 hour infusion (both arms), followed immediately by a 30 minute infusion of carboplatin in arm B.

Patients in both arms received concomitant treatment with prednisone 5mg twice daily during the whole treatment. Chemotherapy in both arms was continued until disease progression, unacceptable toxicity or completion of 10 courses (whichever comes first).

The primary objective of this study is to assess the activity of docetaxel plus carboplatin relative to a re-challenge with docetaxel monotherapy in docetaxel pre-treated patients, with progression free survival (PFS) as primary outcome. The PFS is measured from the first day of docetaxel-based chemotherapy until disease progression, including death or the off-study date. Disease progression during study is defined as a (confirmed) PSA increase over the baseline value (50% increase for patients with, an 25% increase for patients without an initial PSA response since start of the treatment, with a minimum rise of 5ng/ml) and/or progression on imaging according to the RECIST criteria (definition described in the inclusion criteria section).

Secondary objectives include the toxicity profile (according to the NCI-CTC 3.0 criteria), PSA response and duration of PSA response (defined as a PSA decline of ≥50% confirmed at least 4 weeks later), objective tumour response (according to RECIST criteria), overall survival (measured from the initiation of the therapy to the date of death) and quality of life (QoL, measured by FACT-P questionnaires).

Disease assessments were performed at fixed moments; PSA was measured at start of therapy, every 3 weeks before the next treatment cycle, at end of chemotherapy and during follow-up. A CT scan was performed within 21 days before the first infusion

(together with a bone scan), every 9 weeks, at end of chemotherapy and at the moment of PSA or clinical progression during follow-up. The bone scan was repeated after 30 weeks and on clinical indication.

Statistical analysis

A sample size of 150 subjects was established to be needed to find a clinical significant increase in PFS of 2 months for the combination of docetaxel+carboplatin (HR=1.67). This calculation was made using the log rank test, with a power of 80% at a significance level of 0.05%. The following assumptions were made; an accrual time of 20 months, follow-up time of 15 months, median PFS in the docetaxel group of 3 months and 5 months in the group with combination therapy. An interim analysis was planned after a total of 75 randomized patients to evaluate of PSA- and/or tumor response, the outcome being decisive for further study continuation. The Kaplan Meier method and Log Rank test are used to test for significant differences in PFS, OS, PSA and tumor response between both treatment arms. For the interim analysis, the conditional power is calculated using the SEQTEST lifetable method, testing for futility. With this test, the probability (β) of a Type II error (accepting a null hypothesis that is actually false) is calculated based on the interim data. Analyses were performed using the STATA software package, version 13.1 for Windows (Stata Corporation LP, College Station, TX, USA).

Results

As a result of insufficient recruitment, the study was discontinued early after inclusion of 75 patients, instead of the targeted 150 patients. At the stage of the planned interim analysis, analysis on the primary and secondary endpoints was performed. Inclusion was lower than expected, mostly because of the availability of new treatment options in trials (enzalutamide and abiraterone). Besides, some patients refused retreatment with docetaxel because of the lack of experience or earlier experienced side effects (neuropathy).

Patients were included between July 2009 and April 2013 in 24 hospitals in the Netherlands. Thirty-seven patients were included in arm A (docetaxel monotherapy) and 38 patients in arm B (docetaxel+carboplatin).

Table 1 Baseline characteristics

	Arm A; docetaxel (N=37)	Arm B; docetaxel + carboplatin (N=38)
Age (mean, range)	69.2 (61-85)	70.1(60-84)
Performance status		
0	16 (43%)	16 (42%)
1	18 (49%)	20 (53%)
2	2 (5%)	1 (2.6%)
Unknown	1 (2.7%)	1 (2.6%)
Serum PSA ng/ml, median (range)	75 (5-1113)	49 (5-1450)
Gleason score		
6-7	9 (24%)	9 (24%)
8	18 (49%)	15 (39%)
9-10	9 (24%)	12 (32%)
Unknown	1 (2.7%)	2 (5.3%)
Previous therapy		
Max 1 line of chemotherapy	37 (100%)	38 (100%)
Hormonal therapy		
Radiation		
Surgery		
Months since last docetaxel mean (range)	11.9 (4.0-43.2)	12.4 (3.0-67.5)
Site of metastasis		
Site of primary	13 (35%)	20 (53%)
Bone	30 (81%)	38 (100%)
Lymph nodes	21 (57%)	18 (47%)
Liver	4 (11%)	5 (13%)
Lung	4 (11%)	5 (13%)
Other	5* (14%)	3# (12%)

*pleural, adrenal gland left/right, pelvis
#pleural, soft tissue

The baseline characteristics, summarized in Table 1, are comparable between the two groups, except for a significant higher incidence of bone metastases in the combination treatment group. Almost all patients stopped the initial docetaxel treatment because of completion of ten cycles. None of these patients stopped because of progressive disease (these patients would not meet the inclusion criteria). Six patients stopped because of side effects at that moment, which were resolved before inclusion in this trial (mostly fatigue and neuropathy).

The median time between the last docetaxel infusion in the first-line docetaxel treatment and inclusion in the study was 11.9 months (docetaxel monotherapy) and 12.4 months (docetaxel+carboplatin) respectively. The median time of follow up from the start of treatment in the trial was 18.0 months.

In both treatment arms, the median number of treatment cycles was 7 (range 1-10). A 20% dose reduction was necessary in 3 patients (8.1%) in the docetaxel group, versus 9 patients (23.7%) in the combination treatment group (in am B, the dose was reduced by 25%; 60mg/m^2 to 45mg/m^2). Delay of 1 week occurred 6 versus 8 times, and a delay of more than 1 week in 1 versus 4 cases (NS). A dose reduction of the carboplatin of 25% (AUC 4 to AUC 3) was necessary in 11 patients.

In the docetaxel group, 16.2% of the patients discontinued treatment due to toxicity, versus 39.5% of the patients in the combination treatment arm (p=0.025). Progressive disease was the reason of discontinuation in 29.7% versus 21.1% (p=0.39) of the patients respectively. Fourteen patients in group A (37.8%) and nine patients in group B (23.7%) fulfilled the whole treatment schedule (p=0.18).

All patients had progressive disease at the moment of analysis.

The median PFS was 12.7 months (95% CI 9.9-17.5 months) in the docetaxel monotherapy group and 11.7 months (95% CI 8.5-21.0 months) for the combination treatment arm (p=0.98), as displayed in Figure 2.

The median OS was 18.5 months (95%CI 11.8-24.5 months) versus 18.9 months (95%CI 16.0-23.7 months) (p=0.79), as shown in Figure 3. Five and seven patients are still alive and are censored at the date of the most recent follow-up.

As the study was discontinued early due to insufficient recruitment, we performed a post-hoc conditional power analysis (SEQTEST procedure lifetable method). The standardized Z score of -0.13413 in this analysis is smaller than the corresponding lower boundary 4.13109 (representing the probability β of a Type II error; incorrectly accepting the null hypothesis) (Figure 4). This means that the study can be stopped at this stage, accepting the null hypothesis, as the chance of finding a significant difference between study arms after completion of inclusion resembles zero, i.e. there is no evidence for a difference between both study arms (p=0.3901).

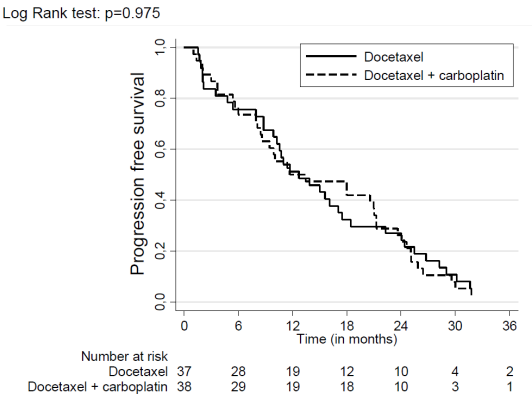

Figure 2 Progression free survival

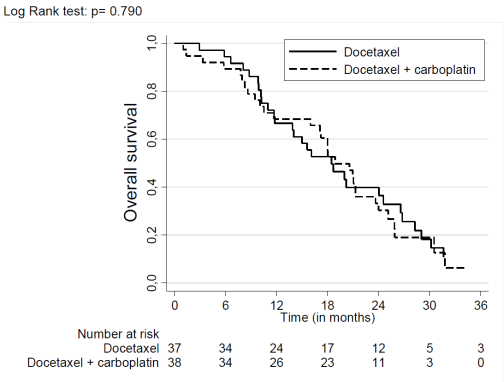

Figure 3 Overall survival, measured from the first day of docetaxel-based chemotherapy

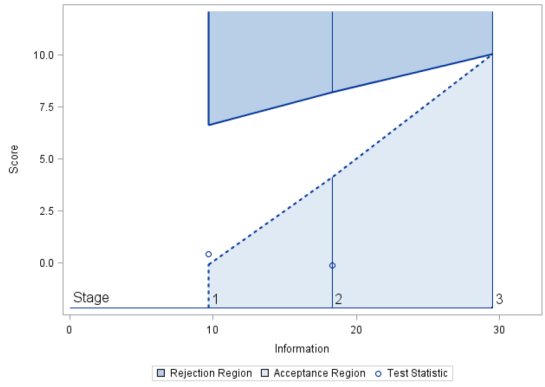

Figure 4 Acceptance of H0 based on post-hoc power analysis

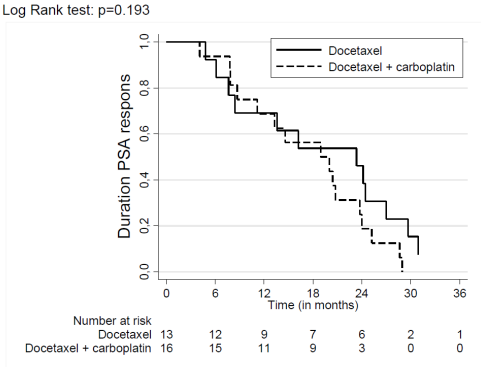

Figure 5 duration of PSA response in PSA responders

The PSA response (35.1% versus 42.1%) was comparable in both groups, similarly as the duration of PSA response (Figure 5).

The best radiological response was defined in 22 and 16 patients with measurable disease at the start of the study in group A and B respectively. A complete response was not observed, but there was a partial response in 6 (27.3%) and 5 (31.3%) patients, no change in 12 (54.5%) and 9 (56.3%), and progressive disease in 3 (13.6%) and 1 (6.3%) patient. Both groups contained one non-evaluable patient.

As table 2 shows, the incidence of grade 3/4 infections (all kinds pooled together) and gastro-intestinal adverse events was significantly higher in the combination treatment group (2.7% versus 25% P=0.007 and 0 versus 13.9% p=0.025 respectively). The difference of 0 versus 3 episodes of febrile neutropenia is not significant.

In the analysis of the Quality of Life, we did not find any significant difference in FACT-P scores at baseline or during treatment, nor did we find any differences in patterns of differences during or after treatment.

Table 2 Incidence of grade 3/4 toxicity

Grade 3/4 toxicity	***Arm A; Docetaxel N=37***	***Arm B; Docetaxel+carboplatin N=36***	***Significance P***
Hematologic			
Anemia	0	3 (8.3%)	NS
Neutropenia	4 (10.8%)	5 (13.9)	NS
Leukopenia	3 (11.1%)	2 (5.6%)	NS
Thrombopenia	1 (2.7%)	3 (8.3)	NS
Infection/fever (all)	1 (2.7%)	9 (25%)	0.007
Febrile neutropenia	0	3 (8.3%)	NS
Infection (not neutropenic)	0	2 (5.6%)	NS
Fever	0	1 (2.8%)	NS
Sepsis (not neutropenic)	0	1 (2.8%)	NS
Other infections	1 (2.7%)[1]	2 (5.6%)[2]	NS
Gastrointestinal	0	5 (13.9%)	0.025
Diarrhea	0	2 (5.6%)	NS
Obstipation	0	2 (5.6%)	NS
Vomiting	0	1 (2.8%)	NS
Fatigue	5 (13.5%)	7 (19.4%)	NS
Cardial	2 (5.4%)3a	5 (13.9%)3b	NS
Neurology	1 (2.7%)[4a]	2 (5.6%)[4b]	NS
Pain	2 (5.4%)	1 (2.8%)	NS
Hemorrhage	0	1[5]	NS
Renal/genitourinary	2 (5.4%)	1 (2.8%)	NS
Other	3(11.1%)[6a]	8 (22.2%)[6b]	NS

1: local infection. 2: klebsiella pneumonia, upper respiratory tract infection. 3a: hypertension, 3b: hypertension (3) left ventricular dysfunction, atrial flutter. 4a: sensory neuropathy. 4b: TIA, CNS ischemia. 5: GI bleeding. 6a: malaise, nail changes, thrombosis. 6b hypotension, weight loss, mucositis, hyperglycemia, bone fracture, hypercalcemia, hypophosphatemia, pulmonary embolism.

Discussion

This study was discontinued early due to insufficient recruitment. However, the post-hoc conditional power analysis showed that the study would not have shown a significant difference between both study arms if the study was completed according to protocol. Therefore, this trial suggests that the addition of carboplatin to retreatment with docetaxel does not prolong the PFS or OS in patients with mCRPC, while the combination resulted in more toxicity.

The studies that suggest benefit of the use of carboplatin monotherapy, or the combination with docetaxel, are all performed in different patient groups and different settings and used different dosages of chemotherapy. In this trial, patients in the combination arm were treated with a relatively low dose of chemotherapy (docetaxel 60mg/m^2 plus carboplatin AUC 4), based on an earlier publication of Ross *et al*[15]. Later studies showed that higher dosed schedules were safe as well (docetaxel 70mg/m^2 plus carboplatin AUC 5 for Oh *et al*, and docetaxel 75mg/m^2 plus carboplatin AUC 5 in the trial of Aparicio *et al*.). The lower dose in this trial might have influenced the results. The study of Oh *et al*. investigated the combination of estramustine, docetaxel and carboplatin and showed a PSA response of >50% in 68% of the patients, with a median PFS of 8.1 months and a median OS of 18 months[14]. However, this study was performed as first-line treatment and is therefore not comparable to our trial. The same applies to the carboplatin monotherapy studies mentioned in the review-article of Oh *et al*. which show a PSA response rate of 8-28% and a duration of response of 3-7months[13]. As presented by Aparicio *et al*. the addition of carboplatin to cabazitaxel in first-line treatment resulted in a significant increase in median PFS for patients with ≥2 defects in Tp53, RB1 or PTEN (aggressive tumors), but did not increase the PFS for patients without these gene defects[23]. The latter supports our findings for this selected group of patients with a good initial response to docetaxel. As our trial shows a promising PFS of 12 months for docetaxel monotherapy, addition of carboplatin seems, based on these results, redundant in this group of patients. However, based on previously described literature, our results are probably not applicable to patients with clinical features of an anaplastic prostate carcinoma, or patients with mutations that cause DNA repair defects, as a benefit of carboplatin addition is these groups is shown in different trials[17, 18].

To our knowledge, the trial of Di Lorenzo *et al*. is the only other prospective trial investigating docetaxel re-treatment as a single agent study[22]. This single arm study included 45 patients and showed a median PFS of 5 months (95% CI 2-8 months) with a

median OS of 13 months (95% CI 7-18 months). A striking difference with our study is found in the baseline characteristics; the median treatment free interval since first-line docetaxel in this trial was 7 months (inclusion criterion PFI ≥5 months), compared to11.9 months in our study. This might suggest that the trial of Di Lorenzo *et al*. selected a slightly different study population, which is also suggested by the difference in the number of administered treatment cycles (median number of 3 cycles for Di Lorenzo *et al*. versus 7 cycles in this trial). Two retrospective studies showed an important impact of the initial PFS after first-line docetaxel on the effect of re-treatment with docetaxel. From the study of Loriot *et al*. it is known that the response, PFS and OS are significantly better for patients with an initial PFS after first-line treatment of ≥ 3 months (PFS 3.4 months versus 6.3 months, p=0.04 and OS 12.8 months versus 19.4 months, p=0.04)[20]. These results are confirmed by Oudard *et al*. who found a median OS of 20.4 months (95% CI 16.8-25.7) for patients with an initial response >6 months, versus 17.1 months (95% CI 13.3-24.6) for patients with an initial response of 3-6 months and 15.7 months (95% CI 11.8-20.3) for the patients with an initial response <3 months[19]. This might account for the difference between the study of Di Lorenzo and this trial.

Also, data from several retrospective studies are suggestive for a beneficial effect of docetaxel re-challenge after a certain taxane-free interval , with PSA response rates of 28-48%, median PFS of 4.3-6.3 months and median OS of 15.8-21.8 months[19, 20, 22, 24-26]. Time between the last cycle of first-line treatment and start of the re-challenge with docetaxel was definitely shorter in all these trials.

Although the inclusion criteria allowed inclusion after a progression free interval of 3 months after first-line docetaxel, the median interval was 11.9 months. The results of our trial are therefore only applicable to a selected patient group. Although not included in this trial, a rechallenge with docetaxel could also be considered for hormone naïve prostate cancer patients initially treated with ADT plus docetaxel ('CHAARTED or Stampede schedule), as these patients are also likely to have a long initial response to this treatment [27, 28]. However, it is not possible to determine whether they responded on hormonal treatment and/or docetaxel.

Nowadays, cabazitaxel is registered as second-line chemotherapy for patients with progressive mCRPC after docetaxel containing treatment. To our knowledge, no clinical trials have been performed comparing re-treatment with docetaxel with cabazitaxel containing treatment. As the patients treated in the Tropic trial [8] are remarkably different from the patients in this trial (median time from last docetaxel dose to disease progression was 0.8 months), we cannot compare our data with this trial. This hinders definite

conclusions on the best strategy, but to our opinion, it is very plausible that cabazitaxel can play a role at the moment of disease progression after re-treatment with docetaxel. Hereby, re-treatment with docetaxel adds an extra step in the treatment of these patients.

Conclusion

For patients with mCRPC and an initial good response to docetaxel, re-treatment with docetaxel monotherapy is a feasible and save treatment option. Addition of carboplatin resulted in more toxicity. Docetaxel re-challenge could be considered for selected mCRPC patients with a relatively long progression-free interval after docetaxel treatment.

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