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A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

The Use of Cabazitaxel in Men with Castrate Resistant Metastatic Prostate Cancer Previously Treated with Docetaxel

S. Hotte, A. Haynes, N. Fleshner, and A. Loblaw

Report Date: October 25, 2011

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CED-CCO Special Advice Report 23

The Use of Cabazitaxel in Men with Castrate Resistant Metastatic Prostate Cancer Previously Treated with Docetaxel

S. Hotte, A. Haynes, N. Fleshner, and A. Loblaw

Report Date: October 25, 2011

SUMMARY

QUESTION

Does the use of cabazitaxel, either alone or in combination, for the treatment of patients with castrate resistant metastatic prostate cancer who were previously treated with a docetaxel-containing regimen result in improved outcomes?

Outcomes of interest include overall survival, progression-free survival, time-to-progression, time-to-next treatment, time-to-treatment failure, objective and prostatic-specific antigen (PSA) response rates, pain response rate, palliation, quality of life, and adverse events.

TARGET POPULATION

Adult patients with castrate resistant metastatic prostate cancer who have been previously treated with a docetaxel-containing regimen.

RECOMMENDATIONS

The following recommendations reflect the opinions of the authors of this special advice report.

- Cabazitaxel is recommended to improve survival in patients with metastatic castrate-resistant prostate cancer (CRPC) who have progressed following therapy with a docetaxel-containing regimen. Patients should be counselled on the risk of adverse events, especially hematological adverse events.

- Patient preferences need to be taken into account when considering ANY further therapy in patients with metastatic CRPC who progress following therapy with a docetaxel-containing regimen. Clinicians should discuss with these patients the goals of treatment, including what is most important to them. Increased survival, symptom

relief, and the risk of adverse events associated with each treatment option are important considerations that should be discussed with each patient.

QUALIFYING STATEMENTS

- The evidence regarding the most appropriate patient to receive cabazitaxel is incomplete. However, based on the available evidence and expert opinion, cabazitaxel may be most appropriate for patients who have progressed on or within six to 12 months after completing docetaxel. In patients who have a very prolonged benefit from first-line docetaxel, retreatment with the same agent may be appropriate, but all decisions should be at the discretion of the treating oncologist.

- The evidence regarding the optimal regimen is incomplete. However, based on the available evidence and expert opinion, the regimen from the TROPIC trial (10 cycles or less of cabazitaxel 25 mg/m^2 intravenously (i.v.) over one hour every three weeks plus 10 mg of oral prednisone daily) may be most appropriate for most patients prescribed cabazitaxel. In singular instances—where patients continue to benefit from cabazitaxel with minimal toxicity—more than 10 cycles could be given, at the discretion of the treating physician and the patient.

- According to established guidelines, prophylactic granulocyte-colony stimulating factor (G-CSF) should not be routinely given in patients receiving cabazitaxel and dose reductions should be considered in patients who are felt to be at high risk from febrile neutropenia complications. Use of G-CSF in subsequent cycles should occur according to these same guidelines.

KEY EVIDENCE

One randomized controlled trial was identified that investigated the use of cabazitaxel in men with castrate resistant metastatic prostate cancer (1). Patients were randomized to receive either cabazitaxel and prednisone (n=378) or mitoxantrone and prednisone (n=377). The authors reported a significant difference in overall survival in favour of cabazitaxel compared to mitoxantrone (median, 15.1 months versus [vs.] 12.7 months; hazard ratio [HR] 0.70, p<0.0001). Although the authors did not report whether statistical comparisons were made on the rates of adverse events between the treatment arms, more patients in the cabazitaxel arm experienced hematological adverse events and diarrhea, both of any grade or grade 3/4, than the mitoxantrone arm (see Full Report, Table 4).

RELATED PROGRAM IN EVIDENCE-BASED CARE GUIDELINES

- Evidence-based Series (EBS) 3-15: Non-Hormonal Systemic Therapy in Men with Metastatic Hormone-Refractory Prostate Cancer.
  Available at:
  https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/genito-ebs/.

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REFERENCES—SUMMARY

1. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels J-P, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010 Oct 2;376(9747):1147-54.

FULL REPORT

QUESTION

Does the use of cabazitaxel, either alone or in combination, for the treatment of patients with castrate resistant metastatic prostate cancer who were previously treated with a docetaxel-containing regimen result in improved outcomes?

Outcomes of interest include overall survival, progression-free survival, time-to-progression, time-to-next treatment, time-to-treatment failure, objective and prostatic-specific antigen (PSA) response rates, pain response rate, palliation, quality of life, and adverse events.

INTRODUCTION

Approximately 25,500 new cases of prostate cancer are estimated to be diagnosed in Canada in 2011 (1), making prostate cancer the most commonly diagnosed new cancer in men. Approximately 27.5% of all new cases of cancer will be in the prostate. Prostate cancer has the fourth-highest mortality rate overall, and the third-highest in men, with 4,100 deaths estimated for 2011 (1). Approximately 10.2% of all cancer deaths will be due to prostate cancer (1).

Castrate-resistant prostate cancer (CRPC) presents as a spectrum of disease ranging from rising PSA levels without metastases or symptoms, and despite androgen deprivation therapy, to metastases and significant debilitation from cancer symptoms. Prognosis is associated with several factors, including performance status, presence of bone pain, extent of disease on bone scan, and serum levels of alkaline phosphatase. Bone metastases will occur in 90% of men with CRPC and can produce significant morbidity, including pain, pathologic fractures, spinal cord compression, and bone marrow failure. Paraneoplastic effects are also common, including anemia, weight loss, fatigue, hypercoagulability, and increased susceptibility to infection.

Docetaxel continues to be the recommended first-line treatment for chemotherapy-naive patients with metastatic CRPC, because of its positive effects on survival and palliative effects (2,3). In patients who have failed docetaxel-based therapy, treatment options have been limited until recently and no treatment to date has shown survival improvements. Treatments options are based on patient and physician preferences and may include mitoxantrone, clinical trials, retreatment with docetaxel or symptomatic management only. Although not formally evaluated in randomized trials in the post-docetaxel setting, mitoxantrone is, for many oncologists, a de facto standard of care for these patients and an appropriate comparator for second-line clinical trials.

The Committee to Evaluate Drugs—Cancer Care Ontario (CED-CCO) subcommittee asked the Genitourinary (GU) Disease Site Group (DSG) of the Program in Evidence-based Care (PEBC) to provide advice on the use of cabazitaxel in patients with castrate resistant metastatic prostate cancer who were previously treated with a docetaxel-containing regimen.

METHODS

This advice report, produced by the PEBC, CCO, is a convenient and up-to-date source of the best available evidence on the use of cabazitaxel in patients with castrate resistant metastatic prostate cancer who were previously treated with a docetaxel-containing regimen, developed through a systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is editorially independent of the Ontario Ministry of Health and Long-Term Care.

The PEBC has a formal standardized process to ensure the currency of each clinical guidance report. This process consists of the periodic review and evaluation of the scientific

literature and, where appropriate, integration of this literature with the original clinical guidance report information.

Literature Search Strategy

MEDLINE (Ovid) (1996 to September Week 2 [September 26], 2011), EMBASE (Ovid) (1996 to Week 38 [September 26], 2011), and the Cochrane Database of Systematic Reviews (CDSR) (Issue 10, October 2011) were searched. The search strategies for MEDLINE and EMBASE are shown in Appendix 1. Search strategies in other databases were similar.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO), 2007–2011, were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp), the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp), and the National Institute for Clinical Excellence (http://www.nice.org.uk/) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials. Personal files were also searched.

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were published full report articles or published meeting abstracts of the following:

1. Randomized trials comparing the use of cabazitaxel, either alone or in combination, to another agent, combination of agents, or placebo. Patients must have castrate-resistant metastatic prostate cancer and have been previously treated with a docetaxel-containing regimen. Data must be reported on at least one of the following outcomes: overall survival, progression-free survival, time-to-progression, objective tumour response, PSA response, pain response, palliation, quality of life, or adverse events.
2. Systematic reviews that included randomized trials comparing the use of cabazitaxel (alone or in combination) to another agent, combination of agents, or placebo in patients with castrate resistant metastatic prostate cancer who were previously treated with a docetaxel-containing regimen.

Exclusion Criteria

Studies were excluded if they were:

1. Letters, comments, books, notes, or editorial publication types.
2. Articles published in a language other than English, due to financial considerations for translation.

Synthesizing the Evidence

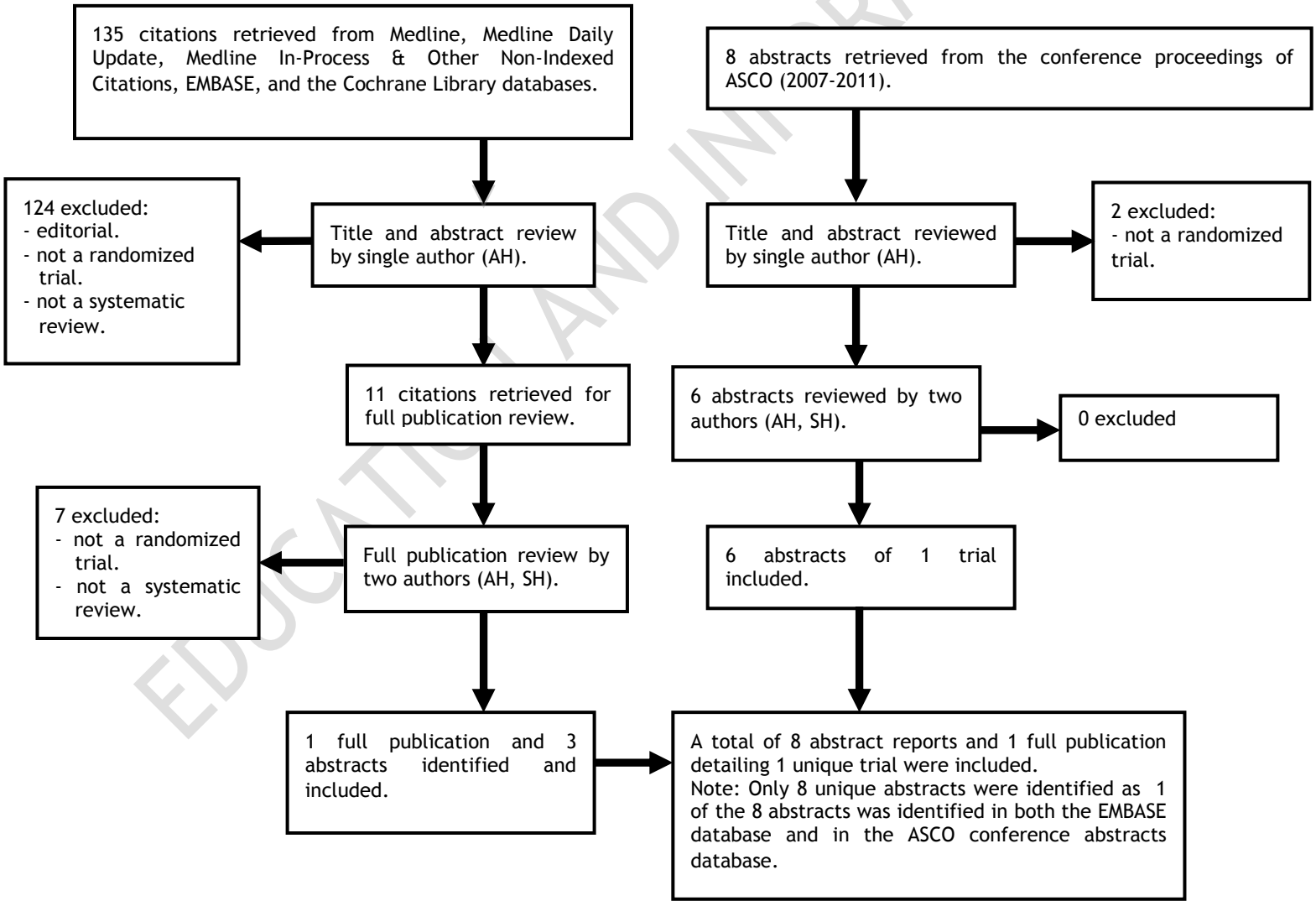
No meta-analysis was conducted as only one randomized controlled trial (RCT) was identified.

Literature Search Results

A total of 135 citations were retrieved from the OVID MEDLINE and EMBASE databases and the Cochrane Database of Systematic Reviews. Of those, one full publication was identified that met the eligibility criteria (4), as well as three abstracts from the conference proceedings of ESMO (5), the European Association of Urology (6), and ASCO (7) (all identified in EMBASE). The conference proceedings of ASCO were searched separately, and a total of six

abstracts were identified that met the eligibility criteria. The ASCO abstract identified in EMBASE was also identified through the separate search of ASCO. In total, eight abstracts were identified that reported results from the trial reported in the identified full publication (4) (the TROPIC trial). Three of the abstracts (5-7) reported the same results as those in the full publication. As the full publication reported either a more recent analysis of the trial results or more details of that analysis, none of those three abstracts are discussed further. Of the five remaining abstracts, two reported subgroup survival analyses based on prior docetaxel (8,9), two reported on the prophylactic use of granulocyte-colony stimulating factor (G-CSF) in patients enrolled in the RCT (10,11), and one reported on estimating the mean overall survival for use in health economic analyses (12). The three abstracts (8,9,12) that conducted additional survival analyses are not discussed further as details regarding how these retrospective analyses were conducted were not included, thus making it difficult to determine the generalizability of those results.

Figure 1. Selection of studies investigating cabazitaxel in patients with CRPC, who were previously treated with a docetaxel-containing regimen, from the search results of MEDLINE, EMBASE, and the Cochrane Library databases, and the conference proceedings of ASCO.



Patient Characteristics, Study Design, and Trial and Patient Characteristics

One fully published RCT was identified that investigated the use of cabazitaxel in patients with castrate resistant metastatic prostate cancer who were previously treated with a docetaxel-containing regimen (Table 1). de Bono et al (4) enrolled patients aged 18 years or older, with pathologically proven prostate cancer. Patients must have had documented disease progression during or after treatment that included docetaxel. Patients with measurable disease had to have progression documented by Response Evaluation Criteria in Solid Tumours (RECIST), with at least one visceral or soft-tissue metastatic lesion. Patients with non-measurable disease had to have rising PSA concentrations, defined as two increases in PSA values relative to a reference value that were measured at least one week apart, or patients had to have at least one new radiographic lesion.

Table 1. Trial and patient characteristics in trials investigating the use of cabazitaxel in patients with castrate resistant metastatic prostate cancer who were previously treated with a docetaxel-containing regimen.

Author, year (ref)	Patient characteristics	Treatment	N
de Bono, 2010 (4)	Patients, aged ≥18 years, with pathologically proven prostate cancer with disease progression during or after completion of treatment with docetaxel. ECOG PS 0-2. Patients were excluded if they had previous mitoxantrone therapy, radiotherapy to 40% or more of bone marrow, or cancer therapy other than luteinising-hormone-releasing hormone within 4 weeks of enrolment.	Cabazitaxel 25 mg/m^2 i.v. over 1h d1 + prednisone 10 mg/d, q21d for a maximum of 10 cycles. Premedication administered 30 min prior to cabazitaxel consisted of i.v. antihistamine, corticosteroid, and histamine H_2-antagonist.	378
		Mitoxantrone 12 mg/m^2 i.v. over 15-30 min d1 + prednisone 10 mg/d, q21d for a maximum of 10 cycles.	377

Notes: d=day(s); ECOG=Eastern Cooperative Oncology Group; h=hour; i.v.=intravenous; min=minute(s); N=number randomized; PS=performance status; q=every; ref=reference.

Patients were randomized to receive cabazitaxel (n=378) or mitoxantrone (n=377) (Table 1). The randomization was stratified by the measurability of disease (measurable versus [vs.] not measurable) and by the Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs. 2). Select quality characteristics of the RCT can be found in Table 2. Neither the patients nor the treating physicians were masked to treatment allocation; however, the study team was blinded to the data analysis. The authors reported that the treatment arms were balanced at baseline for a number of factors, including demographics, disease characteristics, and previous treatments, and that the sample size requirement (Table 2) was met for the primary outcome and overall survival. Secondary outcomes included progression-free survival, time-to-progression, and several measures of response including the following: PSA response (decrease of 50% or more in serum PSA concentration in patients with a baseline value of 20 μg/L or more); PSA progression (increase of 25% or more over nadir PSA concentration, given that the increase in absolute PSA value was 5 μg/L or more in those with no PSA response or 50% or more over nadir for PSA responders); objective tumour response (for patients with measurable disease and based on RECIST criteria); pain response (determined only in patients with a median McGill-Melzack present pain intensity [PPI] scale (13) score ≥2 or a mean analgesic score of ≥10 points at baseline, or both, and defined as decrease of 2 points or more from baseline median PPI score without increasing analgesic score, or decreases of more than 50% in analgesic use without an increase in pain score, over three or more weeks); and, pain progression (increase in median

PPI score of 1 or more points from the reference value or an increase of 25% or more in the mean analgesic score or a requirement for palliative radiotherapy). The authors reported that although the allocation schedule was randomized and centralized, patients and treating physicians were not blind to treatment assignment. The study team was blinded to data analyses. In addition, the authors reported that the analysis was final and intention-to-treat. Although the trial protocol included planned interim analyses, for futility and efficacy, the trial was not terminated early.

Table 2. Quality characteristics of identified RCT.

Author, year (ref)	Primary outcome	Required sample size	Secondary outcomes	Randomization method	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Losses to follow-up	Ethical Approval
de Bono, 2010 (4)	OS	720 pts req'd to detect a 25% reduction in HR for death cabazitaxel vs. mitoxantrone with 90% power, with two-sided α=0.05 and an estimated median survival of 8 months in the mitoxantrone group.	PFS[A], response[B], TTP	Centralized, computer-generated randomization with stratification	Yes	Study team blinded to data analysis	Yes	Yes	No	2 pts	Yes

Notes: ITT=intent-to-treat; OS=overall survival; PFS=progression-free survival; pts=patients; ref=reference; req'd=required; TTP=time-to-progression; vs.=versus.

[A]Progression-free survival was defined as the time between randomization and progression as measured by either PSA progression, tumour progression, pain progression, or death.

[B]Several response measures were used: PSA response (25% or more increase over nadir PSA concentration so long as absolute PSA value was 5 μg/L or more for men with no PSA response, or a 50% or more increase over nadir for PSA responders; objective tumour response for measurable disease based on RECIST criteria; pain response, and pain progression.

Efficacy Outcomes

Efficacy outcomes for the identified RCT can be found in Table 3.

Survival

The authors reported a significant difference in overall survival in favour of cabazitaxel compared to mitoxantrone (median, 15.1 months vs. 12.7 months; hazard ratio [HR], 0.70; p<0.0001; Table 3).

Disease Control and Response

The authors reported statistically significant differences in time-to-tumour-progression, time-to-PSA-progression, objective tumour response, and PSA response in favour of cabazitaxel (Table 3). The authors also reported a significant difference in progression-free survival in favour of cabazitaxel compared to mitoxantrone (median, 2.8 months vs. 1.4 months; HR, 0.74; p<0.0001). Progression-free survival was a composite outcome calculated from the time between randomization and date of progression as measured either by PSA response, tumour progression, or death.

Adverse Events

Adverse events were reported for 371 patients in the cabazitaxel arm and 371 patients in the mitoxantrone arm. The authors did not report statistical comparisons between the treatment arms with respect to any of the reported adverse events, either any grade or grade 3/4. Table 4 shows the rates of grade 3/4 adverse events that were reported in more than 1% of patients in either arm. Of note, high rates of grade 3/4 neutropenia and leucopenia were reported in both arms, although the rates were higher in the cabazitaxel arm (Table 4). The following grade 3/4 adverse events were reported in 2% or less of patients in both study arms: nausea, vomiting, hematuria, abdominal pain, pain in extremity, dyspnea, constipation, pyrexia, arthralgia, urinary-tract infection, pain, and bone pain.

The following adverse events (any grade) were reported in more than 10% of patients in either arm: diarrhea (47% vs. 11%, cabazitaxel vs. mitoxantrone, respectively), fatigue (37% vs. 27%), asthenia (20% vs. 12%), back pain (16% vs. 12%), nausea (34% vs. 23%), vomiting (23% vs. 10%), hematuria (17% vs. 4%), abdominal pain (12% vs. 4%), dyspnea (12% vs. 5%), constipation (20% vs. 15%), pyrexia (12% vs. 6%), and arthralgia (11% vs. 8%). The following hematological adverse events (any grade) were reported: neutropenia (94% vs. 88%, cabazitaxel vs. mitoxantrone, respectively), leucopenia (96% vs. 92%), anemia (97% vs. 81%), and thrombocytopenia (47% vs. 43%). The following adverse events (any grade) were reported in 10% or less of patients in both arms of the study: pain in extremity, urinary-tract infection, pain, and bone pain.

Ozguroglu et al reported, in abstract form at the 2011 ASCO annual meeting (11) and at the 2011 ASCO Genitourinary Cancers Symposium (10), a subgroup analysis of G-CSF prophylaxis in patients enrolled in the TROPIC trial reported by de Bono et al (4). The authors conducted the analysis given the fact that a higher proportion of patients in the cabazitaxel group experienced grade 3/4 neutropenia and febrile neutropenia compared to patients in the mitoxantrone group (Table 4). The trial protocol did not allow primary prophylaxis with G-CSF for neutropenia during the first cycle of treatment. G-CSF use was permitted in subsequent cycles if patients first experienced neutropenia lasting seven days or more or patients experienced neutropenia with fever or infection (4). For their analysis, G-CSF use was considered prophylactic if administered within three days of chemotherapy; conversely, it was considered therapeutic if administered more than three days after chemotherapy (10,11). The authors reported that 3,246 cycles of chemotherapy were administered from cycle 2 onward (10,11). Of these , 2,322 (72%) did not receive G-CSF and 924 (28%) received G-CSF. In patients who did not receive G-CSF, the percentages of the 2,322 cycles with grade 3/4 neutropenia was similar between the treatment groups—cabazitaxel 44.6% and mitoxantrone 38.4%. However, in patients randomized to the cabazitaxel arm, the percentage of cabazitaxel cycles with grade 3/4 neutropenia was significantly lower in the group of patients who received G-CSF prophylaxis compared with the group who received G-CSF therapeutically (24.7% vs. 57.7%, respectively, $p<0.0001$). A similar trend was observed in the mitoxantrone group with grade 3/4 neutropenia in 9.3% of prophylactic G-CSF cycles compared to 33.3% of therapeutic G-CSF cycles ($p<0.0001$). Although the authors concluded that G-CSF use reduced the incidence and severity of neutropenia in men receiving cabazitaxel, the design of the main study and the retrospective nature of this analysis prohibited any conclusion on the impact of this reduction of neutropenia on the incidence of febrile neutropenic events. The authors also suggested that G-CSF should continue to be given as recommended by practice guidelines.

Quality of Life

Quality of life outcomes were not reported by the authors (4).

Table 3. Efficacy outcomes in trials of cabazitaxel in patients with castrate resistant prostate cancer who were previously treated with a docetaxel-containing regimen.

Author, year (ref)	Treatment	N	OS (mdn, mos)	PFS (mdn, mos)	TTP-Tumour (mdn, mos)	TTP-PSA (mdn, mos)	TTP-Pain (mdn, mos)	OR (%)	PSA response (%)	Pain response (%)	Follow-up (mdn, mos)
de Bono, 2010 (4)	Cabazitaxel	378	15.1	2.8	8.8	6.4	11.1	14.4	39.2	9.2	12.8
	Mitoxantrone	377	12.7 HR 0.70 CI 0.59-0.83; p<0.0001	1.4 HR 0.74 CI 0.64-0.86; p<0.0001	5.4 HR 0.61 CI 0.49-0.76; p<0.0001	3.1 HR 0.75 CI 0.63-0.90; p=0.001	NYR HR 0.91 CI 0.69-1.19; p=0.52	4.4 p=0.0005	17.8 p=0.0002	7.7 p=0.63	

Notes: CI=95% confidence interval; HR=hazard ratio; mdn=median; mos=months; N=number of patients randomized; OR=objective tumour response; OS=overall survival; TTP-Pain=time-to-pain-progression; TTP-PSA=time-to-pain-progression; TTP-Tumour=time-to-tumour-progression.

Table 4. Grade 3 or 4 adverse events occurring in more than 1% of patients in either study arm in the identified RCT.

Author, year (ref)	Treatment	N	Neutropenia (%)	Febrile neutropenia (%)	Leukopenia (%)	Anemia (%)	Thromo-cytopenia (%)	Diarrhea (%)	Fatigue (%)	Asthenia (%)	Back pain (%)	Nausea (%)	Vomiting (%)	Hematuria (%)	Abdominal pain (%)	Pain in extremity (%)	Pain (%)	Bone pain (%)
de Bono, 2010 (4)	Cabazitaxel	371	82	8	68	11	4	6	5	5	4	2	2	2	2	2	1	1
	Mitoxantrone	371	58	1	42	5	2	<1	3	2	3	<1	0	1	0	1	2	2

Notes: N=number of patients evaluable for adverse events; ref=reference.

DISCUSSION

The results of the trial reported by de Bono et al (4) demonstrate that the longer median overall survival for the cabazitaxel arm compared to the mitoxantrone arm is statistically significant in patients with metastatic CRPC who previously received docetaxel. Clinically, the median difference may result in 2.3 months or approximately 10 weeks longer survival for patients who receive cabazitaxel. However, as is the case for all studies of patients with very advanced disease, the improvement in the HR is more helpful in determining the impact of cabazitaxel on survival. In TROPIC, the HR of 0.8 translates into a 20% improvement in the chance of being alive at any point during the follow-up period of the trial, which is statistically significant and is likely to be clinically relevant to patients and physicians as well.

It is interesting to note that no statistically significant difference was demonstrated for the cabazitaxel arm compared to the mitoxantrone arm in time-to-progression of pain score (HR, 0.91; p=0.52) or in pain response (9.2% vs. 7.7%; p=0.63). Furthermore, higher incidences of adverse events such as neutropenia, febrile neutropenia, and diarrhea in patients receiving cabazitaxel highlight the fact that this agent may be more suitable in relatively more fit patients who are not experiencing serious difficulties in pain control.

Abiraterone is an orally active agent that has also been recently approved for use in men with CRPC post-docetaxel. Although not studied in a head-to-head comparative trial, the abiraterone therapeutic ratio (14) may be somewhat superior to cabazitaxel, as there appears to be similar efficacy with less toxicity with abiraterone compared to cabazitaxel. For this reason, cabazitaxel will likely be utilized in third line or perhaps for younger men as second line in light of its toxicity profile, but final decisions regarding the choice and order of treatment will likely be made through discussions between the patient and his oncologist.

CONCLUSIONS

The authors of this special advice report make the following recommendations:

- Cabazitaxel is recommended to improve survival in patients with metastatic castrate-resistant prostate cancer who have progressed following therapy with a docetaxel containing regimen. Patients should be counselled on the risk of adverse events, especially hematological adverse events.

- Patient preferences need to be taken into account when considering ANY further therapy in patients with metastatic CRPC who progress following therapy with a docetaxel-containing regimen. Clinicians should discuss with these patients the goals of treatment including what is most important to them. Increased survival, symptom relief, and the risk of adverse events associated with each treatment option are important considerations that should be discussed with each patient.

Qualifying Statements:

- The evidence regarding the most appropriate patient to receive cabazitaxel is incomplete. However, based on the available evidence and expert opinion, cabazitaxel may be most appropriate for patients who have progressed on or within six to 12 months after completing docetaxel. In patients who have a very prolonged benefit from first-line docetaxel, retreatment with the same agent may be appropriate, but all decisions should be at the discretion of the treating oncologist.

- The evidence regarding the optimal regimen is incomplete. However, based on the available evidence and expert opinion, the regimen from the TROPIC trial (10 cycles or

less of cabazitaxel 25 mg/m^2 intravenously [i.v]. over one hour every three weeks plus 10 mg of oral prednisone daily) may be most appropriate for most patients prescribed cabazitaxel. In singular instances—where patients continue to benefit from cabazitaxel with minimal toxicity—more than 10 cycles could be given, at the discretion of the treating physician and the patient.

- According to established guidelines, prophylactic G-CSF should not be routinely given in patients receiving cabazitaxel and dose reductions should be considered in patients who are felt to be at high risk from febrile neutropenia complications. Use of G-CSF in subsequent cycles should occur according to these same guidelines.

ONGOING TRIALS

The National Cancer Institute clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and the National Institutes of Health Clinical Trials database (http://clinicaltrials.gov/) were searched for reports of new or ongoing randomized trials investigating the use of cabazitaxel in patients with metastatic castrate resistant prostate cancer. Details of the identified trials can be found in Appendix 2.

CONFLICT OF INTEREST

The authors of this special advice report disclosed potential conflicts of interest relating to the topic of this special advice report. The authors (SH, AH) declared that they had no conflicts of interest.

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Appendix 1. Literature search strategies.

Ovid MEDLINE

1. cabazitaxel:.mp.
2. jevtana:.mp.
3. 1 or 2
4. exp prostatic neoplasms/
5. prostat: cancer:.mp.
6. prostat: carcinom:.mp.
7. or/4-6
8. 3 and 7
9. limit 8 to English language

EMBASE

1. exp cabazitaxel/
2. cabazitaxel:.mp.
3. jevtana:.mp.
4. or/1-3
5. exp prostate carcinoma/
6. prostat: cancer:.mp.
7. prostat: carcinom:.mp.
8. or/5-7
9. 4 and 8
10. limit 9 to English language

Appendix 2. Ongoing trials.

Randomized, open-label multi-centre study comparing cabazitaxel at 20 mg/m^2 and at 25 mg/m^2 every 3 weeks in combination with prednisone for the treatment of metastatic castration resistant prostate cancer previously treated with a docetaxel-containing regimen.

Protocol ID:	NCT01308580
Last date modified:	October 13, 2011
Trial type:	Randomized, open-label
Accrual:	1200
Primary outcome:	Progression-free survival, objective tumour response, PSA response, pain response
Sponsorship:	Sanofi-Aventis
Status:	Ongoing, recruiting

Randomized, open label, multi-centre study comparing cabazitaxel at 25 mg/m^2 and at 20 mg/m^2 in combination with prednisone every 3 weeks to docetaxel in combination with prednisone in patients with metastatic castration resistant prostate cancer not pretreated with chemotherapy

Protocol ID:	NCT01308567
Last date modified:	October 13, 2011
Trial type:	Randomized, open label
Accrual:	1170
Primary outcome:	PFS, objective tumour response, PSA response, pain response
Sponsorship:	Sanofi-Aventis
Status:	Ongoing, recruiting