Horizon Scanning in Oncology

Second-line chemotherapy with cabazitaxel (Jevtana®) for the treatment of castration-resistant metastatic prostate cancer

HTA-Zentrum Bremen

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1 Drug description

Generic/Brand name/ATC code:

Cabazitaxel (XRP-6258)/Jevtana®/not yet available

Developer/Company:

Sanofi-Aventis

Description:

cabazitaxel, a new molecular entity, belongs to the taxanes

Cabazitaxel, a new molecular entity, is an anticancer drug which belongs to the taxanes. This novel taxane inhibits microtubules which are crucial for cell division. Cabazitaxel binds to tubulin and thus promotes the assembly of tubulin into microtubules while simultaneously inhibiting disassembling, resulting in the inhibition of mitosis and accordingly in cell death [1]. One characteristic of cabazitaxel is a low affinity for P-gylcoprotein, a multidrug resistance transporter, which can cause resistance to docetaxel, another taxane which is the standard therapy for castration-resistant prostate cancer [2-4]. In preclinical test and in initial clinical trial, cabazitaxel was active in docetaxel-sensitive and in docetaxel-resistant cancers [1].

active in docetaxel-resistant cancers

Cabazitaxel is administered intravenously at a dose of 25mg/m^2 every three weeks. 10mg prednisone per os should be administered daily throughout the therapy with cabazitaxel. An injection kit, containing 60mg/1.5mL cabazitaxel, is available [5]. No explicit recommendation on the optimal treatment duration was found.

dose: 25mg/m^2 intravenously every three weeks

2 Indication

Cabazitaxel is indicated for the treatment of patients with castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

for 2nd line therapy of castration-resistant metastatic prostate cancer

3 Current regulatory status

positive opinion of EMA's Committee for Medicinal Products for Human Use in January 2011

In January 2011, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for the marketing authorization for cabazitaxel in combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen [6].

licensed in the US since June 2010

The US Food and Drugs Administration (FDA) granted market authorization for Jevtana® in combination with prednisone for the treatment of patients with castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen in June 2010 [5].

4 Burden of disease

most common cancer in men

usually diagnosed at an early stage

~150 patients per year with metastatic cancer in Austria

Prostate cancer is the most common cancer in Austrian men and the second most common cancer-related cause of death [7, 8]. Median age at diagnosis is 72 years. In 2008, about 4,400 men were newly diagnosed with this cancer and 1,200 died. In Germany, 60,100 patients were diagnosed with prostate cancer and 11,600 died in 2006 [9]. Due to widespread prostate-specific antigen (PSA) testing, prostate cancer is mostly diagnosed at an early, asymptomatic stage of disease, resulting in about 5% of patients diagnosed after the tumour has spread [8]. In Austria, disseminated disease was found in about 3.3% of patients, resulting in about 150 patients with metastatic prostate cancer per year [8]. Applying the same numbers to Germany would result in about 2,000 patients with disseminated prostate cancer.

risk factors are age, ethnicity, genetic factors,…

Risk factors for developing prostate cancer include age, ethnicity, family history, diet and genetic factors such as mutations in BRCA1 and BRCA2 genes [10].

symptoms might include urinary urgency, erectile dysfunction, pain…

If not detected by PSA screening, clinical findings include asymmetric areas of induration or frank nodules in the prostate during digital rectal examination, genitourinary symptoms (e.g. urinary urgency, nocturia, erectile dysfunctions) and, in the minority of patients, symptoms of metastatic disease. As prostate cancer mainly metastasises to bone, most common symptoms at this stage are bone pain. To establish diagnosis of prostate cancer, a histologic examination should be performed [10].

Staging is done by using the tumour, node, metastasis (TNM) system which provides information for choosing the initial therapy. Other factors which impact on the choice of initial therapy are life expectancy, comorbidities, therapeutic side-effects and patients' preferences [11].

TNM system, Gleason score and pre-treatment levels to establish prognosis

Besides the TNM system, the Gleason score is used in addition to establish prognosis. This score is a histopathologic grading system which distinguishes well and poorly differentiated prostate tissue [11, 12]. By taking the TNM system, the Gleason score and pre-treatment PSA levels into account, five patient groups with different probabilities of cure can be derived [10].

Prognosis strongly depends on the stage at diagnosis. If the tumour is confined to the prostate gland, a median survival of more than 5 years can be expected. For locally advanced forms of prostate cancer, cure is rarely possible, but median survival is still about 5 years. Patients with metastasised tumours have a median survival of 1-3 years [12].

median survival for patients with metastasised tumours is 1 - 3 years

5 Current treatment

Metastatic prostate cancer is not curable; therefore the main objective of therapy for this stage is to maintain quality-of-life (QoL) and to control the disease [10]. Therapy includes:

- Androgen deprivation therapy (ADT) (synonym: hormone therapy, castration) is the standard initial therapy for patients with metastatic prostate cancer. Surgical castration (synonym: orchiectomy) or medical castration using a luteinizing hormone-releasing hormone (LHRH) agonist is the optimal ADT. In addition, antiandrogens for at least 7 days should be administered either prior to or simultaneously to LHRH agonists to patients with metastases who are likely to develop symptoms associated with an initial increase in testosterone ("flare") with LHRH-agonists only [7, 12].

hormone therapy is standard initial therapy

In nearly all cases, disease progresses on ADT. If PSA level rises despite castrate levels of testosterone (serum testosterone < 20-50 ng/dl) the cancer is called "castrate-resistant", "hormone-refractory" or "androgen-independent" [10]. Systemic therapy options for men with metastatic prostate cancer are then:

- Multiple and sequential secondary hormone therapy including withdrawal of ADT, antiandrogen therapy, cytochrome P450 inhibitors, oestrogens and corticosteroids. Even though no improvements in survival have been demonstrated for this therapies, the favourable toxicity profile justifies their use before the administration of chemotherapies [10, 13].
- Chemotherapy:
  - As 1st-line chemotherapy the combination of docetaxel and prednisone showed improved overall survival and improved QoL in comparison to mitoxantrone and prednisone [2, 10, 14, 15]. Therefore docetaxel is the standard of care for the initial chemotherapy in men with castration-resistant prostate cancer [4, 10, 13-15].
  - Because the combination of mitoxantrone and prednisone compared with prednisone alone achieved pain reduction in patients with bony metastases, mitoxantrone might also be used as 1st -line chemotherapy [10, 11, 13] which is considered appropriate for patients with slowly progressing disease and those who are averse to adverse effects of docetaxel [16].
  - 2nd-line chemotherapy needs to be considered after docetaxel therapy has failed. Guidelines are tentative in giving a clear recommendation of what should be applied next. Even though the combination of mitoxantrone and prednisone can be considered *de fac-*

options if disease progresses:

sequential secondary hormone therapy,

docetaxel standard of care for 1st-line chemotherapy,

mitoxantrone has a palliative treatment effect and is de-facto 2nd – line chemotherapy, but impact on survival is unclear,

to 2nd-line chemotherapy its impact on survival within this setting remains unclear [2, 10, 11].

sipuleucel-T,

- Immunotherapy with sipuleucel-T has demonstrated prolonged overall survival for minimally symptomatic patients with castrate-resistant prostate cancer and is therefore indicated for minimally symptomatic/asymptomatic and chemotherapy-naïve patients [11].
- Symptom palliation for advanced prostate cancer is mainly done by systemic therapy, which includes analgesics, radiation therapy and bisphosphonates for bone metastases [12].

clinical trials

For further lines of therapies, no standard exists. Patients might then be included into clinical trials [11].

6 Evidence

one phase III trial, the TROPIC trial, was found

In addition to a free text search including the websites of the EMA and the US FDA, a systematic literature search was conducted in PubMed, EMBASE and the Centre for Review and Dissemination Database on the 13th of December 2010. Search terms included were "Prostatic Neoplasms", "prostate cancer", "XRP-6258", "jevtana" and "cabazitaxel".

44 relevant references were identified of which one phase III study, the TROPIC trial, was included [17].

6.1 Efficacy and safety - Phase III studies

Table 1: Summary of efficacy

Study title Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial			
Study identifier	NCT00417079, EFC6193, EudraCT: 2006-003087-59, TROPIC trial		
Design	Phase III, randomized, multi-centre, multinational, open label, computer generated allocation schedule		
	Duration	Enrolment: January 2007 – October 2008 Median follow-up: 12.8 months Cut-off date for final analysis: September 2009	
Hypothesis	Superiority		
Treatment groups	Intervention	Cabazitaxel 25mg/m² iv on day 1 of each 21 day cycle + 10mg prednisone/d, for a maximum of 10 cycles, 378 patients	
	Control	Mitoxantrone 12mg/m² iv on day 1 of each 21 day cycle + 10mg prednisone/d, for a maximum of 10 cycles, 377 patients	
Endpoints and definitions	overall survival (primary outcome)	OS	time interval from date of randomisation to death due to any cause
	progression-free survival	PFS	time between randomisation and the first date of progression as measured by PSA progression, tumour progression, pain progression, or death
	time to tumour progression	TTP	number of months from randomisation until evidence of progressive disease (RECIST [18])
	PSA progression	-	increase of ≥25% over nadir PSA concentration provided that the increase in the absolute PSA value was ≥5 µg/L for men with no PSA response, or ≥50% over nadir for PSA responders

	pain progression	-	increase in median present pain intensity (PPI) score of ≥1 point from the reference value or an increase of ≥25% in the mean analgesic score or requirement for palliative radiotherapy
	pain response	-	two point or greater reduction from baseline median PPI score without an increased analgesic score (AS) or a decrease of 50% or more in the AS without an increase in the PPI score, maintained at least for 3 weeks
	tumour response	-	for patients with measurable disease based on RECIST [18]
	PSA response	-	a ≥50% reduction in serum PSA concentration, established only for patients with a serum PSA concentration of ≥20µg/L at baseline

Results and analysis			
Analysis description	Primary analysis: Intention-to-treat analysis, final analysis planned when 511 deaths had occurred		
Analysis population	Characteristics	median age: mitoxantrone 67 years vs cabazitaxel 68 years, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1: mitoxantrone 91% vs cabazitaxel 93%, median serum PSA concentration: mitoxantrone 128µg/L vs cabazitaxel 144µg/L, Bone metastases: mitoxantrone 87% vs cabazitaxel 80%, Visceral metastases: mitoxantrone 25% vs cabazitaxel 25%, Measurable disease: mitoxantrone 54% vs cabazitaxel 53%, Pain at baseline: mitoxantrone 45% vs cabazitaxel 46%	
	Inclusion	pathologically proven prostate cancer with documented disease progression during or after completion of docetaxel treatment, ECOG PS of 0–2, previous and on-going castration by orchiectomy or LHRH agonists, or both; anti-androgen withdrawal followed by progression had to have taken place at least 4 weeks (6 weeks for bicalutamide) before enrolment	
	Exclusion	previous mitoxantrone therapy, radiotherapy to 40% or more of the bone marrow, or cancer therapy (other than LHRH analogues) within 4 weeks before enrolment	
Descriptive statistics and estimate Variability	Treatment group	*Control (mitoxantrone)*	*Intervention (cabazitaxel)*
	Number of subjects	377	378
	OS (months) median 95% CI	12.7 11.6 to 13.7	15.1 14.1 to 16.3
	PFS (months) median 95% CI	1.4 1.4 to 1.7	2.8 2.4 to 3.0
	TTP (months) median 95% CI	5.4 2.3 to 10.0	8.8 3.9 to 12.0
	time to PSA progression (months) median 95% CI	3.1 0.9 to 9.1	6.4 2.2 to 10.1
	time to pain progression (months) median 95% CI	not reached -	11.1 2.9 to not reached
	Number of subjects	204	201
	tumour response rate % 95% CI	4.4 1.6 to 7.2	14.4 9.6 to 19.3
	Number of subjects	325	329
	PSA response rate % 95%CI	7.7 3.7 to 11.8	9.2 4.9 to 13.5

	Number of subjects	168	174
	pain response rate % 95% CI	7.7 3.7 to 11.8	9.2 4.9 to 13.5
	QoL	Not reported	Not reported
Effect estimate per comparison	*Comparison groups*		*mitoxantrone vs cabazitaxel*
	OS	Hazard ratio	0.7
		95% CI	0.59 to 0.83
		P value	<0.0001
	PFS	Hazard ratio	0.74
		95% CI	0.64 to 0.86
		P value	<0.0001
	TTP	Hazard ratio	0.61
		95% CI	0.49 to 0.76
		P value	<0.0001
	time to PSA progression	Hazard ratio	0.75
		95% CI	0.63 to 0.90
		P value	0.001
	time to pain progression	Hazard ratio	0.91
		95% CI	0.69 to 1.19
		P value	0.52
	QoL		Not reported

Table 2: Most frequent adverse events

		TROPIC trial	
Grade (according to CTCAE version 3.0 [19])	**Outcome**	**Control (mitoxantrone)** (n=371)	**Intervention (cabazitaxel)** (n=371)
Grade 5	AE-associated deaths ≤30 days after last dose of study	3 (1%)	18 (5%)
Grades 1 – 4	Haematological		
	Leukopenia, n (%)	343 (92%)	355 (96%)
	Anaemia, n (%)	302(81%)	361 (97%)
	Neutropenia, n (%)	325 (88%)	347 (94%)
	Non-haematological		
	Diarrhoe, n (%)	39 (11%)	173 (47%)
	Fatigue, n (%)	102 (27%)	136 (37%)
	Nausea, n (%)	85 (23%)	127 (34%)

Grades ≥3	Haematological		
	Neutropenia, n (%) febrile neutropenia, n (%)	215 (58%) 5 (1%)	303 (82%) 28 (8%)
	Leukopenia, n (%)	157 (42%)	253 (68%)
	Anaemia, n (%)	18 (5%)	39 (11%)
	Non-haematological		
	Diarrhoe, n (%)	1 (<1%)	23 (6%)
	Fatigue, n (%)	11 (3%)	18 (5%)
	Asthenia, n (%)	9 (2%)	17 (5%)

The TROPIC trial, a phase III study, investigated cabazitaxel + prednisone in comparison to mitoxantrone + prednisone in 755 men suffering from castration-resistant metastatic prostate cancer who had received previous hormone therapy, but had progressed during docetaxel containing therapy. The majority of patients had a good functional status (ECOG PS 0 or 1) and were slightly younger than patients usually are at diagnosis.

TROPIC trial included 755 patients with castration-resistant metastatic prostate cancer and disease progression during docetaxel therapy

Median OS was 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group (HR=0.70, $p<0.0001$) and was thus significantly improved. When patients were analysed according to their baseline characteristics, patients with better performance status and those who progressed during docetaxel therapy seemed to benefit more from cabazitaxel than patients with ECOG PS 2 and men whose disease progressed ≥3 months after docetaxel. Improvements were also found for other outcomes, such as PFS, tumour and PSA response rate and time to tumour progression. No differences were found for pain-related outcomes measures.

in comparison to mitoxantrone improvements in OS and other outcomes such as PFS

AEs, even of grade 3 and higher, were very frequent, with haematological being the most common ones. For example, grade ≥3 neutropenia occurred in 82% of patients treated with cabazitaxel and in 58% of patients in the mitoxantrone group. Deaths within 30 days of last study drug dose were observed twice as often in the taxane group (5%) than in the comparison group (2%). Of these, 1% in the mitoxantrone group and 5% in the cabazitaxel group were deaths related to AEs. Because febrile neutropenia grade ≥3 was observed in 7% and the most frequent cause of death in the cabazitaxel group was neutropenia, the study authors suggest careful monitoring, dose reductions and prophylactic treatment with granulocyte colony-stimulating factor (G-CSF) for the management of these toxicities.

adverse events very frequent

deaths twice as often in cabazitaxel group than in mitoxantrone group

Twice as many patients in the cabazitaxel group completed study treatment in comparison to the mitoxantrone group, but more patients discontinued cabazitaxel treatment due to AEs than patients in the mitoxantrone arm (cabazitaxel 18% vs mitoxantrone 8%).

6.2 Efficacy and safety - further studies

No further studies were identified for the investigated indication.

7 Estimated costs

no price available yet for Austria

based on estimates from the US, monthly costs of € 9,500

No price estimates for cabazitaxel are yet available for Austria. In the US, one vial containing 60mg cabazitaxel costs an estimated $ 9,600.- (≈ € 7,100) [20]. Applying these cost estimates and assuming an average number of six treatment cycles (median number of treatment cycles was six in the TROPIC trial) would result in total costs of € 42,600.- and in monthly costs of about € 9,500.-.

prophylaxis with G-CSF recommended

As the FDA recommends prophylaxis with G-CSF in order to prevent infection-related deaths in patients prone to neutropenia complications (e.g. age>65 years, poor performance status, previous episodes of febrile neutropenia [5]) these costs have to be taken into account additionally.

8 Ongoing research

Only one phase III trial was identified on clinicaltrials.gov:

on clinicaltrials.gov: 1 single arm phase III study

NCT01254279: a single arm open-label phase III clinical trial to provide early access to cabazitaxel in patients with metastatic hormone refractory prostate cancer previously treated with a docetaxel-containing regimen and to document safety of cabazitaxel in these patients. Official completion date is December 2015, but the trial will end in individual countries when cabazitaxel becomes commercially available.

4 phase I/II studies

Besides, four phase I/II trials were found on clinicaltrials.gov, most of which were safety studies.

FDA post-market requirement: 2 RCTs

Acoording to post-marketing requirements (PMR) postulated by the FDA two further phase 3 randomized controlled trials have to be conducted with the final report to be submitted in 2018. Both studies are supposed to evaluate OS as well as drug-related deaths and safety [21]:

- PMR 1649-3 obliges the developer to conduct a comparison of 75mg/m^2 docetaxel plus prednisone with cabazitaxel 25mg/m^2 plus prednisone and cabazitaxel 20mg/m2 plus prednisone as first-line chemotherapy in patients with hormone-refractory metastatic prostate cancer.

- PMR 1649-4 obliges the developer to conduct a comparison of cabazitaxel 25mg/m^2 plus prednisone and cabazitaxel 20mg/m^2 plus prednisone as second-line chemotherapy in 1,222 patients with hormone-refractory metastatic prostate cancer previously treated with docetaxel.

9 Commentary

Cabazitaxel received a positive opinion for market authorizations by EMA's CHMP in January 2011 and was licensed by the FDA in June 2010. The approved indication is cabazitaxel in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who were previously treated with a docetaxel-containing treatment regimen.

cabazitaxel received positive opinion of EMA's CHMP, already licensed in the US

The FDA's decision was based on the results of the TROPIC trial, a phase III trial, which compared cabazitaxel and mitoxantrone in 755 patients with castration-resistant metastatic prostate cancer previously treated with docetaxel. The median OS was prolonged by 2.4 months in patients who had received cabazitaxel in comparison to mitoxantrone. The relative risk of death was reduced by 30% (HR=0.70, $p<0.0001$), whereas the absolute risk reduction was 13% (74% died in the mitoxantrone group and 61% died in the cabazitaxel group). Similar results were found for other endpoints such as PFS. AEs, foremost haematological ones, were more frequent in the cabazitaxel group (e.g. grade ≥3 neutropenia in 82% in the taxane group vs 58% in the mitoxantrone group) and more patients discontinued therapy due to AEs in this group (cabazitaxel 18% vs mitoxantrone 8%). Additionally, twice as many patients died within 30 days of last study drug dose in the cabazitaxel group as in the control group (cabazitaxel 5% vs mitoxantrone 2%), of which 5% in the cabazitaxel group and 1% in the mitoxantrone group were related to AEs. The study authors mention that a reduced dose (20mg/m^2 instead of 25mg/m^2) might offer a means to reduce AEs, but this might compromise efficacy too.

TROPIC trial: median OS prolonged by 2.4 months in comparison to mitoxantrone, relative risk of death reduced by 30%

most common AEs were haematologic ones

twice as many patients died in the cabazitaxel group within 30 days after last study drug dose

Docetaxel is the standard of care for patients with castration-resistant metastatic prostate cancer but if disease progresses, therapeutic options are limited and no consensus on the best therapy exists [12]. Thus, new regimens are clearly needed. Cabazitaxel has shown, for the first time, statistically significant increases in survival for the 2nd-line treatment of patients with castration-resistant metastatic prostate cancer. But it should be mentioned that the protocol of the TROPIC trial was amended after 59 patients to exclude patients previously receiving a cumulative docetaxel dose lower than 225 mg/m^2 [17]. As patients with rapid progression might represent the truly docetaxel-refractory subgroup and their omission can thus lead to an overestimation of cabazitaxel actitivity in doxetacel resistant patients.

in the meantime: OS improvements also for another drug

due to significant toxicities of cabazitaxel, comparison to arbiraterone of interest

Even if cabazitaxel was the first therapy for which improvements in OS after docetaxel-failure were found, it should be mentioned, that an increase in OS was meanwhile also shown for another drug. Preliminary results of a phase III report improved results on OS for arbiraterone in docetaxel-pretreated patients (14.8 months abiraterone + prednisone vs 10.9 months placebo + prednisone). Considering the significant toxicity of cabazitaxel a comparison of cabazitaxel with abiraterone as 2nd -line therapy might be worthwhile in the future [22].

if docetaxel fails, new regimens are needed

for the first time, improvements in OS in the 2nd-line setting

but truly docetaxel-refractory patients might have been excluded in TROPIC trial, could lead to overestimation of cabazitaxel activity

Moreover, the gain in median OS by 2.4 months was achieved in comparison to mitoxantrone, a drug which offers advantages in terms of symptom palliation and can thus be considered *de-facto* standard 2nd line therapy, but has an unclear impact on survival itself [2, 10, 11]. Furthermore, an additional 2.4 months in this difficult to treat disease offers an incremental benefit, but a more distinct increase in OS might be derived if cabazitaxel was used in

the 1st-line setting. The comparison of cabazitaxel to docetaxel in the front-line setting is thus of great interest.

cabazitaxel in comparison to mitoxantrone with unknown impact on survival

In addition, these results have to be balanced against serious and very frequent AEs, as the gains in OS might come at the expenses of QoL, an outcome for which, despite planned trials, no results are available yet [17]. Based on the results of the TROPIC trial, elderly patients aged ≥65 years seemed to be even more likely to experience certain AEs (e.g. neutropenia, asthenia, pyrexia) than younger patients [5]. Since patients in this trial were younger than patients usually are at diagnosis, AEs might occur even more frequently [5].

no data on QoL, gains in OS might come at expenses of QoL

elderly patients more prone to AEs

However, based on these findings, cabazitaxel as 2nd-line therapy received a category 1 recommendation in the National Cancer Comprehensive Network's guidelines for prostate cancer [11] and a category A recommendations from the European Association of Urology [23]. The UpToDate Guidelines, on the other hand, issued only a 2B recommendation, which corresponds to a weak recommendation [10].

besides costs for cabazitaxel, expenses for prophylactic therapy with G-CSF and treatment of AEs have to be considered

Although the price for cabazitaxel still remains unknown in Austria, not only the costs for the drug itself have to be considered, but also those for prophylactic therapy with G-CSF in high-risk patients (age ≥65 years, poor performance status, previous episodes of febrile neutropenia) as well as the treatment costs for side-effects, which might entail hospital admission.

Open questions which should be addressed in further clinical trials are the optimal dosing regimen, the comparison of cabazitaxel to docetaxel in the 1st-line setting [24] and, as already mentioned, data on QoL.

reliable estimates of drug's significance not possible to date

In summary, cabazitaxel is one of the first therapies which showed improvements of OS in patients with castration-resistant metastatic prostate cancer after failure of docetaxel therapy. But this result is put into perspective as this modest gain in OS was established in comparison to mitoxantrone, a therapy with an unknown impact on survival itself. Moreover, very frequent serious and sometimes life-threatening AEs in combination with missing data on QoL prevent to date reliable estimates of the drug's true significance.

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