Cabazitaxel in metastatic Castration-Resistant Prostate Cancer (mCRPC): Real-life use, effectiveness, safety and quality of life (QoL) in the FUJI cohort

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Background

Prostate cancer is the most common cancer in men in France; it evolves slowly but its prognosis is poor at the metastatic stage. Several therapeutic strategies are available for patients with metastatic castration-resistant prostate cancer (mCRPC). Since 2004, docetaxel has been the first-line treatment of mCRPC. Since 2011, cabazitaxel (CAB), abiraterone acetate, and enzalutamide have obtained an European marketing authorization as second-line treatment, then as a first-line treatment for the latter two. Little data on CAB use in real-life practice is available. French Health Authorities have requested a post-authorization study to assess the performance of CAB in a real-life setting.

Objectives

- To evaluate the overall survival (OS) and PSA response in mCRPC patients treated by CAB.
- To evaluate the safety profile during CAB treatment.
- To evaluate the quality of life (QoL) and pain during CAB treatment with a prospective follow-up.

Methods

Study design

- French multicenter cohort study including a main cohort of 401 patients in 42 centers and a QoL cohort of 61 patients in 22 centers.

Recruitment process and follow-up

- Identification of potential centers based on drug sales.
- Main cohort: retrospective identification of patients initiating CAB from nominative hospital pharmacy registries between Sept. 2013 and Aug. 2015, with 18-months follow-up.
- QoL cohort: prospective identification of patients by physicians between March 2016 and March 2017, with 6-month follow-up.

Data collection

- Data were collected from medical files using a standardized electronic Case Report Form.
- For QoL cohort: specific questionnaires were completed by patients with FACT-P questionnaire for QoL and Brief Pain Questionnaire - Short form (BPI-SF) for pain before each CAB infusion, and up to 45 days after the last CAB infusion.

Clinical outcomes and data analysis

- Adverse events (AE), based on the data collected through the medical files, were coded using NCI-CTCAE v4.0 and the MedDRA thesaurus.
- OS estimated using Kaplan-Meier method.
- Multivariate analysis using the Cox proportional hazard risk model to assess the factors associated with death, performed for main cohort. Factors tested were: Gleason score, primary cancer history, age, PSA value, metastases at CAB initiation (visceral, bone, number of bone metastases, synchronous status), number of chemotherapies, cancer drugs with OS impact ≥ 3, other drugs > 5 before CAB, time from last docetaxel infusion to CAB initiation, disease progression after docetaxel, analgesics prescription, ≥ grade 3 AE during CAB use, CAB dose reduction, CAB infusion report.
- QoL and pain were analyzed from raw data and after multiple imputation of missing data (Monte Carlo Markov Chain method).

Declaration of Interest Statement

The FUJI study, an ENCePP study seal *(EU PAS register: ENCEPP/SDPP/10391),* was carried out by the Bordeaux PharmacoEpi platform with an unconditional grant from Sanofi-Aventis and supervised by a scientific committee composed of independent experts.

Results

Characteristics of patients and real-life use of treatment

Table 1. Baseline characteristics of patients and CAB use for main and QoL cohorts

	Main cohort n = 401	QoL cohort n = 61
Baseline characteristics		
Median age at CAB initiation, years	70.0	72.0
Median time of cancer history before CAB initiation, years	5.5	6.8
Visceral metastases at CAB initiation, n (%)	79 (19.7)	12 (19.7)
> 5 bone metastases at CAB initiation, n (%)	136 (44.9)	48 (81.4)
Median PSA value at CAB initiation, ng/ml	112.5	109.5
Number of drugs >5 (excluding cancer treatments), n (%)	83 (20.7)	16 (26.2)
Number of treatments* before CAB initiation, n (%)		
1 treatment	72 (18.0)	15 (24.6)
2 treatments	155 (38.7)	18 (29.5)
3 treatments	91 (22.7)	16 (26.2)
4 or 5 treatments	83 (20.7)	12 (19.7)
Docetaxel before CAB initiation, n (%)	401 (100.0)	60 (98.4)
Abiraterone acetate before CAB initiation, n (%)	307 (76.6)	37 (60.7)
Enzalutamide before CAB initiation, n (%)	134 (33.4)	37 (60.7)
Cabazitaxel use		
CAB perfusion every 3 weeks, n (%)	364 (90.8)	52 (85.2)
Median CAB use, months	3.4	3.4

** apart from 1st generation hormonotherapies*

In the main cohort, 95% had discontinued CAB at 18-month follow-up; the main reasons were disease progression or disease-related death (83.2%) and AE (15.2%). In the QoL cohort, 63.9% had discontinued CAB at 6-month follow-up; the main reasons were 89.7% for progression or disease-related death and 25.6% for AE.

Safety

Table 2. Safety profile according to grade NCI-CTCAE in main and QoL cohorts

	Main Cohort, n=401		QoL Cohort, n=61	
Adverve event (AE)	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
≥ 1 AE, n (%)	**397 (99.0)**	**222 (55.4)**	**61 (100.0)**	**28 (45.9)**
≥ 1 haematologic AE, n (%)	**371 (92.5)**	**160 (39.9)**	**57 (93.4)**	**19 (31.1)**
Anemia	363 (90.5)	108 (26.9)	56 (91.8)	13 (21.3)
Thrombopenia	116 (28.9)	21 (5.2)	20 (32.8)	3 (4.9)
Neutropenia	108 (26.9)	60 (15.0)	17 (27.9)	8 (13.1)
Leucopenia	100 (24.9)	38 (9.5)	22 (36.1)	5 (8.2)
Febrile neutropenia	32 (8.0)	32 (8.0)	2 (3.3)	2 (3.3)
General disorders, n (%)	**331 (82.5)**	**17 (4.2)**	**46 (75.4)**	**3 (4.9)**
Fatigue and asthenia	279 (69.6)	13 (3.2)	38 (62.3)	2 (3.3)
Gastrointestinal disorders, n (%)	**274 (68.3)**	**17 (4.2)**	**39 (63.9)**	-
Diarrhea	160 (39.9)	10 (2.5)	17 (27.9)	-
Nausea	120 (29.9)	4 (1.0)	20 (32.8)	-
Vomiting	79 (19.7)	5 (1.2)	11 (18.0)	-
Renal and urinary disorders, n (%)	**152 (37.9)**	**37 (9.2)**	**17 (27.9)**	**3 (4.9)**
Hematuria	81 (20.2)	6 (1.5)	10 (16.4)	-
Renal failure	30 (7.5)	29 (7.2)	3 (4.9)	3 (4.9)
Urinary retention	24 (6.0)	2 (0.5)	-	-
Infections and infestations, n (%)	**124 (30.9)**	**20 (5.0)**	**14 (23.0)**	**3 (4.9)**
Septicemia and septic shock	20 (5.0)	20 (5.0)	3 (4.9)	3 (4.9)

Survival outcomes

- The 18-month OS rate was 32.4% [95%CI, 27.8-37.1] and median OS was 11.9 months [95%CI, 10.1-12.9] for main cohort (**Figure 1**). Factors associated with the risk of death are presented in **Table 3**.

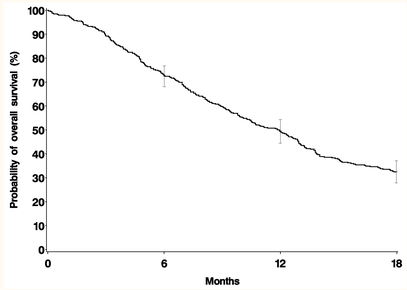

Figure 1. 18-month overall survival in main cohort (Kaplan-Meier method)

Table 3. Factors associated with the risk of death in the main cohort

	212 vs 113 HR [95%CI]		p
At least one grade ≥ 3 adverse event during CAB use	2.05	[1.53 – 2.73]	<0.0001
Visceral metastases	1.98	[1.40 – 2.80]	0.0001
Number of drugs > 5 (excluding cancer treatments)	1.74	[1.23 – 2.45]	0.0016
> 5 bone metastases at CAB initiation	1.74	[1.20 – 2.53]	0.0038
Disease progression after docetaxel initiation			0.0198
Within 3 months of last docetaxel cycle	1.51	[1.07 – 2.14]	
Disease progression during docetaxel	1.69	[1.13 – 2.53]	
≥ 3 drugs such as docetaxel, acetate abiraterone, enzalutamide before CAB	1.39	[1.00 – 1.92]	0.0488
PSA ≥ 135 ng/ml at CAB initiation	1.36	[1.01 – 1.82]	0.0404
≥ 10-year cancer history before CAB	0.66	[0.46 – 0.96]	0.0297
≥ 6 months from last docetaxel dose to CAB initiation	0.71	[0.52 – 0.97]	0.0325

Results adjusted for the following covariates "Evolution of analgesics prescription over time" (non significant covariate but confounding factor with "Number of drugs excluding cancer treatment > 5") and "age"

PSA Response

- After at least 3-month CAB use, PSA response defined by ≥ 50% decrease from baseline concerned 39.9% of 258 patients with evaluable PSA dosage for main cohort and 32.6% of 43 evaluable patients for QoL cohort (**Figure 2**).

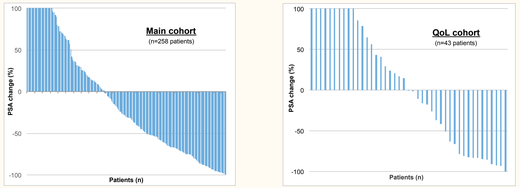

Figure 2. Waterfall plot showing maximum PSA change from baseline in main and QoL cohorts

Quality of life and Pain evaluation

- QoL: 49 patients were evaluable for QoL. At CAB initiation, total FACT-P score was 93.3 on a scale of 0 to 156. QoL changes from baseline during CAB use are presented in **Table 4**.

Table 4. QoL changes from baseline during CAB use in QoL cohort

	QoL evaluable Patients (Raw data) n = 49	QoL evaluable Patients (Imputed data) n = 56
Total FACT-P score (Changes from baseline - 10 points)		
Maintaining of QoL, n (%)	**17 (34.7)**	**16 (28.6)**
Improving of QoL (≥ +10), n (%)	**18 (36.7)**	**23 (41.1)**
Median time to 1st improving of QoL (days)*	42.5	42.0
Deterioration of QoL (≤ -10), n (%)	**18 (36.7)**	**21 (37.5)**
Median time to 1st deterioration of QoL (days)*	45.5	42.0

** Concerned patients*

- Pain: 44 patients were evaluable for pain. At CAB initiation, 68.2% of patients having a mild pain ("Pain severity" score [0-3]), 27.3% of patients an intermediate pain (score [4-6]) and 4.5% a strong pain (score [7-10]). QoL changes from baseline during CAB use are presented in **Table 5**.

Table 5. Pain changes from baseline during cabazitaxel use in QoL cohort

	Pain evaluable Patients (Raw data) n = 44	Pain evaluable Patients (Imputed data) n = 56
Maintaining of level « Pain severity », n (%)	**23 (52.3)**	**28 (50.0)**
Improving, ≥ 1 decrease of level « Pain severity », n (%)	**12 (27.3)**	**14 (25.0)**
Median time to decrease of level « Pain severity », (days) *	21.0	21.0
Deterioration, ≥ 1 increase of level « Pain severity », n (%)	**9 (20.5)**	**14 (25.0)**
Median time to increase of level « Pain severity », (days) *	42.0	42.0

** Concerned patients*

Conclusion

- Real-life median OS at 18-month in FUJI was lower than in the TROPIC trial (OS=11.9 *vs.* 15.1 months), but only 2 patients satisfied TROPIC inclusion criteria (*Bono et al., 2010*: e.g., good ECOG, normal haematologic, hepatic, renal and cardiac functions, CAB in 2nd-line…). Moreover, 33.4% of FUJI patients were older than 75 years (*vs* 18% in TROPIC). In FUJI, CAB was used in 3rd-line or more for 82% of patients, showing the change in the medical care of prostate cancer.

- Safety profile in FUJI cohort was similar to that reported for TROPIC trial (AE grade ≥ 3: 55.4% *vs.* 57.4%).
- QoL and pain were improved/stable in respectively 70% and 75% of patients treated by CAB. These results are similar to those observed in the literature with patients treated by 2nd-generation hormonotherapies.

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