Pharmacologie médicale

Bordeaux BPE PharmacoEpi

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CIC Bordeaux CIC1401

FUJI study: Follow-Up of Jevtana® in real life

"French retrospective and protective multicenter observational study describing the survival, safety and quality of life of patients treated by cabazitaxel according to previous treatment lines in real-life setting"

Summary of study results

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Bordeaux PharmacoEpi
Plateforme de recherche en pharmaco-épidémiologie
Service de Pharmacologie médicale, CIC Bordeaux CIC1401
INSERM - Université de BORDEAUX - CHU de Bordeaux - Adera
Bâtiment Le Tondu - Case 41
146 rue Léo Saignat - 33076 Bordeaux Cedex

université de BORDEAUX

CHU Hôpitaux de Bordeaux

Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

Adera

RESULTS

Main cohort with retrospective identification of patients initiating cabazitaxel from Sept 2013 to Aug 2015, with 18-month follow-up

401 men initiating cabazitaxel between 1st September 2013 and 31 August 2015 in 42 French centres were included in the main FUJI cohort study. These men were treated for locally advanced[a] or metastatic prostate cancer, previously treated with docetaxel and 1st generation hormone therapies (thus presumed to be castration-resistant prostate cancer). Their median age was 70 years, and they were mainly followed in private cancer centres (60.8%). Median Gleason[b] score was 7 at primary diagnosis. Approximately 60% of patients had metachrone metastases and 40% synchrone metastases. Median time to metastases diagnosis was 22.8 months for the overall cohort. The main metastatic sites were bone (75.6%), lymph node (43.6%), and visceral (7.2%). All patients were previously treated with docetaxel before cabazitaxel. Eighteen percent of the patients had only one previous treatment line, 38.7% had two previous treatment lines, 22.7% had 3 previous treatment lines, and 20.7% had 4 or 5 previous treatment lines. Most patients (81.5%) had been previously treated by second-generation hormone therapies (abiraterone acetate and/or enzalutamide). Median prostate-specific antigen (PSA) concentration at baseline was 112.5 ng/ml. Cabazitaxel was administered every three weeks in 9 out of 10 patients (90.8%). The starting dose of cabazitaxel was 25 mg/m^2 for 46.1% of patients, below 25 mg/m^2 in 48.9% of patients, and more than 25 mg/m^2 in 3.2%. The median duration of cabazitaxel treatment was 3.4 months with a median of 5 cycles. Among patients who had discontinued cabazitaxel at 18 months (95%), the main reasons for discontinuation were disease progression or disease-related death (83.2%) and adverse events (AE) (15.2%).

The 18-month overall survival (OS) rate was 32.4% (95% CI [27.8 - 37.1]); the median OS was 11.9 months [10.1 - 12.9], ranging from 9.9 months [6.6 - 12.9] for patients with one previous treatment-line to 12.9 months [10.0 - 14.7] for patients with 3 previous treatment lines before cabazitaxel initiation. In multivariate analyses, factors independently associated with a lower OS were: occurrence of at least one AE of grade ≥ 3 during cabazitaxel (HR = 2,05 [1,53 - 2,73]), visceral metastases at baseline (HR = 1.98 [1.40 - 2.80]), polypharmacy with more than 5 non-cancer drugs at baseline (HR = 1.74 [1.23 - 2.45]), more than 5 bone metastases at baseline (HR = 1.74 [1.20 - 2.53]), disease progression during docetaxel treatment (HR = 1.69 [1.13 - 2.53]) or within 3 months of the last docetaxel infusion (HR = 1.51 [1.07 - 2.14]), at least 3 previous cancer treatments with impact on survival before cabazitaxel initiation (HR = 1.39 [1.00 - 1.92]), and baseline PSA concentration ≥ 135 ng/ml (HR = 1.36 [1.01 - 1.82]). Conversely, factors independently associated with a better OS were: at least 10-years cancer history before cabazitaxel initiation (HR = 0.66 [0.46 - 0.96]) or at least 6 months between the last docetaxel infusion and cabazitaxel initiation (HR = 0.71, [0.52 - 0.97]). The median progression-free survival (PFS) was 3.9 months [3.5 - 4.6]. In multivariate analysis factors independently associated with a lower PFS were: change of analgesic use to level III (HR = 2.31 [1.70 - 3.14]), disease progression within 3 months of the last docetaxel infusion and before cabazitaxel initiation (HR = 2.30 [1.68 - 3.15]), and at least one AE of grade ≥ 3 during cabazitaxel treatment (HR = 1.50 [1.14 - 1.97]).

Almost all patients (99.0%) experienced AE (any grade) during cabazitaxel treatment. At least one AE occurred after the first cabazitaxel infusion in 96% of patients with a median of 20 AE per patient during the follow-up period. The most frequent AE were haematological (92.5%), fatigue and asthenia (69.6%), and gastrointestinal (68.3%). At least one AE-related hospitalisation occurred in 41.1% of patients with a median of 2 AE per patient. The first AE occurred during the first or second cabazitaxel infusion for half of patients (52.1%). The most frequent AE related to hospitalisation were: general physical health deterioration (11.5%); haematological reactions (10.7%) with febrile neutropenia (6.7%) and anaemia (3.0%);

[a] 2 in 401 patients had locally advanced disease with development of metastases after initiation of cabazitaxel.

[b] Histological classification system for prostate cancer. Cancer Cell Scale developed in 1966 by Dr. Donald F. Gleason of the University of Minnesota.

gastrointestinal reactions (10.5%) with vomiting (3.5%), diarrhoea (2.5%), abdominal pain (2.5%) and gastrointestinal bleeding (1.7%); renal or urinary reactions (10.0%) with haematuria (4.5%), urinary retention (3.7%) and renal failure (1.5%); infectious reactions (8%) with sepsis and septic shock (2.7%); and musculoskeletal reactions (5.2%) with back pain (2.7%). At least one AE of grade ≥ 3 was observed for 55.4% of patients, of which 26.6% related to hospitalisation. First AE of grade ≥ 3 occurred after the first cabazitaxel infusion for half of the patients (50.0%), and the most frequent were: haematological (39.9%) with anaemia (26.9%), neutropenia (15.0%) and febrile neutropenia (8.0%), leukopenia (9.5%), and thrombocytopenia (5.2%); renal or urinary (9.2%) with renal failure (7.2%), haematuria (1.5%) and urinary retention (0.5%); gastrointestinal (4.2%) with diarrhoea (2.5%), nausea and vomiting (2.2%) and gastrointestinal bleeding (0.2%); septicaemia and septic shock (5.0%); and fatigue and asthenia (3.2%). According to physician, six cabazitaxel-related deaths occurred during cabazitaxel treatment, five related to sepsis or septic shock with febrile neutropenia. These patients had at least one G-CSF treatment before or during the cycle concerned by the occurrence of febrile neutropenia, except one patient who had an infectious shock after the first cabazitaxel infusion.
Analgesic use was more frequent (70.3%) during cabazitaxel treatment than during the 15-day period before cabazitaxel initiation (44.9%). During cabazitaxel treatment, level I analgesics, excluding NSAIDs, were the most frequently used (70.9%), followed by level III (62.8%) and/or level II (36.5%). Among patients with analgesic treatment at initiation of cabazitaxel (data from medical records), about a third (30.9%) used analgesic treatments at a lower level during the follow-up period. An increase of treatment level (i.e. without any decrease during cabazitaxel treatment) was observed for 17.5% of patients. After discontinuation of cabazitaxel, the frequency of analgesic use remained stable for 67% of those concerned. The most frequently used analgesics were level III (82.1%), and/or level I excluding NSAIDs (63.4%).

Quality of life (QoL) cohort with prospective identification of patients initiating cabazitaxel from March 2016 to March 2017, with 6-month follow-up

Sixty-one men initiating cabazitaxel treatment between March 2016 and March 2017 in 22 French centres were included in the FUJI QoL cohort study. These men were treated for metastatic prostate cancer, previously treated by docetaxel and 1st generation hormone therapies (thus presumed to be castration-resistant prostate cancer). Their median age was 72 years, and they were mainly followed in private cancer centres (62.3%). Median Gleason score was 7 at primary diagnosis. About 60% of patients (62.3%) had metachronous metastases and 37.7% synchronous metastases. Median time to metastases diagnosis was 35 months for the overall cohort. The main metastatic sites were bone (83.6%), lymph node (32.8%), and visceral (9.8%). All patients were previously treated by docetaxel before cabazitaxel initiation, except one patient treated by paclitaxel. About a quarter of patients (24.6%) had only one previous treatment line, 29.5% had two previous treatment lines, 26.2% three previous treatment lines, and 19.7% 4 or more previous treatment lines. Most patients (75.4%) were previously treated by second-generation hormone therapies (abiraterone and/or enzalutamide). Median PSA concentration at baseline was 109.5 ng/ml.

Cabazitaxel was administered every three weeks for most patients (85.2%). Among these patients, the starting dose of cabazitaxel was 25 mg/m^2 for approximately half (48.1%) and below 25 mg/m^2 in the other half (51.9%). The median duration of cabazitaxel treatment was 3.4 months with a median of 5 cycles. About two-thirds of patients (63.9%) had discontinued cabazitaxel at 6 months. The main reasons for discontinuation were disease progression or disease-related death (89.7%) and AE (25.6%).

The 6-month overall survival rate for the QoL cohort was 83.6% (95% CI [71.7; 90.8]), and the median had not been reached at the end of the 6-month follow-up. The median progression-free survival was 3.7 months (95% CI [3.0 – 4.5]).

All patients in the QoL cohort experienced AE (any grade) during cabazitaxel. At least one AE occurred after the first cabazitaxel infusion in 87% of patients with a median of 24 AE per patient during the follow-up period. The most frequent AE were haematological (93.4%), gastrointestinal (63.9%) and fatigue/asthenia (62.3%). All-grade AE-related hospitalisation

occurred in 24.6% of patients and AEs grade ≥ 3 in 45.9%. At least one expected AE was observed in 95.1% of patients with predominantly haematological AEs (93.4%), fatigue/asthenia (62.3%), and gastrointestinal AEs (59.0%). 13.1% of patients had at least one expected AE-related hospitalisation (anaemia 4.9%, febrile neutropenia 3.3%, diarrhoea 1.6%, vomiting 1.6%, abdominal pain 1.6% and fever 1.6%). 31.1% of patients had at least one expected AE of grade ≥ 3 (anaemia 21.3%, neutropenia 13.1%, leukopenia 8.2%, thrombocytopenia 4.9%, febrile neutropenia 3.3%, fatigue/asthenia 3.3%). Unexpected AEs excluding the history and/or not disease-related were observed in 68.9% of patients and were mainly: neurological (26.2%); biological with high levels of transaminases (18.0%); gastrointestinal (16.4%) with dry mouth (n=2) and hemorrhoids (n=2); general disorders (14.8%) with a deterioration in the general condition (4.9%); infections (13.1%) with sepsis and septic shock (4.9%) and bronchitis (3.3%). 8.2% had at least one unexpected AE excluding the history and/or not related to the disease associated with hospitalisation (n = 5 patients with 1 septic shock, 1 septic shock and erysipelas, 1 dental abscess and general deterioration of the health status, 1 pneumonia / pulmonary disorder, 1 cholecystitis) and 9.8% had at least one unexpected AE ≥ grade 3 excluding the history and/or not related to the disease (n=6 patients with 1 increased transaminases, 3 septic shocks, 1 cardiac arrest, 1 hypokalaemia). Two deaths not related to cabazitaxel occurred during cabazitaxel treatment, according to the participating physician: one cardiac arrest and one hypoglycaemic coma. The initial patient characteristics, effectiveness and safety of cabazitaxel in the patients analysable for quality of life and pain were similar to those of the total QoL cohort. These characteristics were also comparable to those of patients in the main cohort, except for the use of enzalutamide before the initiation of cabazitaxel (80.4% in the QoL cohort *vs*. 41.0% in the main cohort).

The quality of life was assessed from the FACT-P questionnaires. At cabazitaxel initiation, the mean total FACT-P score was 93.3 for all analysable patients on a scale from 0 to 156. For QoL analysable patients (n=49), the total FACT-P score change from baseline indicated at least an improvement in the quality of life of +10 points in more than one third of patients (36.7%), maintenance of the quality of life for 34.7% of patients, and a deterioration in the quality of life of at least -10 points in about one third of patients (36.7%). These results were not very different after multiple imputation of the missing data (n=56 patients), with at least an improvement in the quality of life of +10 points in 41.1% of patients, maintenance of the quality of life in 28.6% of patients, and a deterioration in the quality of life of at least -10 points in about one third of patients (37.5%). Among the 19 patients who discontinued cabazitaxel (mainly for disease progression) and had maintenance or at least one improvement in the quality of life during treatment, 13 patients (68.4%) were still benefiting 45 days after discontinuing the cabazitaxel.

Pain in patients included in the QoL cohort was collected using two data sources, medical records and questionnaires, mainly the BPI-SF completed by the patients. In the medical records, cancer pain was identified during the week prior to initiation of cabazitaxel in 47.5% of patients and in 55.7% of patients during cabazitaxel. In BPI-SF questionnaires of the 44 patients evaluable for pain, at cabazitaxel initiation, the mean “Pain Severity” score was 3.1 on a scale from 0 to 10, among which 68.2% reported mild pain, 27.3% moderate pain and 4.5% severe pain. The “Pain Severity” score change from baseline during treatment, indicated at least one decreased level of pain in more than a quarter of patients (27.3%), maintenance of the pain level for approximately half of patients (52.3%) and at least one increase in the level of pain in a fifth of patients (20.5%). These results were similar after multiple imputation of the missing data (n=56) with at least a decreased level of pain in a quarter of the patients (25.0%), maintenance of the level in half of patients (50.0%) and at least an increase in the pain level in a quarter of patients (25.0%). Among the 25 patients (58.1%) who had discontinued cabazitaxel (mainly for disease progression) and had maintenance or at least a decreased level of pain during treatment, 23 (92.0%) were still benefitting 45 days after discontinuing cabazitaxel.
Analgesics use at initiation and during treatment with cabazitaxel from the two data sources concerned, 40 to 60% of patients according to the medical records, and more than 90% of patients from the questionnaires, with however a good concordance between the two sources for level II and III analgesics use which concerns about 20% of patients for each

level. Approximately one third of patients (36.7%) reported a decreased level of analgesic use during cabazitaxel regardless of the source and approximately two thirds of patients (67.3%) reported no increase in level of use. The introduction of a level II or III analgesic was observed in 5 to 10% of patients regardless of the data source considered. In addition, about 90% of the patients who had decreased analgesic use during follow-up also showed a biological medical benefit (complete, partial or stable response according to the physician).

DISCUSSION

To our knowledge, the FUJI study is the largest observational study to date of patients treated by cabazitaxel: a main cohort of 401 patients initiating cabazitaxel between 1st September 2013 and 31 August 2015 and followed for 18 months; and a QoL cohort of 61 patients initiating cabazitaxel between 1st March 2016 and 13 March 2017 and followed for 6 months. The results of the FUJI cohorts allow to address the request of the Health Authorities regarding effectiveness, safety, the quality of life and analgesic use of patients treated with cabazitaxel in a real-life setting.

Effectiveness results of the main cohort, with 32.4% (95% CI [27.8 - 37.1]) OS at 18-months after cabazitaxel initiation are different from those found in the literature. Indeed, the median OS of the FUJI cohort is lower than in the TROPIC clinical trial (de Bono JS et al., Lancet 2010): 11.9 months [10.1 - 12.9] *versus* 15.1 months [14.1 - 16.3], respectively. Taking into account the characteristics of the FUJI patients close to those of patients included in TROPIC trial (n=72 exclusively treated by docetaxel prior to cabazitaxel), the median OS remains lower (9.9 months [6.6 - 12.9]) in FUJI than in TROPIC (15.1 months [14.1 - 16.3]). Patients included in TROPIC had to meet several inclusion criteria, such as a good performance status (ECOG score 0 or 1); normal haematological, hepatic, renal or cardiac functions; no cancer treatment in the last 4 weeks before inclusion, etc. Only 2 in 401 patients included in FUJI study strictly fit within the criteria for inclusion in the TROPIC trial (in particular, treated exclusively by docetaxel before initiation), showing the change in medical management of prostate cancer since that trial. In real-life, the therapeutic care of prostate cancer may depend on age, stage of disease, comorbidities, or other prognosis factors that may impact on survival. In the FUJI cohort, 33.4% of patients were older than 75 years (*versus* 18% in TROPIC) and median PSA concentration at baseline was 112.5 ng/ml (*versus* 122.8 ng/ml and 152.0 ng/ml according to OS ≥ 2 years and OS < 2 years in TROPIC (Bahl A. et al, Ann Oncol 2013). Furthermore, 18% of patients only treated by docetaxel (as in TROPIC) before cabazitaxel initiation had a lower seniority of prostate cancer (2 years in median) with 55.6% of synchronous metastases compared to patients treated by more than 2 treatments (median value of 5 to 9 years for seniority of cancer) with 30.8% to 42.2% synchronous metastases. In addition, the therapeutic care for metastatic castration-resistant prostate cancer (mCRPC) has considerably progressed between the inclusion period in TROPIC trial and cabazitaxel initiation for patients included in the FUJI main cohort, particularly between 2012 and 2014: abiraterone acetate received market approval for its use in 2nd-line treatment for mCRPC in September 2011 (Transparency Commission (TC) opinion, Feb 2012), then for 1st-line treatment in December 2012 (TC opinion, June 2013); enzalutamide received a market approval for its use in 2nd-line treatment for mCRPC in June 2013 (TC opinion, Nov 2013), then in 1st-line treatment in November 2014 (TC opinion, March 2015). Finally, patients treated after marketing were not identical to those included in the TROPIC clinical trial. Nevertheless, in FUJI the median overall survival ranged from 9.9 months [6.6 - 12.9] for patients with only one treatment line before cabazitaxel initiation to 12.9 months [10.0 - 14.7] for those with 3 treatment lines before cabazitaxel.

The most frequent AE observed in the FUJI main cohort were haematological (92.5%) with 26.9% neutropenia. At least one AE grade ≥ 3 was found for 55.4% of patients with 15.0% neutropenia and 8.0% febrile neutropenia for haematological AE, and 7.2% renal failure, 5% sepsis and septic shock, and 2.5% diarrhoea for non-haematological AE. AE leading to hospitalisation were observed for 41.1% of patients with general physical health deterioration (11.5%); haematological events (10.7%) with febrile neutropenia (6.7%); gastrointestinal events (10.5%); renal or urinary events (10.0%); infectious events (8%) with sepsis and septic shock (2.7%). Moreover, 44% of patients were treated with a dose of cabazitaxel

below 25 mg/m^2. The safety profile of cabazitaxel was similar to that reported for TROPIC trial or other real-life studies (Heidenreich et al., Wissing et al., Lee et al., Bracarda et al). The frequency of AE grade ≥ 3 in FUJI was comparable to those reported in TROPIC (55.4% *vs.* 57.4%). The lower frequency of neutropenia reported in FUJI (15.0%) compared to TROPIC (82% of biological neutropenia) could be explained by a less intensive biological monitoring in real-life practice than required in a clinical trial; in addition, in TROPIC neutrophils were systematically measured in nadir (8 to 10 days after each infusion of cabazitaxel); events are not systematically recorded in patient medical records in real-life practice; the medical care has changed since TROPIC trial with a use of lower doses of cabazitaxel more frequently in real-life than in TROPIC. However, the frequency of febrile neutropenia was the same in both studies (8%). Six deaths due to sepsis or septic shock, associated in five with febrile neutropenia, were related to cabazitaxel according to physician.

Regarding the usage patterns of cabazitaxel, among the 1 007 patients identified by hospital pharmacies, almost all (99.7%) were treated for a prostate cancer. Most patients of the FUJI cohort (90.8%) had a treatment regimen once every 3 weeks and half started this regimen at a dose of 25 mg/m^2. Dose adjustments are recommended for specific populations such as patients with hepatic failure. Hepatic history was found for 11.2% of patients who received a dose reduced to 20 mg/m^2. Cabazitaxel usage profile with a lower dosage at initiation corresponds to that described in the PROSELICA trial (Eisenberger *et al*. JCO 2017) showing a non-inferior cabazitaxel effectiveness at a dosage of 20 mg/m^2 and less toxicities. In accordance with the Summary of Product Characteristics (SmPC), all patients were treated by docetaxel before initiation of cabazitaxel. The results of the FUJI main cohort found that cabazitaxel was globally used in real-life setting according to the SmPC at the time of the study.

Evaluation of quality of life and pain from the QoL cohort showed an overall stability in the quality of life and pain in patients treated with cabazitaxel at a very advanced stage of mCRPC. Improvement or stability in the quality of life during treatment with cabazitaxel was observed in 70% of patients even though they received intensive treatment prior to cabazitaxel initiation, with cabazitaxel in 3-rd-line or more for three-quarters of the patients. 41% of the patients had, during the treatment, at least a clinically significant improvement (+10 points FACT-P score) in the quality of life compared to initiation of treatment. In the literature, the proportion of patients with improvement of at least 10 points in the FACT-P score ranged from 42% with enzalutamide (Fizazi *et al.* 2014) to 48% with abiraterone acetate (Harland et al. 2013): FUJI quality of life results are close to those observed with 2nd generation hormone therapies, although FUJI patients are likely to be at a more advanced stage of their disease than those included in the 2nd generation hormone therapies trials. The FUJI study described stability in pain (Pain Severity score) during treatment with cabazitaxel for half of the patients. These results are similar to those described in mCRPC patients treated with enzalutamide (Fizazi *et al.* Lancet 2014), for whom stabilisation of pain is a benefit for these patients with advanced stage of mCRPC. Despite the low numbers, FUJI showed no worsening of pain in the 45 days after discontinuing cabazitaxel. Analgesics use confirms the data regarding the quality of life and pain since one third of patients reported a decreased level of analgesic during treatment with cabazitaxel regardless of the data source (medical record or patient questionnaires) and about two thirds reported no increase. The introduction of a level II or III analgesic remained uncommon and only concerned 5 to 10% of patients regardless of the data source.