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Treatment-Related Burden of Illness of Castration-resistant Prostate Cancer with Bone Metastases in France

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Abstract

Background: Prostate cancer is the most common cancer in men in France; 10–20% of patients with prostate cancer develop castration-resistant prostate cancer (CRPC) within 5 years.

Purpose: This analysis aimed to identify clinical characteristics, treatment patterns, and burden of CRPC.

Methods: This was a retrospective analysis of real-world data from patients with metastatic CRPC (mCRPC) in France. Each participating physician provided data for 5–12 patients. Patients were grouped by metastatic site (bone only; bone + visceral) and first-line treatment (abiraterone; enzalutamide; docetaxel). All analyses were descriptive in nature.

Results: Overall, 591 patients were included; 81% had bone only metastases, 14% had bone and visceral metastases (exact information regarding metastases unknown by physician for 5% of patients). Of the 481 patients with data available at first-line, abiraterone, docetaxel and enzalutamide was received by 55%, 33%, and 12%, respectively, at first-line, and 54%, 19%, and 20%, respectively, at second-line; 61% of patients received a single line of therapy. Abiraterone was the most common first-line treatment for patients with bone metastases only, and docetaxel for patients with bone+visceral metastases. Overall, 14% of patients experienced ≥1 symptomatic skeletal event (SSE). Pathologic fracture was experienced by 4.7%, 5.4% and 16.1% of patients receiving abiraterone, docetaxel, and enzalutamide, respectively, and 6.3%, 7.3% and 12.9% of patients receiving abiraterone, enzalutamide, and docetaxel, respectively, had bone radiotherapy.

Conclusion: Abiraterone was the most common first-line treatment in mCRPC in France, followed by docetaxel; docetaxel was the most frequently-used treatment for patients with bone+visceral metastases.

Keywords: Abiraterone, Bone metastases, Burden of illness, Castration-resistant prostate cancer, Docetaxel, Real-world, Symptomatic skeletal event.

Introduction

Prostate cancer is the second most common cancer in men globally [1], and is the most common cancer in men in France [2]. A total of 56,841 men were diagnosed with prostate cancer in France in 2012 (29% of all incident male cancer cases excluding non-melanoma skin cancer), with 8,606 men dying from the disease [1]; more recent epidemiological data are not available [2].

In a real-world European study of 3,477 patients with prostate cancer, 40% had castration-resistant prostate cancer (CRPC) at the time of the study. Of patients with CRPC, 80% had metastatic disease (mCRPC), with bone metastases in 78% of those with mCRPC [3]. A systematic review of international observational studies reported ≥84% of patients to have radiologic evidence of bone metastases on diagnosis of CRPC [4]. Bone metastases disrupt skeletal homeostasis and can lead to symptomatic skeletal events (SSEs), including malignant hypercalcemia and anemia due to decreased hematopoiesis [5,6].

Androgen-deprivation therapy (ADT) is recommended for locally-advanced and metastatic prostate cancer in French national clinical guidelines [7], guidelines from the European Society of Medical Oncology [8], and guidelines from the US National Comprehensive Cancer Network [9]. However, although ADT can delay progression, 10–20% of patients with prostate cancer develop CRPC within 5 years [4].

For those patients progressing to mCRPC, the chemotherapeutic agent docetaxel has been the standard of care for more than a decade [10]. However, recently several new agents have been developed for this indication. These include novel hormonal therapies targeting androgen-mediated pathways (e.g. enzalutamide, abiraterone), the chemotherapeutic agent cabazitaxel, targeted alpha therapies (e.g. radium-223), and immunotherapeutic agents (e.g. sipuleucel-T), although the last of these is no longer available in Europe [10,11]. Enzalutamide, abiraterone, cabazitaxel and radium-223 have all shown survival benefits in mCRPC [11]. Although, at present radium-223 is not reimbursed in France.

Methods

Study design

This was a retrospective analysis of cross-sectional real-world data related to patients with CRPC and bone metastases. Data were collected by hospital- and office-based physicians in France; physicians were identified from an existing ISO-certified healthcare professional research panel. Potentially suitable physicians were asked to complete a short screening questionnaire to assess eligibility and willingness to participate. Physicians and sites were recruited to ensure an even regional distribution, to account for regional variations in treatment practices.

To be included, physicians had to be practicing oncologists or urologists responsible for treatment decisions for mCRPC patients, who treated a minimum of 5 mCRPC patients meeting the inclusion criteria. Eligible physicians recruited the next 5–12 consecutive consulting patients meeting the eligibility criteria for patients. Participating physicians provided patient-level data via the Electronic Data Capture (EDC) platform. Electronic patient record forms (ePRFs) were completed by each physician for each of 5–12 patients meeting the inclusion criteria. Physicians were requested to select consecutive, most recently seen patients who met the study criteria, to reduce selection bias. Pilot studies were conducted with physicians ahead of finalisation to validate the ePRF, which recorded demographic data, clinical characteristics, and treatment history. Information on SSE's, defined as pathologic fracture, spinal fracture, bone radiotherapy and bone surgery was also captured, which included the type of SSE experienced and the date of occurrence. The data collection period was from June 2015 through to September 2015.

This study received favourable opinion for its conduct by the Conseil National de l'Ordre des Médecins (CNOM) and was reviewed and approved by The Freiburg Ethics Commission International (FEKI), an Institutional Review Board, and complied with the Loi Bertrand and all relevant legislative and ethical standards.

Study population

Patients were required to be male, aged ≥18 years, with histologically or cytologically confirmed adenocarcinoma of the prostate at some time in their disease history, and with CRPC with clinically or radiologically confirmed bone metastases (≥2 hot spots, confirmed at any point in disease history); they could have visceral metastases in addition to bone metastases. For inclusion, patients also had to have initiated treatment for mCRPC at least 12 months prior to data collection, to not be currently receiving treatment for CRPC as part of a clinical trial, or to have participated in a clinical trial within the previous 12 months, and to have not received radium-223 at any point during their treatment history.

Data transformation

Treatment groups: Systemic therapies were grouped by first-line treatment and treatment sequence. Analysis of mCRPC treatment sequencing focused on four key treatments of interest: abiraterone, enzalutamide, docetaxel and cabazitaxel. Sequencing was analysed based on switching patterns between these treatments, with other treatments being excluded from the analysis. Initiation of any of these treatments at least 28 days after the start date of the previous treatment was considered a new treatment line.

Metastatic hormone-sensitive prostate cancer: The phases before mCRPC were either non-metastatic CRPC (nmCRPC) or metastatic hormone-sensitive prostate cancer (mHSPC); these terms were not defined in the protocol, but it was assumed that all physicians would use these definitions.

Data analysis: For all analyses, patients were grouped by site of metastases (bone only versus visceral and bone) and first-line systemic treatment (abiraterone versus enzalutamide versus docetaxel).

Analyses were descriptive in nature. Continuous variables were summarised as mean, median, standard deviation and interquartile range (IQR) and categorical variables were summarised as the number and percentage of subjects in each category. Survival analysis of time to SSE following first bone metastases was performed using Kaplan-Meier plots.

Data analysis was performed using Stata statistical software release 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

Study population

A total of 1189 potentially suitable physicians were identified and 223 were asked to complete the screening questionnaire. Of these, 91 physicians from 60 centres were invited to participate in the study, to provide a representative sample in terms of regions within France and CRPC treatment patterns. Overall, 79 physicians were hospital-based, 11 were hospital- and office-based and 1 was office-based. The majority (76) were oncologists, with the remaining 15 being urologists.

Data were collected for 833 patients, but some patients were

excluded from the analysis either because an mCRPC diagnosis date could not be calculated (n=172), or diagnosis of mCRPC was within 12 months of data collection (n=70). Data for 591 patients were therefore included in these analyses, and all findings reported relate to these 591 patients.

Patient characteristics

Key characteristics for the total study population (N=591) are shown in Table 1. Mean age was 71.2 years and mean body mass index was 24.51 kg/m^2 at initiation of treatment for mCRPC. The mean times from prostate cancer diagnosis and from CRPC diagnosis to data collection were 49 months and 18 months, respectively. At initial prostate cancer diagnosis, 83% of the study population had stage III or IV cancer. Among the total study population, on initiation of treatment for mCRPC, 75% of patients had an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1, and 6% had an ECOG status of ≥3, with the remaining 20% having an ECOG status of 2.

Overall, 77% of patients had metastases prior to diagnosis of CRPC (i.e. had mHSPC). Of patients with mHSPC, a mean of 7 bone metastases was reported prior to diagnosis of CRPC. Of these patients 13.2% (n=60) received docetaxel at mHSPC. The mean time from diagnosis of prostate cancer to diagnosis of mHSPC was 7 months (54% of patients had stage IV prostate cancer on diagnosis), and the mean time from diagnosis of mHSPC to diagnosis of mCRPC was 19 months.

Location of metastases

Of the 591 patients included in the total study population, 481 (81%) had bone only metastases, 83 (14%) had bone and visceral metastases (metastases of the lung, liver or pancreas). An additional 27 (5%) had bone metastases for which the physician did not have sufficient data to complete the ePRF; these were classified as 'other'. Key characteristics for patients stratified by location of metastases are shown in Table 1.

There was no difference in age or BMI between patients with bone only metastases and those with bone and visceral metastases. Mean time from prostate cancer diagnosis to diagnosis of mHSPC was shorter in patients with bone and visceral metastases versus bone only metastases. No difference was observed in mean time from prostate cancer diagnosis to data collection and from CRPC diagnosis to data collection between patient subgroups based on location of metastases.

A similar proportion of patients with bone only metastases and with bone and visceral metastases had stage IV (metastatic) disease at initial diagnosis of prostate cancer, but more patients with bone only metastases had low (0–1) ECOG status on initiation of treatment for mCRPC compared with those with bone and visceral metastases. A greater proportion of patients with visceral and bone metastases (89%), compared with bone only metastases (74%), had metastases prior to diagnosis of CRPC (i.e. had mHSPC).

Systemic treatment for mCRPC

Patient characteristics – by treatment line: Details regarding treatments received were available for 480 patients who received one of the four treatments of interest (abiraterone, enzalutamide, docetaxel and cabazitaxel) as first-line systemic treatment for mCRPC. Of these 480 patients, 262 (55%) received abiraterone, 58 (12%) received enzalutamide, and 160 (33%) received docetaxel at first-line. One patient was reported to receive abiraterone and enzalutamide in combination. Key characteristics for patients stratified by first treatment line received are shown in Table 1.

Patients receiving docetaxel as first-line treatment were younger and had a lower BMI compared with those receiving enzalutamide or abiraterone. Patients receiving docetaxel or enzalutamide as first-line treatment had a shorter mean time from prostate cancer diagnosis to data collection compared with those receiving abiraterone, but there was no difference in mean time from CRPC diagnosis to data collection between patients receiving different first-line treatment.

The time from diagnosis of mHSPC to diagnosis of mCRPC was associated with first-line treatment, with a longer time observed in those receiving abiraterone, compared with docetaxel or enzalutamide.

Treatment lines and durations: Details of the number of treatment lines and treatments received at first and second-line for mCRPC are shown in Table 2.

In the total study population, 61% (360/591) of patients received a single line of therapy for mCRPC.

For those patients for whom detailed treatment data were available, abiraterone was the most commonly reported treatment, accounting for 55% (263/481) of first-line treatments, and 54% (65/121) of second-line treatments (as monotherapy or in combination with abiraterone) in the total study population. Abiraterone was used as second-line treatment in 62 patients receiving docetaxel as first-line treatment, and 2 patients receiving enzalutamide as first-line treatment. Docetaxel was the second most commonly reported treatment; 33% (160/581) of patients received this as first-line treatment, and 19% (23/121) as second-line. Although enzalutamide accounted for only 12% (59/481) of first-line treatments, it was given as second-line to 20% (24/121) of patients, and to 8 of the 19 patients (42%) who received third-line therapy. Cabazitaxel was not given as first-line to any patient, and was given as second-line to only 9% (11/121) of patients, but 53% (10/19) of third-line treatments were with this agent.

For patients with bone metastases only, mCRPC treatment was most commonly initiated with abiraterone (57% - 228/399), while patients with bone and visceral metastases were more often treated with docetaxel as first-line (52% - 34/66). Of the 121 patients receiving more than one line of systemic therapy, the most common first to second-line switch was between docetaxel and abiraterone (50%), followed by abiraterone to docetaxel (17%).

Table 1: Key Patient Characteristics

Parameter	Total study population (N=591)	Subgroups - Location of metastases		Subgroups - First-line treatment		
		Visceral & bone metastases (N=83)	Bone metastases only (N=481)	Abiraterone (N=262)	Enzalutamide (N=58)	Docetaxel (N=160)
Age at initiation of treatment for mCRPC (years)						
N	587	83	477	261	57	159
Mean	71.2	69.46	71.61	72.87	73.32	68.81
SD	8.31	9.96	7.97	6.59	7.74	8.60
Median	72	71	72	73	73	69
Range	44–90	44–90	45–90	50–90	52–90	44–90
95% CI	70.53, 71.88	67.28, 71.63	70.89, 72.32	72.07, 73.67	71.26, 75.37	67.46, 70.16
BMI at initiation of treatment for mCRPC (kg/m^2)						
N	461	73	368	207	51	108
Mean	24.51	24.28	24.62	24.59	24.95	23.77
SD	3.26	3.86	3.14	2.55	2.50	2.35
Median	24.21	23.81	24.22	24.22	24.45	23.70
Range	17.76–56.18	19.36–49.23	17.76–56.18	19.14–38.97	21.16–36.14	19.59–31.83
95% CI	24.21, 24.81	23.38, 25.18	24.30, 24.94	24.24, 24.94	24.25, 25.66	23.32, 24.22
ECOG status at initiation of treatment for mCRPC, n (%)						
0	136 (23.0)	16 (19.3)	112 (23.3)	66 (25.2)	8 (13.8)	33 (20.6)
1	303 (51.3)	41 (49.4)	249 (51.8)	130 (49.6)	28 (48.3)	94 (58.8)
2	116 (19.6)	16 (19.3)	98 (20.4)	55 (21.0)	19 (32.8)	23 (4.4)
≥3	33 (5.6)	10 (12.0)	19 (4.0)	9 (3.4)	3 (5.2)	9 (5.6)
Not assessed	3 (0.5)	0 (0.0)	3 (0.6)	2 (0.8)	0 (0.0)	0 (0.0)
Stage at first prostate cancer diagnosis, n (%)						
Stage I	19 (3.2)	5 (6.0)	13 (2.7)	5 (1.9)	5 (8.6)	2 (1.3)
Stage II	84 (14.2)	13 (15.7)	70 (14.6)	43 (16.4)	10 (17.2)	19 (11.9)
Stage III	171 (28.9)	21 (25.3)	139 (28.9)	72 (27.5)	8 (13.8)	62 (38.8)
Stage IV	317 (53.6)	44 (53.0)	259 (53.8)	142 (54.2)	35 (60.3)	77 (48.1)
Metastases prior to CRPC diagnosis,n (%)						
Yes	454 (76.8)	74 (89.2)	356 (74.0)	198 (75.6)	44 (75.9)	130 (81.4)
No	137 (23.2)	9 (10.8)	125 (26.0)	64 (24.4)	14 (24.1)	30 (18.8)
Number of bone metastases prior toinitiation of treatment for mCRPC						
N	580	83	481	257	58	157
Mean	7.4	5.1	8.0	7.6	6.2	9.2
SD	7.5	3.8	7.9	7.6	3.7	8.9
Median	5	4	6	6	5.5	6
Range	0–65	1–30	0–65	0–65	1–19	0–41
95% CI	6.7, 8.0	4.3, 5.9	7.3, 8.7	6.7,8.6	5.3, 7.2	7.8, 10.6
SSE prior to mCRPC diagnosis, N n (%)						

Parameter	Total study population (N=591)	Subgroups - Location of metastases		Subgroups - First-line treatment		
		Visceral & bone metastases (N=83)	Bone metastases only (N=481)	Abiraterone (N=262)	Enzalutamide (N=58)	Docetaxel (N=160)
N	549	78	453	253	54	143
Yes	35 (6.4)	18 (23.1)	16 (3.5)	15 (5.9)	7 (13.0)	7 (4.9)
No	514 (93.6)	60 (76.9)	437 (96.5)	238 (94.1)	47 (87.0)	136 (95.1)
Time from prostate cancer diagnosis to mHSPC diagnosis (months)						
N	437	73	341	245	43	127
Mean	7.01	5.81	7.25	9.82	4.40	6.57
SD	18.80	12.84	20.12	22.98	11.73	17.56
Median	0.00	0.00	0.00	0.00	0.00	0.00
Range	0.00–129.51	0.00–55.03	0.00–129.51	0.00–129.52	0.00–49.51	0.00–96.00
95% CI	5.24, 8.78	2.81, 8.81	5.11, 9.39	6.54, 13.09	0.79, 8.01	3.49, 9.66
Time from mHSPC diagnosis to mCRPC diagnosis (months)						
N	422	72	327	182	42	123
Mean	19.06	19.23	19.04	25.02	17.24	16.12
SD	19.41	14.27	20.23	21.32	18.36	15.35
Median	13.16	16.03	13.01	21.17	11.06	12.94
Range	0.00–168.28	1.77–64.10	0.00–168.28	0.00–168.28	0.59–69.78	0.00–88.34
95% CI	17.21, 20.92	15.88, 22.59	16.84, 21.24	21.90, 28.14	11.52, 22.96	13.38,18.86
Time from prostate cancer diagnosis to data collection (months)						
N	564	82	456	246	56	152
Mean	49.16	46.41	49.70	58.56	46.50	46.78
SD	36.15	30.00	37.15	38.18	32.30	35.11
Median	37.29	37.26	36.68	49.74	35.91	32.21
Range	12.16–190.09	13.93–135.10	12.17–190.09	13.27–188.32	13.77–144.66	12.16–182.60
95% CI	46.17, 52.15	39.82, 53.00	46.28, 53.12	53.77, 63.36	37.85, 55.15	41.15, 52.40
Time from CRPC diagnosis to data collection (months)						
N	589	83	479	262	57	160
Mean	18.44	19.27	18.25	19.20	19.89	17.50
SD	11.15	10.75	11.34	13.86	11.36	7.91
Median	15.41	15.38	15.41	16.16	15.28	15.18
Range	12.02–182.60	12.09–67.15	12.02–182.60	12.02–182.60	12.16–67.15	12.02–55.46
95% CI	17.54, 19.35	16.93, 21.62	17.23, 19.27	17.73, 21.10	16.88, 22.91	16.26, 18.73

BMI: body mass index; CI: confidence interval; CRPC: castration-resistant prostate cancer; ECOG: Eastern Cooperative Oncology Group; FE: Fisher's exact test; mCRPC: metastatic CRPC; mHSPC: metastatic hormone-sensitive prostate cancer; SD: standard deviation; SSE: symptomatic skeletal events

Only 44% of patients who received docetaxel as first-line received one line of therapy, compared with 89% of patients treated with abiraterone, and 97% of patients who had received enzalutamide as first-line therapy.

The treatment reported as currently ongoing (at any treatment line) for the highest number of patients was abiraterone (n=281); the mean duration of ongoing treatment with this agent at the time of data collection was 13.0 months. Treatment with enzalutamide (at any treatment line) was currently ongoing for 90 patients, with a mean duration of 9.4 months, while 50 patients were receiving ongoing treatment with docetaxel, with a mean duration of 7.5 months.

The mean duration of completed treatments across lines was highest for abiraterone (11.1 months), followed by enzalutamide (8.2 months) and docetaxel (5.5 months). The mean durations of completed first-line treatment were 10.4 months for abiraterone, 8.6 months for enzalutamide and 5.5 months for docetaxel. Mean aggregate (completed and ongoing) duration for abiraterone was 12.8 months, for enzalutamide was 9.4 months and for docetaxel was 6.0 months.

Symptomatic skeletal events

Where the number of SSEs could be derived, 83 of the 591 patients in the total study population (14%) developed at least one SSE. Of these, 49% (n=41) had a single SSE, 40% (n=33) experienced two SSEs and 11% (n=9) experienced three or more SSEs. Overall, 155 SSEs were reported, with 45 events experienced prior to mCRPC diagnosis (in the 549 patients for which this information was available), 67 events experienced

Table 2 : Treatment for mCRPC

Parameter	Total study population (N=591)	Subgroups - Location of metastases		Subgroups - First-line treatment		
		Visceral & bone metastases (N=83)	Bone metastases only (N=481)	Abiraterone (N=262)	Enzalutamide (N=58)	Docetaxel (N=160)
Lines of systemic therapy received post-mCRPC diagnosis, n (%)						
0	110 (18.6)	17 (20.5)	82 (17.0)	NA	NA	NA
1	360 (60.9)	37 (44.6)	311 (64.7)	232 (88.5)	56 (96.6)	71 (44.4)
2	102 (17.3)	24 (28.9)	77 (16.0)	26 (9.9)	2 (3.4)	74 (46.3)
3	15 (2.5)	5 (6.0)	9 (1.9)	4 (2.5)	0 (0.0)	11 (6.9)
4	4 (0.7)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	4 (2.5)
Treatment received at first-line postm-CRPC diagnosis, N n (%)	481	66	399			
Abiraterone	262 (54.5)	23 (34.8)	228 (57.1)	NA	NA	NA
Docetaxel	160 (33.3)	34 (51,5)	121 (30.3)	NA	NA	NA
Enzalutamide	58 (12.1)	9 (13.6)	49 (12.3)	NA	NA	NA
Enzalutamide & abiraterone	1 (0.2)	0 (0.0)	1 (0.3)	NA	NA	NA
Treatment received at second-line postm-CRPC diagnosis, N n (%)	121	29	88	30	2	89
Abiraterone	63 (52.1)	12 (41.4)	49 (55.7)	0 (0.0)	2 (100.0)	61 (68.5)
Abiraterone & docetaxel	2 (1.7)	2 (6.9)	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.1)
Cabazitaxel	11 (9.1)	5 (17.2)	6 (6.8)	1 (3.3)	0 (0.0)	10 (11.2)
Docetaxel	21 (17.4)	5 (17.2)	16 (18.2)	21 (70.0)	0 (0.0)	0 (0.0)
Enzalutamide	24 (19.8)	5 (17.2)	17 (19.3)	7 (23.3)	0 (0.0)	17 (19.1)

mCRPC: metastatic castration-resistant prostate cancer

at mCRPC diagnosis, and 34 events experienced after mCRPC diagnosis; the timing of the SSE was missing for 9 events.

The most common SSEs after or on the day of mCRPC diagnosis were bone radiotherapy (45/101; 45%) and pathological fracture (31/101; 31%); the most common SSE prior to mCRPC diagnosis was pathological fracture (23/45 SSEs; 51%), followed by spinal cord compression (8/45 SSEs; 8%). The majority of patients experienced their first SSE at or following mCRPC diagnosis (n=60; 67%) with 67 patients having a first SSE following the development of bone metastases. There was little difference in the proportion of patients experiencing an SSE prior to mCRPC diagnosis based on patient subgroups stratified by location of metastases or first-line treatment for mCRPC (Table 1).

Lower proportions of patients receiving abiraterone or docetaxel (4.7% and 5.4 %, respectively) as first-line therapy experienced pathologic fracture, compared with enzalutamide (16.1%). The proportion of patients having bone radiotherapy was 6.3%, 7.3% and 12.9% for those receiving abiraterone, enzalutamide, and docetaxel, respectively, as first-line therapy. The mean time from first bone metastases to first SSE was similar for patients receiving abiraterone or enzalutamide as first-line therapy, with a mean of 26 and 29 months, respectively; it was somewhat shorter with docetaxel, at 16 months. Kaplan-Meier survival analysis demonstrated a 10% and 24% likelihood of developing an SSE within the first 2 and 5 years, respectively, of being diagnosed with bone metastases (Figure 1).

Discussion

This real-world study in France found that the majority of patients in a population with mCRPC had metastases prior to developing CRPC. This might reflect the predominance of oncologists amongst the participating physicians, as this might result in patients only being diagnosed with CRPC when they have developed metastatic disease.

In the total study population, 81% of those patients with mCRPC had bone only metastases; a finding consistent with that of a systematic review reporting ≥84% of patients with bone metastases on diagnosis of CRPC [4].

In this population of patients with mCRPC, abiraterone was the preferred treatment at both first and second-line, followed by docetaxel for first-line and enzalutamide for second-line; cabazitaxel was the preferred treatment for the small numbers of patients receiving a third-line treatment. Treatments in the current study were used in accordance with European [8], and French national [7], guidelines. Docetaxel has been available in France since February 1996, after it was approved for use in mCRPC

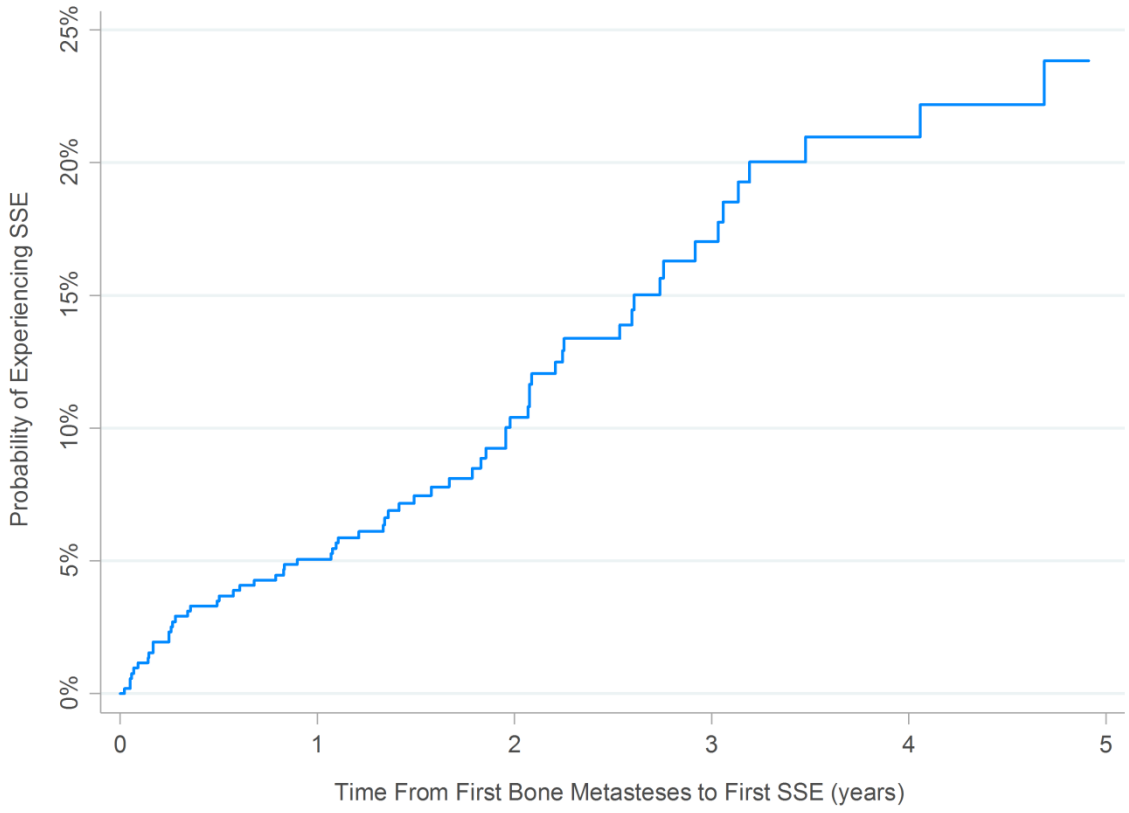

Figure 1: Kaplan-Meier survival curve for the development of first SSE

SSE: symptomatic skeletal event

by the European Medicines Agency (EMA) in November 1995. Abiraterone was approved by the EMA in September 2011 for the treatment of patients with mCRPC that is nonresponsive, or no longer responsive, to docetaxel; the indication was extended in January 2013 to include patients who are asymptomatic or mildly symptomatic after failure of ADT and in whom chemotherapy is not yet clinically indicated. The French Agency for National Medical Security provided patient access to abiraterone before its commercial availability via a Temporary Authorization for Use issued in December 2010 [12]. Cabazitaxel was approved by the EMA in March 2011 for mCRPC that is nonresponsive, or no longer responsive, to docetaxel. Enzalutamide received EMA approval in June 2013 for mCRPC nonresponsive, or no longer responsive, to docetaxel, with an extension to include patients who are asymptomatic or mildly symptomatic after failure of ADT and in whom chemotherapy is not yet clinically indicated approved in October 2014.

The finding that more than half (61%) of patients received only one line of systemic therapy after diagnosis of mCRPC is not unexpected. It is not uncommon for the number of patients receiving treatment for metastatic cancer to reduce markedly from line to line. Also, the extension of the labels for abiraterone and enzalutamide means that these agents can now be used without a patient first receiving docetaxel [10]. However, there is frequently a lag after approval of a new agent or new indication before it becomes established in routine clinical practice, and updated French national guidelines recommending the use of abiraterone, enzalutamide and cabazitaxel in mCRPC were only published in 2016, after data were collected for this study [7]. Of patients who received docetaxel as first-line therapy, only 44% received this as a single line of treatment, compared with 89% of patients treated with abiraterone, and 97% of patients who had received enzalutamide as first-line therapy. This is reflective of docetaxel being long-established as the standard treatment for patients progressing to CRPC, together with the relatively recent approval of other agents for first-line use.

Only 14% of the patients included in this analysis experienced one or more SSEs at some point in the course of their disease, with almost half of these having a single SSE and only 11% of patients having three or more SSEs. This is low compared to data from clinical trials; the percentage of treated patients experiencing SSEs in trials has been reported as 32–37% [13–15]. The low number of SSEs reported in this study might be indicative of improved patient outcomes related to the use of newer therapies such as abiraterone as first and second-line treatments. However, it cannot be ruled out that SSEs were under-reported in this study as a result of missing data in patient records, for instance if the physician was not made aware that the patient had attended an emergency room or GP for an SSE. It is of interest that around 30% of SSEs occurred prior to the patient being diagnosed with mCRPC, suggesting that metastases have often developed prior to a formal diagnosis of mCRPC. Further investigation of the incidence of SSEs in patients with mCRPC in the real-world setting in France is warranted.

A number of potential limitations of this study are acknowledged. Although participating physicians were considered to be representative of those treating patients with prostate cancer, they were recruited via an online research panel, and as such may have a greater interest in research, potentially including the use of newer treatments, than the broader physician population. Patients included were consecutive consulting patients who initiated treatment at least 12 months prior to data collection; deceased patients were not included and the complications of mCRPC, such as the development of SSEs, may therefore be underestimated. Data are based on the first year post-mCRPC diagnosis so are only representative of this period, and patient data available to the physicians might be incomplete, with details of relevant events missing. Data collection was in Q3 of 2015, and therefore reflects clinical practice from approximately 2014 onwards; as abiraterone and enzalutamide received approval for use in the pre-chemotherapy population in 2013 and 2015 respectively, the current use of these agents may now be higher than found in this study. The numbers of patients in each of the subgroups stratified by site of metastases and first-line systemic treatment differed considerably; consequently, comparisons between these groups should be treated with caution.

As with all real-world studies, information bias and data errors might have arisen, but actions were taken to minimize these as far as possible. Pilot studies were conducted to ensure understanding of disease progression, treatment use and sequencing, patient pathways and other features of mCRPC, and research materials designed taking these into consideration. PRFs had 'don't know' options to allow inclusion of patients who met entry criteria but whose records were not complete, while minimizing the collection of erroneous data.

Conclusion

In conclusion, this study shows that treatment of mCRPC in clinical practice in France incorporates the use of newer agents, reflecting national guidelines. Further research could help confirm if the introduction of new targeted alpha therapies might reduce or delay the occurrence of SSEs, as seen in clinical studies [16], in a real-world situation.

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