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Original article

Clinical outcomes in a contemporary series of "young" patients with castration-resistant prostate cancer who were 60 years and younger

Orazio Caffo, M.D.[a,*], Cinzia Ortega, M.D.[b], Giuseppe Di Lorenzo, Ph.D.[c], Teodoro Sava, M.D.[d], Ugo De Giorgi, M.D.[e], Carla Cavaliere, M.D.[f], Sveva Macrini, M.D.[g], Gilbert Spizzo, M.D.[h], Michele Aieta, M.D.[i], Caterina Messina, M.D.[j], Marcello Tucci, M.D.[k], Michele Lodde, M.D.[l], Giovanni Mansueto, M.D.[m], Paolo Andrea Zucali, M.D.[n], Daniele Alesini, M.D.[o], Alessandro D'Angelo, M.D.[p], Francesco Massari, M.D.[q], Franco Morelli, M.D.[r], Giuseppe Procopio, M.D.[s], Raffaele Ratta, M.D.[t], Lucia Fratino, M.D.[u], Giovanni Lo Re, M.D.[v], Maria Cristina Pegoraro, M.D.[w], Fable Zustovich, M.D.[x], Giovanni Vicario, M.D.[y], Fiorella Ruatta, M.D.[b], Piera Federico, M.D.[c], Francesca La Russa, M.D.[d], Salvatore Luca Burgio, M.D.[e], Francesca Maines, M.D.[a], Antonello Veccia, M.D.[a], Enzo Galligioni, M.D.[a]

[a] *Medical Oncology Department, Santa Chiara Hospital, Trento, Italy*
[b] *Medical Oncology Department, Institute for Cancer Research and Treatment, Candiolo, Italy*
[c] *Oncologia Urologica, Azienda Ospedaliera Universitaria "Federico II", Napoli, Italy*
[d] *Medical Oncology Department, General Hospital, Verona, Italy*
[e] *Medical Oncology Department, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST)—IRCCS, Meldola, Italy*
[f] *Department of Uro-Gynaecological Oncology, Istituto Nazionale Tumori "Fondazione G. Pascale"—IRCCS, Naples, Italy*
[g] *Medical Oncology Department, Santa Maria della Misericordia Hospital, Udine, Italy*
[h] *Medical Oncology Department, General Hospital, Merano, Italy*
[i] *Medical Oncology Department, Referral Cancer Center of Basilicata—IRCCS, Rionero in Vulture, Italy*
[j] *Medical Oncology Department, Papa Giovanni XXIII Hospital, Bergamo, Italy*
[k] *Medical Oncology Department, San Luigi Hospital, University of Torino, Orbassano, Italy*
[l] *Urology Department, General Hospital, Bolzano, Italy*
[m] *Medical Oncology Department, General Hospital, Frosinone, Italy*
[n] *Department of Medical Oncology and Haematology, Humanitas Clinical and Research Center, Rozzano, Milan, Italy*
[o] *Department of Radiological, Oncological and Anatomopathological Sciences, La Sapienza, University of Rome, Rome, Italy*
[p] *Medical Oncology Department, San Vincenzo Hospital, Taormina, Italy*
[q] *Medical Oncology, Azienda Ospedaliera Universitaria Integrata, University of Verona, Verona, Italy*
[r] *Medical Oncology Department, Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy*
[s] *Oncologia medica genitourinaria—Fondazione Istituto Nazionale Tumori, Milan, Italy*
[t] *Medical Oncology Department, University Campus Bio-Medico, Rome, Italy*
[u] *Medical Oncology Department, National Cancer Institute, Aviano, Italy*
[v] *Medical Oncology Department, Santa Maria degli Angeli Hospital, Pordenone, Italy*
[w] *Medical Oncology Department, ULSS5 Ovest Vicentino, Montecchio Maggiore, Italy*
[x] *Medical Oncology Unit 1, Department of Clinical and Experimental Oncology, Istituto Oncologico Veneto IOV—IRCCS, Padua, Italy*
[y] *Medical Oncology Department, San Giacomo Apostolo Hospital, Castelfranco Veneto, Italy*

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* Corresponding author. Tel.: +39-461-902478; fax: +39-461-903364.
E-mail address: orazio.caffo@apss.tn.it (O. Caffo).

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Abstract

Background: The prognosis of younger patients with prostate cancer is unclear, and the very few studies assessing those with metastatic castration-resistant prostate cancer (mCRPC) have mainly involved patients treated with older therapies. The aim of this observational study was to evaluate the clinical outcomes of a contemporary series of docetaxel-treated patients with mCRPC who were 60 years and younger.

Patients and methods: We retrospectively identified 134 patients who were 60 years and younger who were treated with docetaxel in 25 Italian hospitals and recorded their predocetaxel history of prostate cancer, their characteristics at the start of chemotherapy, and their postdocetaxel treatment history and outcomes.

Results: Most of the 134 consecutive patients with mCRPC received the standard 3-week docetaxel schedule; median progression-free survival (PFS) was 7 months, and 90 patients underwent further therapies after progression. The median overall survival (OS) from the start of docetaxel treatment was 21 months, but OS was significantly prolonged by the postprogression treatments, particularly those based on the new agents such as cabazitaxel, abiraterone acetate, or enzalutamide. OS was significantly shorter in the patients with a shorter interval between the diagnosis of prostate cancer and the start of docetaxel treatment; those who received hormonal treatment for a shorter period; those with shorter prostate-specific antigen doubling times; and those with lower hemoglobin levels, a worse performance status, and higher lactate dehydrogenase levels before starting treatment with docetaxel.

Conclusions: The findings of this first study of clinical outcomes in a contemporary series of younger patients with mCRPC showed that their survival is similar to that expected in unselected patients with mCRPC who were of any age.

Keywords: Metastatic castration-resistant prostate cancer; Docetaxel; Young; Abiraterone acetate; Cabazitaxel; Enzalutamide

1. Introduction

Prostate cancer (PC) is usually considered a disease of advanced age [1], with the risk increasing from 1 of 43 subjects in their 60s to 1 of 9 subjects 70 years and older [2]. However, although a diagnosis of PC is still rare in men younger than 60 years, its frequency has progressively increased with the growing use of prostate-specific antigen (PSA) testing [3].

The prognostic significance of being diagnosed as having PC at a young age is unclear because most of the published studies involved patients with localized disease who were undergoing radical treatment and led to conflicting results, and the worst prognosis suggested by the studies published before the advent of PSA testing has not been confirmed by more recent findings [4]. Furthermore, most of the studies investigated clinical outcomes in patients who were young at the time of diagnosis; very few have described young men with more advanced disease or metastatic castration-resistant prostate cancer (mCRPC) [5–7], and these largely involved patients treated before docetaxel was introduced into clinical practice [8,9].

Therefore, there are few data concerning the outcomes of contemporary patients with mCRPC whose treatment options have been significantly enriched by the availability of a number of newer agents capable of improving patient survival: cabazitaxel [10], abiraterone acetate [11,12], enzalutamide [13,14], and radium 223 [15].

The aim of this retrospective observational study was to investigate clinical outcomes in a contemporary series of docetaxel-treated patients with mCRPC who were 60 years and younger.

2. Patients and methods

2.1. Data collection

The patients included in the study had a histologically confirmed diagnosis of prostate cancer, developed metastatic castration resistance over time, and were 60 years and younger when they received first-line docetaxel-based chemotherapy. We recorded their predocetaxel history of PC (Gleason score and the presence/absence of metastatic disease at the time of diagnosis, the time between the diagnosis of PC and the development of mCRPC, and the duration of hormonal therapy before developing mCRPC), their characteristics at the time of starting chemotherapy (PSA level; pretreatment PSA doubling time calculated using the Memorial Sloan Kettering Cancer Center website; hemoglobin, alkaline phosphatase, and lactate dehydrogenase levels; performance status; and the presence/absence of pain), their docetaxel treatment history and outcomes, and their postdocetaxel history. A record was also made of each patient's vital status, biochemical and instrumental responses, the date of progression, and the date of the last follow-up examination. The safety data were analyzed using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

2.2. Statistical analysis

The continuous variables were expressed as median values and the discrete variables as relative frequencies. Responses were assessed based on the biochemical response rate (defined as the percentage of patients showing at least a 50% reduction in PSA levels in comparison with

those recorded at the time of starting treatment), the objective response rate (oRR, defined as the percentage of complete and partial responses based on the Response Evaluation Criteria In Solid Tumors criteria), overall survival (OS, calculated from the start of docetaxel treatment until death or the time of the last follow-up visit, whichever occurred first), and PFS (calculated using the Kaplan-Meier method from the start of docetaxel treatment until progression or the time of the last follow-up visit, whichever occurred first). Cox regression analysis was used to calculate the differences in OS between groups stratified based on the patients' Gleason scores at the time of diagnosis; the time between the diagnosis of PC and the development of mCRPC; the duration of hormonal treatment before starting docetaxel; PSA levels and PSA doubling time; baseline Eastern Cooperative Oncology Group performance status; hemoglobin, alkaline phosphatase, and lactate dehydrogenase levels; and the presence/absence of pain and visceral metastases. The continuous variables were categorized based on their median values, and the categorical variables were compared using the chi-squared test. The data were statistically analyzed using SPSS 12 software (SPSS Inc., Chicago, IL).

3. Results

We retrospectively selected a consecutive series of 134 patients with mCRPC who were 60 years and younger who were treated with docetaxel between March 2002 and March 2013 in 25 Italian Hospitals. The main characteristics of the patients are summarized in Table 1. Gleason scores at the time of diagnosis were <8 in 44 patients (32.8%), ≥ 8 in 79 (59.0%), and unknown in 11 (8.2%). A total of 62 patients showed localized disease at the time of diagnosis and underwent radical treatment: prostatectomy (21 patients), prostatectomy plus external radiotherapy (21 patients), or external radiotherapy alone (20 patients). The median time from the diagnosis of PC to the development of mCRPC was 20 months (range: 2–151), with lung and liver metastases being recorded in 13% and 8% of cases, respectively.

Chemotherapy was started after 1 to 4 hormonal manipulations. Most of the patients received a standard 3-week docetaxel schedule: 83 (62%) received the standard dose of 75 mg/m^2, 34 (25%) received the dose of 70 mg/m^2 as they were enrolled in a clinical trial, and 2 (1%) received a reduced dose of 60 mg/m^2 because of their worse performance status; the remaining 15 patients (11%) received a weekly schedule of docetaxel at doses ranging from 25 to 36 mg/m^2, once again because of their worse performance status. Estramustine phosphate was combined with docetaxel in 19 patients.

The treatment was well tolerated (41 patients experienced grade 3–4 toxicity) (Table 2) and was prematurely stopped because of progressive disease in 54 patients (40%), toxicity in 9 (7%), and comorbidities in 1 (1%); the remaining 70 patients (52%) discontinued the treatment after completing the planned number of courses or because their PSA levels had normalized.

In 61 patients (45%) there was $\geq 50\%$ reduction in PSA levels when compared with baseline. The oRR among the 105 patients who were radiographically re-evaluated after docetaxel treatment was 19% (4 complete and 15 partial responses). The median PFS was 7 months (95% CI: 6–8), with 90 patients receiving further therapy after progression: 25 (19%) received at least 1 docetaxel rechallenge, 47 (35%) received other chemotherapies (mainly mitoxantrone), 25

Table 1
Patient characteristics

No. of patients	134
Median age at time of starting docetaxel (IQ)	57 (54–59)
Median age at time of diagnosis (IQ)	54 (50–56)
No. of patients aged ≤ 50 y	39 (29%)
Gleason score	
≤ 7	44 (32.8%)
8–10	79 (59.0%)
Unknown	11 (8.2%)
Metastases at time of diagnosis	
Yes	69 (51.5%)
No	62 (46.3%)
Unknown	3 (2.2%)
Local treatments (in patients without metastases at time of diagnosis)	
Prostatectomy	21 (15.7%)
Prostatectomy + radiotherapy	21 (15.7%)
Radiotherapy	20 (14.9%)
Hormonal lines	
1	32 (23.9%)
2	57 (42.5%)
3	23 (17.2%)
4 or more	22 (16.4%)
Median time between PC diagnosis and starting docetaxel, mo (IQ)	20 (12–46.5)
Median duration of hormonal therapy, mo (IQ)	16 (10.2–32.7)
Metastatic sites	
Bone	50 (37.3%)
Nodes	65 (48.5%)
Liver	13 (9.7%)
Lung	18 (13.4%)
Not reported	36 (26.9%)
No. of patients with pain at baseline	66 (49%)
Median baseline hemoglobin, g/dl (IQ)	12.5 (11.0–13.5)
Median baseline prostate-specific antigen, ng/ml (IQ)	82 (23–227)
Median baseline alkaline phosphatase, IU/l (IQ)	202 (97–406)
Median baseline lactate dehydrogenase, IU/l (IQ)	381 (242–593)
Median PSA doubling time, mo (IQ)	2.06 (1.3–3.4)
Performance status	
0	64 (47.8%)
1	52 (38.8%)
2	11 (8.2%)
Unknown	7 (5.2%)
Docetaxel schedule	
Every 3 wk	119 (88.8%)
Weekly	15 (11.2%)

IQ = interquartile range.

Table 2
Recorded toxicities assessed using the NCI's CTCAE, version 4.0 (percentages in brackets)

	All grades	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	74 (55.2)	46 (34.3)	23 (17.2)	5 (3.7)	0 (0.0)
Anemia	55 (41.0)	36 (26.9)	14 (10.4)	5 (3.7)	0 (0.0)
Nausea	44 (32.8)	32 (23.9)	11 (8.2)	1 (0.7)	0 (0.0)
Neutropenia	44 (32.8)	11 (8.2)	15 (11.2)	10 (7.5)	8 (6.0)
Stomatitis	33 (24.6)	20 (14.9)	13 (9.7)	0 (0.0)	0 (0.0)
Diarrhea	30 (22.4)	18 (13.4)	11 (8.2)	1 (0.7)	0 (0.0)
Edema	25 (18.7)	15 (11.2)	9 (6.7)	0 (0.0)	1 (0.7)
Sensitive neuropathy	25 (18.7)	17 (12.7)	6 (4.5)	2 (1.5)	0 (0.0)
Thrombocytopenia	23 (17.2)	15 (11.2)	7 (5.2)	0 (0.0)	1 (0.7)
Vomiting	21 (15.7)	15 (11.2)	5 (3.7)	1 (0.7)	0 (0.0)
Nail changes	21 (15.7)	9 (6.7)	12 (9.0)	0 (0.0)	0 (0.0)
Constipation	11 (8.2)	9 (6.7)	2 (1.5)	0 (0.0)	0 (0.0)
Fever	9 (6.7)	8 (6.0)	1 (0.7)	0 (0.0)	0 (0.0)
Rash	6 (4.5)	3 (2.2)	1 (0.7)	2 (1.5)	0 (0.0)
Liver toxicity	4 (3.0)	3 (2.2)	(0.0)	1 (0.7)	0 (0.0)
Renal toxicity	2 (1.5)	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)
Febrile neutropenia	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)

CTCAE = common terminology criteria for adverse events; NCI = National Cancer Institute.

(19%) received cabazitaxel, and 34 (25%) received 1 new hormonal agent (abiraterone or enzalutamide).

After a median follow-up of 19 months, 98 patients died. The median OS from the start of docetaxel treatment was 21 months (95% CI: 16–26) and was significantly influenced by further treatment (Table 3): it was 27 months in the patients who received further treatment and 12 months in those who did not ($P < 0.0001$). Moreover, among the patients who received additional treatment, those treated with new agents (cabazitaxel, abiraterone acetate, or enzalutamide) had a median OS of 29 months, compared with 17 months in those who received a docetaxel rechallenge, mitoxantrone, or other drugs ($P = 0.004$).

To verify the effect of the further treatments on OS, we compared survival from the time of the first progression after docetaxel treatment using a 3-month landmark analysis to avoid the clear bias caused by the patients who died soon after progression. Once again, OS was significantly longer in the patients who received further therapy than that in those who did not (18 vs. 12 mo, $P = 0.01$), and the patients treated with cabazitaxel, abiraterone acetate, or enzalutamide survived longer than those who underwent a docetaxel rechallenge or received a different chemotherapy after progression (36 vs. 13 mo, $P = 0.03$).

OS was significantly shorter in the patients who had clinically more aggressive disease (a shorter time interval between the diagnosis of PC and the start of docetaxel treatment, a shorter duration of hormonal treatment, and a shorter PSA doubling time) and in those who had lower hemoglobin levels, a worse performance status, or higher lactate dehydrogenase levels before starting docetaxel treatment (Table 4).

4. Discussion

The findings of this first study of clinical outcomes in a contemporary series of younger patients with mCRPC receiving first-line docetaxel treatment (which is also the first study of such patients in the era of the new mCRPC drugs) showed that their survival is similar to that expected in unselected patients with mCRPC of any age [8,9].

The widespread use of PSA testing has led to an increase in the incidence of diagnoses of early-onset PC [3], and this has aroused growing interest in its prognostic relevance [16]. Many studies have evaluated younger patients with localized PC but, although those studies performed in the pre-PSA era generally found that the aggressiveness of the disease led to a worse prognosis in patients undergoing radical treatment [17–19], the findings of more recent analyses do not support this hypothesis [20–23]. Recent epidemiological studies have shown that lower-grade tumors are more frequent and outcomes are more favorable in younger patients with PC [24], and a SEER report showed that the general 10-year, cancer-specific survival of younger men with low-grade cancer is equivalent to that of their older counterparts, although the youngest men with high-grade and advanced PC at the time of diagnosis had a particularly poor prognosis: in particular, men aged 35 to 44 years with stage IV cancer had an approximately 1.5-fold greater risk of prostate cancer-specific mortality when compared with men aged 65 to 74 years [25].

The latter findings have recently been supported by the results of a retrospective study of 2,449 Japanese men with metastatic PC receiving androgen-deprivation therapy [7]: the patients were stratified by age at the time of starting hormonal therapy, and it was found that the cancer-specific survival of those who were 55 years and younger was much shorter than that of the older patients. However, as the authors pointed out, most of the patients were treated in the predocetaxel era, which makes it difficult to apply the results to the contemporary therapeutic scenario in which a number of agents have led to a significant survival gain in patients with mCRPC. Docetaxel remained the standard first-line option for 10 years [8,9], but then it was found that abiraterone and enzalutamide are efficacious after docetaxel treatment [11,13] and in chemotherapy-naïve patients

Table 3
Clinical outcomes by postprogression treatments

	All patients	No treatment	Old therapies[a]	New agents
No. of patients	134	44	51	39
PSA response rate, %	60	56	60	67
Median PFS, mo	7	6	8	9
Median OS, mo	21	12	17	29

[a]Old therapies = docetaxel rechallenge, mitoxantrone, or other old drugs.

Table 4
Cox proportional hazards analysis of overall survival by variable of interest

Variable	Value	Median OS	Univariate analysis			Multivariate analysis[a]		
			HR	95% CI	*P* value	HR	95% CI	*P* value
Visceral metastasis	No	21	0.710	0.418–1.207	0.197			
	Yes	13						
Gleason score	≤7	19	0.865	0.552–1.355	0.519			
	>8	24						
Time between PC diagnosis and starting docetaxel, mo	≤20	16	2.003	1.303–3.078	0.002	2.211	1.266–3.861	0.005
	>20	29						
Duration of hormonal treatment before starting docetaxel, mo	≤17	19	1.958	1.263–3.035	0.003	1.364	0.454–4.096	0.580
	>17	29						
Hemoglobin, g/dl	≤11.0	11	1.671	1.033–2.701	0.036	2.096	1.180–3.722	0.012
	>11.0	24						
Alkaline phosphatase, IU/l	≤406	21	0.858	0.543–1.368	0.101			
	>406	11						
Lactate dehydrogenase, IU/l	≤382	25	0.633	0.402–0.997	0.049	1.023	0.594–1.762	0.935
	>382	16						
PSA doubling time, mo	≤2.08	17	2.274	1.421–3.640	0.001	1.420	0.779–2.588	0.253
	>2.08	28						
Performance status	0	24	0.613	0.397–0.947	0.03	0.715	0.408–1.255	0.243
	1–2	17						
Pain	No	24	0.727	0.483–1.096	0.120			
	Yes	17						
Docetaxel schedule	Every 3 wk	24	1.472	0.817–2.653	0.188			
	Weekly	15						

HR = hazard ratio.
[a]Only variable significant at the univariate analysis.

[12,14] and finally that cabazitaxel and radium 223 improve survival in docetaxel-treated patients [10,15].

Only 2 studies have evaluated outcomes in younger men with mCRPC. Of them, 1 study retrospectively collected data from 8 Cancer and Leukemia Group B studies and showed that the 132 patients who were younger than 60 years were at a 26% greater risk of PC-related death than those aged 70 to 79 years [5]. Unfortunately, the studies included in this analysis were performed between 1992 and 2002, only a minority of the patients received docetaxel-based treatment (which was found to be a strong predictor of OS), and none of them were treated with the new-generation agents.

A more recent retrospective analysis considered 333 patients with mCRPC treated at Princess Margaret Hospital in Toronto [6], but it stratified the patients based on their age at the time of diagnosis of PC and does not provide any information concerning the age at which they developed mCRPC. The findings suggested that the age at the time of PC diagnosis affects the outcome of the patients who subsequently develop mCRPC, with the shortest survival being observed in the >75-year and <55-year age groups.

Ours is the first study describing a contemporary series of patients who were 60 years and younger when they were diagnosed as having mCRPC and received first-line, docetaxel-based chemotherapy. As there was no control group of older patients, the only possible comparison is with the clinical outcomes observed in recent pivotal trials involving patients with mCRPC. The median OS in our population as a whole was 21 months, but there were clear differences between the patients receiving different post-progression treatments: those who did not receive any of the new agents (cabazitaxel, abiraterone acetate, or enzalutamide) had a median OS of 17 months, which is quite similar to that observed in the pivotal TAX327 docetaxel trial [8], whereas the 39 patients treated with new agents after treatment with first-line docetaxel had a median OS of 29 months, which is comparable with the median cumulative survival of 29 and 32.6 months because of the addition of cabazitaxel and abiraterone acetate to first-line docetaxel, respectively [26,27].

Although the survival of younger patients after the appearance of castration resistance seems to be comparable with that obtained in the pivotal trials, they may develop castration resistance more quickly. The cumulative analysis of the Cancer and Leukemia Group B studies showed that the median time between the diagnosis of PC and the development of mCRPC was significantly different in the

different age classes: 2.3 years in younger patients and 5.2 years in the older patients [5]. Our data support this finding, as the median time between the initial diagnosis and the development of mCRPC was 20 months.

This may be explained by the recent finding that patients with early-onset PC more frequently express the TMPRESS2:ERG fusion gene [28], which sustains the more frequent overexpression of ERG [29]: as this androgen-related structural rearrangement is stimulated by androgen receptor signaling, its expression suggests that strong and persistent androgen receptor signaling leads to resistance to hormonal treatment. As the prognosis of younger patients undergoing local radical therapy is similar to that of older patients, it is clear that not all the patients who are young at the time of diagnosis rapidly develop aggressive disease, and efforts should be made to discover the genetic profiles or altered molecular pathways that are capable of identifying those with a worse prognosis.

This study has a number of limitations. Firstly, its retrospective nature makes it methodologically difficult to assess treatment outcomes because activity measures such as the oRR and PFS can be greatly affected by differences in imaging frequency (which may shorten or lengthen PFS or fail to detect a radiological response or progression) or the interpretation bias because objective responses are determined by individual physicians. Furthermore, although the biochemical response rate may better reflect mCRPC treatment activity because PSA levels are routinely assessed in everyday clinical practice, its value as a surrogate parameter is questionable, which is why we mainly considered OS as the most reliable measure of clinical outcome.

Another limitation is the absence of control groups of patients of different ages, which prevented us from drawing any definite conclusions concerning possible differences in prognosis. Moreover, the large number of institutions involved in the study may have affected the homogeneity of the therapeutic protocols or the timing of treatment initiation (although our results show that the delivered treatments were sufficiently standardized to ensure clinical homogeneity), and it is clear that the differences in the number of previously administered hormonal lines reflected differences in the timing of the transfer of patients from urologists to oncologists in the individual institutions. The unusually low rate of bone metastases may also reflect differences in the type and frequency of imaging studies that are impossible to control for in a retrospective study.

Finally, another question is the age at which a patient with PC can be considered "young," which has still not been clearly defined [30]. We chose a cut-off age of 60 years because PC is mainly diagnosed in patients older than 65 years, all our patients developed castration resistance before this age, and the median age of the patients enrolled in recent pivotal studies of mCRPC ranges from 68 to 71 years [8,10–15]; however, others may consider this purely arbitrary.

Despite these limitations, our findings indicate that the survival of a contemporary series of younger patients with mCRPC is similar to that of older patients when they are treated with agents capable of improving survival. Furthermore, our hypothesis that some of the patients who are "young" at the time of diagnosis may have aggressive disease and rapidly develop castration resistance warrants further investigation in larger prospective studies.

5. Conflict of interest

Orazio Caffo received honoraria from Sanofi Aventis, Janssen, and Astellas. Ugo de Giorgi received honoraria from Janssen. Giuseppe Procopio received honoraria from Bayer, Bristol, GSK, BMS, Novartis, Astellas, Janssen, and Pfizer. Franco Morelli received honoraria from Bayer, Novartis, Janssen, Sanofi, and Pfizer. Cinzia Ortega received honoraria from Bayer and Astellas. The other authors have no conflict of interest to declare.

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