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Combining Abiraterone and Radiotherapy in Prostate Cancer Patients Who Progressed During Abiraterone Therapy

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Abstract. *Background/Aim: This multicenter, retrospective, 'field-practice' study investigated treatment outcomes of ongoing abiraterone therapy with the addition of radiotherapy (RT) – initiated for oligoprogression or with a palliative intent. Patients and Methods: Consecutive patients affected by metastatic castration-resistant prostate cancer (mCRPC) treated with abiraterone acetate were considered if they had received RT after the initiation of abiraterone treatment. Results: A total of 32 patients were enrolled in the study. Median duration of abiraterone treatment was 13.0 months (range=3.8-40.9 months). Median duration of abiraterone treatment before RT was 5.9 months (range=0.4-40.0 months), and 7.2 months after RT (range=0.1-29.7 months). Median progression-free survival (PFS) was 12.6 months (95%CI=10.5-14.7) from the initiation of abiraterone treatment. From RT administration, PFS was 9.6 months (95%CI=6.4-12.9). Median overall survival (OS) since abiraterone initiation was 18.9 months (95%CI=4.7-33.0). Conclusion: RT prolongs abiraterone treatment in mCRPC patients leading to better clinical outcomes with this molecule.*

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Prostate cancer is the second most frequently diagnosed cancer worldwide and remains the sixth leading cause of cancer death in males (1).

Although the majority of men with prostate cancer are diagnosed with a localized/regional disease (associated with a 5-year survival rate of 100%), 4% of men with prostate cancer present with a metastatic disease at diagnosis and their 5-year survival rate is only 28.2% (2). Among patients with locally-advanced disease at diagnosis, one out of three will ultimately develop metastases (3).

The therapeutic armamentarium available for men with advanced/metastatic disease is wide and includes prostatectomy, radiotherapy and, particularly, androgen-deprivation therapy (ADT). However, within five years of follow-up, 10-20% of men with aggressive prostate cancer develop an advanced form of disease, which is characterized by progression on surgical or pharmaceutical castration: this advanced form is known as castration-resistant prostate cancer (CRPC) (3). In this subgroup of patients, the median survival ranges from 9 to 30 months (3).

Besides reducing life expectancy, prostate cancer, particularly CRPC, severely impairs quality of life of affected patients, who experience marked pain, decreased sexual functioning, urinary incontinence and changes in bowel function (4). The poor quality of life and the short-term prognosis of these patients have motivated researchers to investigate new treatment strategies for CRCP. Noteworthy, although the castration levels of testosterone reach <50 ng/dl

in CRPC patients, the European Association of Urology (EAU) and the American Urological Association (AUA) guidelines clearly state that ADT should be continued indefinitely both in metastatic and non-metastatic disease (5, 6).

The last years have witnessed major advances in the treatment of metastatic disease (7). According to current EAU/ESTRO/SIOG guidelines, level 1 evidence for the treatment of metastatic CRPC (mCRPC) supports the use of abiraterone acetate plus prednisone, enzalutamide, radium 223 (Ra 223), docetaxel at 75 mg/m^2 every 3 weeks and sipuleucel-T. Therefore, the treatment scenario is now highly complex and clinicians need to have a clear understanding on how to interrupt ongoing treatment.

To this end, recommendations from the Prostate Cancer Working Group 3 (PCWG3) have stated that the first evidence of progression (oligoprogression; one new lesion or increased volume of one single existing lesion) does not imply that treatment should be interrupted (8). In particular, the addition of radiotherapy (RT) to medical treatment has been suggested to treat oligometastases or in case of symptoms worsening (9-11). This approach may also allow to avoid treatment interruption when therapy still retains efficacy, and therefore maximize clinical outcomes (12). However, this suggestion is often not applied in clinical practice, and clinicians tend to interrupt medical treatment at the first signs of progression.

Among different therapeutic options, abiraterone acetate, is a selective inhibitor of cytochrome P450 17alpha-hydroxylase/17,20 lyase (CYP17), a rate-limiting enzyme of steroidogenesis; it was approved in the European Union and the US, in combination with prednisone, for the treatment of men with mCRPC. The approval was based on results shown in the pivotal placebo-controlled, multinational phase III301 and 302 trials, conducted in chemo-pretreated and chemo-naive patients, respectively, that randomly assigned patients with mCRPC to either abiraterone acetate plus prednisone or placebo plus prednisone (13, 14). In the 301 trial, overall survival (OS) was higher in the abiraterone acetate-prednisone group than in the placebo-prednisone group (14.8 months *vs*. 10.9 months); also the median progression-free survival (PFS) supports for the superiority of abiraterone acetate over placebo (5.6 *vs*. 3.6 months) (13). In the 301 study, the use of palliative radiotherapy was permitted in 11.1% of patients in the abiraterone arm and 12.2% of patients in the placebo arm who had localized progression at a single site. The median time to radiation therapy was 15.1 weeks and 8.7 weeks in the abiraterone and placebo groups, respectively (15).

The effectiveness of abiraterone has also been shown in several 'field-practice' studies (16, 17). In detail, Poon *et al*. analyzed a population of 110 mCRPC patients treated with abiraterone, and showed a marked effectiveness of this treatment in patients who have had chemotherapy (16). In another study on 306 patients, the administration of abiraterone acetate was associated with a median OS of 37.1 months (as calculated from the beginning of chemotherapy) (17). However, to our knowledge no 'field-practice' study has specifically investigated whether the addition of RT to abiraterone therapy can influence treatment outcomes in patients with mCRPC.

In line with the PCWG3 recommendations, our therapeutic strategy for patients with radiographic and symptomatic oligoprogression is to continue abiraterone treatment.

This observational, 'field-practice' study aims at investigating treatment outcomes of ongoing abiraterone therapy with the addition of RT – initiated for oligoprogression or with a palliative intent.

Patients and Methods

Setting and design. This was a multicenter, retrospective study conducted at six Italian centers specialized in the treatment of uro-oncological disease. The local Ethical Committees had approved the study design and all patients had signed an informed consent for the use of their data for research purposes.

Patients and treatment. Consecutive patients with histologically or cytogenetically-confirmed diagnosis with mCRPC and had been treated with abiraterone acetate (1 g/day) were considered for analysis if they had received RT after the initiation of abiraterone treatment. All patients were previously treated with chemotherapy or were deemed unfit to chemotherapy because of their clinical conditions, as judged by the treating physician. RT could be either directed on oligometastasis or could have been administered with a palliative intent. The majority of treatments were carried out with a 3D conformational radiotherapy technique with hypofractionated dose. Some treatments were performed with a stereotactic technique by using conventional medical linear accelerator (LINAC) or tomotherapy. All stereotactic treatments were performed by Image guided radiation therapy (IGRT) using a Cone-Beam CT scan to verify patient position before treatment.

Endpoints. The following endpoints were considered: (i) duration of abiraterone treatment (total and before/after RT); (ii) PFS; (iii) OS; (iv)response rate according to the PCWG3 criteria. All data were analyzed in the whole population and then – with an explorative intent - by stratifying patients according to whether they have had previous chemotherapy with docetaxel.

Statistical analysis. Data were analyzed by descriptive statistics. PFS was calculated from both the initiation of abiraterone and from the administration of radiation therapyand was defined as the time from therapy initiation to disease progression or deathby any cause. OS was similarly calculated and defined as the time from therapy initiation to death by any cause. PFS and OS were estimated using the Kaplan-Meier method (Graph Pad Prism 5 software).

Results

Study population. In total, 32 patients were enrolled from April 2014 to October 2015. Table I shows their

Table I. *Details of the study population (n=32).*

Details at diagnosis	n.patients=32
Age	
Median (range), years	71 (55-86)
≤60 years	4 (12.5%)
61-70 years	13 (40.6%)
>70 years	15 (46.9%)
PSA, ng/ml	
Mean±SD	56.4±123.2
<10 ng/ml	11 (34.4%)
10-20 ng/ml	5 (15.6%)
>20 ng/ml	16 (50.0%)
Gleason score	
≤7	16 (50%)
≥8	16 (50%)
Surgery	32/32 (100%)
Hormone treatment	
None	13 (40.6%)
Neo-adjuvant	5 (15.6%)
Adjuvant	17 (53.1%)
Details at the initiation of abiraterone treatment	**n.patients=32**
Age	
Median (range)	77 (59-86)
≤60 years	1 (3.1%)
61-70 years	6 (18.8%)
>70 years	25 (78.1%)
Metastatic sites	
Lymph node	20 (62.5%)
Visceral	2 (6.3%)
Bone	25 (78.1%)
PSA, ng/ml	
Mean±SD	61.0±105.7
ECOG performance status	
0	9 (28.1%)
1	23 (71.9%)
Prior docetaxel treatment	
Yes	10 (31.3%)
No	22 (68.7%)
Concomitant hormone treatment	
LHRH agonist	26 (81.2%)
LHRH antagonist	6 (18.8%)
Concomitant opioids	
Yes	17 (53.1%)

SD: Standard deviation; PSA: prostate-specific antigen; ECOG: Eastern Cooperative Oncology Group; LHRH: luteinizing hormone-releasing hormone.

demographic characteristics and clinical details at diagnosis and at baseline. The median age at initiation of abiraterone treatment was 77 (range=59-86) years and the mean PSA level was 61.0±105.7 ng/ml. At baseline, the most frequent metastatic site was bone (78.1%). The majority of the patients were unfit for chemotherapy (n=22; 68.7%) due to comorbidities, pain or performance status ≥2.

Table II. *Details of CHT-experienced and CHT-unfit patients.*

Details at diagnosis	Prior CHT-treated patients (n=10)	CHT-unfit patients (n=22)
Age		
Median (range), years	68 (55-78)	74 (56-86)
≤60 years	2 (20.0%)	2 (9.1%)
61-70 years	6 (40.0%)	7 (31.8%)
>70 years	2 (20.0%)	13 (59.1%)
PSA, ng/ml		
Mean±SD	24.2±28.0	71.1±146.1
Gleason score		
≤7	6 (60.0%)	10 (45.5%)
≥8	4 (40.0%)	12 (54.5%)
Surgery	10/10 (100%)	22/22 (100%)
Hormone treatment		
None	2 (20.0%)	11 (50.0%)
Neo-adjuvant	7 (70.0%)	10 (45.5%)
Adjuvant	3 (30.0%)	2 (9.1%)
Details at the initiation of abiraterone treatment	**n. patients=10**	**n. patients=22**
Age		
Median (range)	73 (64-83)	78 (59-86)
≤60 years	0 (0.0%)	1 (4.5%)
61-70 years	4 (40.0%)	2 (9.1%)
>70 years	6 (60.0%)	19 (86.4%)
Metastatic sites		
Lymph node	7 (70.0%)	13 (59.1%)
Visceral	0 (0.0%)	2 (9.1%)
Bone	5 (50.0%)	20 (91.0%)
PSA, ng/ml		
Mean±SD	93.3±137.0	46.3±87.9
ECOG performance status		
0	2 (20.0%)	7 (31.8%)
1	8 (80.0%)	15 (68.2%)
Concomitant hormone treatment		
LHRH agonist	8 (80.0%)	18 (81.8%)
LHRH antagonist	2 (20.0%)	4 (18.2%)
Concomitant opioids		
Yes	5 (50.0%)	12 (54.5%)

On the other hand, 10 out of 32 (31.3%) patients were previously treated with docetaxel (DCT). The median follow-up from abiraterone initiation was 12.8 months (range=2.9-41.7). Table II presents the clinical characteristics of patients with prior DCT therapy and those who were DCT-unfit.

Radiation therapy. Patients underwent RT at the median radiation dose of 30 Gy (range=6-58.8 Gy). Most patients (26/32; 81.3%) received palliative RT; the most frequent site of RT was bone (81.3%), followed by lymph node (9.4%),

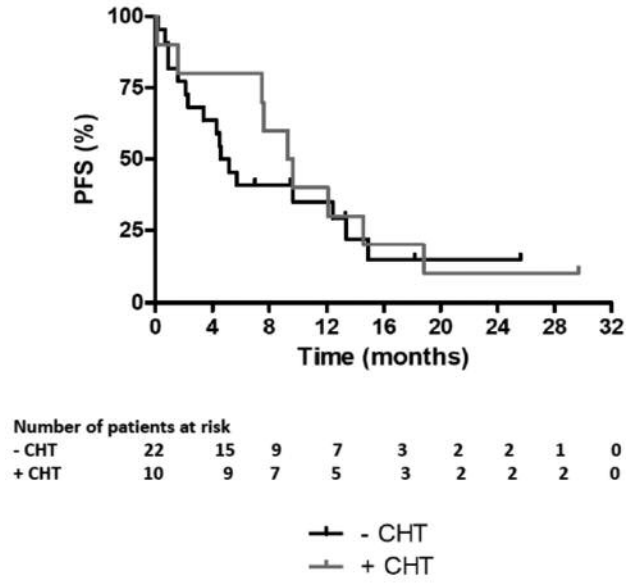

Figure 1. *Progression free survival (PFS) in abiraterone + RT-treated patients, stratified according to prior chemotherapy treatment.*

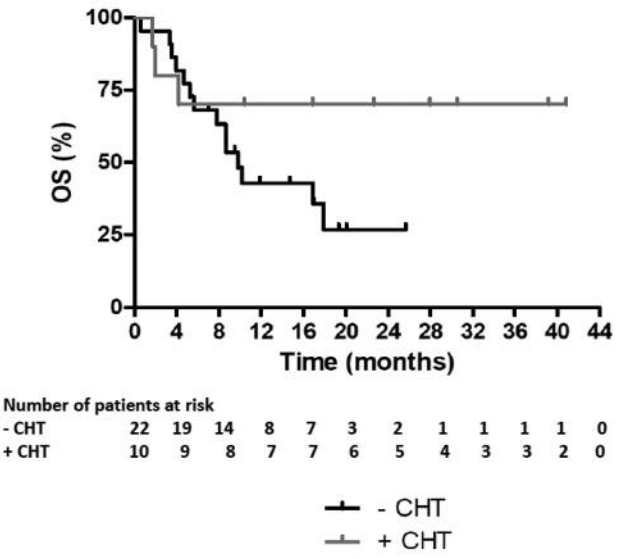

Figure 2. *Overall survival (OS) in abiraterone + RT-treated patients, stratified according to prior chemotherapy treatment.*

prostate (6.2%) and visceral (3.1%). Most patients were treated with 3D conformal radiotherapy: 16 patients (50%) received 30 Gy in 10 fractions; 5 patients (15%) received 8 Gy in single fraction; 3 patients (9%) received 20 Gy in 4 fractions; 2 patients (6%) received 36 Gy in 12 fractions; 1 patient (3%) received 45 Gy in 9 fractions; 1patient received 40 Gy in 20 fractions and 1 patient received 58.8 Gy in 28 fractions. One patient was treated with LINAC for a total dose of 30 Gy in 3 fractions and 1 patient received 6 Gy in single fraction with tomotherapy.

Duration of treatment. Overall, the median duration of abiraterone treatment was 13.0 months (range=3.8-40.9 months). Before RT, median duration of abiraterone treatment was 5.9 months (range=0.4-40 months), and the median duration of abiraterone after RT was 7.2 months (range=0.1-29.7 months).

In DCT-experienced patients, the overall median duration of abiraterone treatment was 13.3 months (range=9.2-30.8 months); before RT the median duration of abiraterone treatment was 5.9 months (range=1.2-15.6 months), and after RT the median duration of abiraterone treatment was 9.5 months (range=0.1-29.7 months).

In DCT-unfit patients, the overall median duration of abiraterone treatment was 11.7 months (range=3.8-40.9 months); before RT the median duration of abiraterone treatment was 5.5 months (range=0.4-40.0 months), and after RT the median duration of abiraterone treatment was 4.9 months (range=0.2-25.6 months).

Survival. In the overall population, median PFS was 12.6 months (95%CI=10.5-14.7 months) from the initiation of abiraterone treatment. From RT administration, PFS was 9.6 months (95%CI6.4-12.9 months). PFS from RT administration was similar in patients with prior treatment with chemotherapy and those unfit to this therapy (9.3 months, 95%CI=6.1-12.5, and 5.2 months, 95%CI=3.7-6.8, respectively; p=0.64) (Figure 1).

In total, 17 patients deceased during the follow-up period. Among them, 14 (82.4%) patients were not previously treated with chemotherapy and 3 (17.6%) received chemotherapy before abiraterone administration.

In the overall population, median OS was 18.9 months (95%CI=4.7-33.0) and 16.9 months (95%CI=5.8-27.9) when calculated as time from abiraterone initiation to death by any cause and time from radiotherapy initiation to death by any cause, respectively. From RT, median OS was not reached for patients who had received prior chemotherapy. On the other hand, the median OS for DCT-unfit patients was 9.8 months (95%CI=7.6-12.0) (Figure 2).

Treatment response. Table III reports the best responses reported. Overall, the disease control rate was 60.0%, with 1 complete response and four partial responses. Among prior DCT-treated patients, only one (11.1%) completely responded to treatment whereas in DCT-unfit patients 4 (19.0%) partial responses were recorded.

Safety. Overall, no adverse events leading to treatment suspension or discontinuation were reported during treatment.

Table III. *Best response to abiraterone plus radiotherapy treatment.*

Overall best response to treatment	n. patients=30
CR	0 (0%)
PR	5 (16.7%)
SD	15 (50.0%)
PD	17 (33.3%)
Disease control rate (CR+PR+SD)	20 (66.7%)
Best response to treatment in prior CHT-treated patients	**n. patients=9**
CR	0 (0%)
PR	1 (11.1%)
SD	5 (55.6%)
PD	3 (33.3%)
Disease control rate (CR+PR+SD)	6 (66.7%)
Best response to treatment in CHT-unfit patients	**n. patients=21**
CR	0 (0%)
PR	4 (19.1%)
SD	10 (47.6%)
PD	7 (33.3%)
Disease control rate (CR+PR+SD)	14 (66.7%)

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; CHT: chemotherapy.

Discussion

Progression is considered an inevitable event in the clinical course of mCRPC. However, in clinical practice physicians often interrupt treatment at the first sign of progression, when treatment still retains efficacy. Of note, this behavior is not in line with current PCWG3 criteria, which recommend continuing therapy in the case of oligoprogression (8).

On the other hand, the effects of ongoing systemic therapies may be enhanced in combination with radiotherapy. Results of 3 randomized studies on locally advanced prostate cancer have suggested that ADT plus RT can substantially extend the survival compared to ADT alone, the combined regimen also strongly favored better outcomes for other end-points, such as PFS, locoregional recurrence and distant metastases (18). In the 301 trial, 1195 men with metastatic mCRPC progressing after docetaxel, received abiraterone/prednisone or placebo/prednisone. The primary endpoint, OS, was 14.8 months in the abiraterone group and 10.9 months in the placebo group; whereas among the secondary end points, median PFS on the basis of radiographic evidence was 5.6 and 3.6 months, respectively (13). These data show the efficacy of abiraterone in the treatment of mCRPC; therefore, treatment with this molecule should be continued as long as the patient experience clinical benefit without relevant toxicity.

In our 'field-practice' study, conducted in an unselected population of mCRPC patients with prior DCT treatment or who were deemed unfit to this therapy because of their clinical conditions, the use of RT allowed continuing therapy with abiraterone for further >7 months, with a total period on abiraterone >1 year. This therapeutic strategy eventually resulted in a PFS of about 13 months and an OS of about 18 months, even if the clinical characteristics of the enrolled population were overall not favorable. Of note, these findings were similar in DCT-pretreated patients and in those who were unfit for this therapy.

These findings are in line with those documented in an interesting case report, published by Hingorani *et al*. in 2015 (12). In this report, RT during abiraterone therapy allowed the continuation of this latter treatment, which eventually led to a marked biochemical response and symptomatic benefit including resolved pain and improved PS.

The addition of RT to ongoing abiraterone therapy has a strong biological rationale. RT induces cell death by disrupting various parameters of cell biology necessary for survival. In addition, radiation stimulates the dying cells to release a range of molecules (often termed "danger signals") that in turn could render cancer cells more susceptible to an immune-mediated cytotoxicity (19). Therefore, RT may exert immunomodulatory effects that lead to an immunogenic tumor cell death by involving dendritic cells, T regulatory cells, and suppressor cells as critical mediators (19). In this light, radiation could affect not only the cells that are directly irradiated but also their non-irradiated neighbors, with initiation of an "abscopal" bystander effect at distant metastatic sites. The possibility of RT to influence distant metastatic disease through activation of an immune-mediated response has been previously reported in hepatocellular carcinoma (20), melanoma (21) and non-small cell lung cancer (22). Noteworthy, these mechanisms may be accentuated in prostate cancer in the presence of an androgen-deprived environment.

This study is not without its limitations, that include the overall limited number of patients, its retrospective nature and the lack of a control group. Despite those limitations our analysis represents, to our knowledge, the first study documenting that RT allows prolonging abiraterone treatment in mCRPC patients – either pretreated with DCT or unfit to this therapy – eventually allowing the achievement of good clinical outcomes with this molecule.

Conflicts of Interest

The Authors declare no conflicts of interest.

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