PSA Flare With Abiraterone in Patients With Metastatic Castration-Resistant Prostate Cancer

Salvatore L. Burgio,1,* Vincenza Conteduca,1,* Britt Rudnas,2 Francesco Carrozza,3 Enrico Campadelli,4 Emanuela Bianchi,1 Paolo Fabbri,5 Marco Montanari,6 Elisa Carretta,7 Cecilia Menna,1 Ugo De Giorgi1

Abstract

In a retrospective study, we analyzed the PSA flare after abiraterone treatment in patients with castration-resistant prostate cancer (CRPC) and correlated it with prostate-specific antigen (PSA) declines and clinical outcome. Early PSA flare occurred in 9 of 103 (8.7%) cases. There were no substantial differences in the clinical outcomes between patients who experienced the PSA flare and those who had an immediate PSA response.

Background: The aim of this study was to assess early serum prostate-specific antigen (PSA) changes in patients treated with abiraterone and to correlate those changes with clinical outcome. Patients and Methods: We retrospectively evaluated 103 patients with castrate-resistant prostate cancer (CRPC) treated with compassionate use of abiraterone in Romagna, Italy. In these patients, serum PSA levels were monitored every 4 weeks, and a time course of serum PSA levels was obtained. The PSA flare phenomenon was evaluated. The log-rank test was applied to compare survival between groups of patients according to early PSA level changes. Results: Of 103 patients, 43 (41.7%) had an immediate PSA response, whereas 9 (8.7%) had an initial PSA flare. Of the 9 patients with PSA flare, 5 attained a subsequent PSA response. The temporary PSA flare exceeded baseline values by a median of 19.7% (range, 5%-62.9%). The median PFS of the 9 patients in the PSA-flare group was higher compared with patients without the PSA flare (10.5 vs. 6.4 months; \( P = .0999 \)) but was similar to the subgroup of patients with immediate PSA response (10.5 vs. 10.7 months; \( P = .7019 \)). In the multivariate analysis, only the PSA response remained as a predictor of progression-free survival (PFS) \( (P < .0001) \) and overall survival (OS) \( (P = .0003) \), respectively. Conclusion: PSA flare occurs not infrequently in patients with CRPC who respond to abiraterone. Patients should be informed of this possible PSA flare phenomenon.

Keywords: Abiraterone, Castration-resistant prostate cancer, Outcome, Progression, PSA flare, Survival

Introduction

Prostate cancer (PC) is the most common noncutaneous cancer in men and the second leading cause of cancer-related deaths for men.1 Castration-resistant prostate cancer (CRPC) is the lethal evolution of the disease that, once it is metastatic, is associated with a median overall survival (OS) of 2 to 3 years despite hormonal manipulations and chemotherapy with docetaxel.2-4 In recent years, abiraterone has emerged as a standard therapy for patients with metastatic CRPC after docetaxel and, most recently, even before chemotherapy in the predocetaxel space.5-7

A prostate-specific antigen (PSA) level decline of at least 50%, confirmed 4 weeks after beginning, was consensually regarded as a criterion of response to treatment.8 However, in the phase trial with abiraterone in patients previously treated with docetaxel, the PSA level was monitored every months.5 In the phase randomized trial with abiraterone in patients without previous

1Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy
2Oncology Unit, Infermi Hospital, Rimini, Italy
3Oncology Unit, City Hospital, Faenza, Italy
4Oncology Unit, Umberto I Hospital, Lugo di Romagna, Italy
5Oncology Unit, Cervesi Hospital, Carollica, Italy
6Oncology Unit, Santa Maria delle Croci Hospital, Ravenna, Italy
7Biostatistic and Clinical Trials Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

Submitted: Feb 28, 2014; Revised: May 10, 2014; Accepted: Jun 3, 2014

Address for correspondence: Ugo De Giorgi, MD, Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Via Maronnelli 40, 47014 Meldola (FC), Italy
Fax: +39-0543-739221; e-mail contact: ugo.degiori@irst.emr.it
chemotherapy, the PSA level was monitored every two 28-day cycles in the first months and then every month. As a consequence, to date no data have been reported in the literature on early PSA changes in the initial few months of abiraterone treatment. In clinical practice, most oncologists currently monitor PSA levels more frequently before each cycle and then almost every month to assess the efficacy of abiraterone and other new high-cost therapeutic options in individual patients with CRPC. However, no information is available about the kinetics of serum PSA during the first few months after the initiation of abiraterone. This prompted us to study retrospectively the time course of serum PSA in a database of patients with metastatic CRPC receiving abiraterone. We observed an important phenomenon: a small proportion of responders to abiraterone initially experienced a rise in serum PSA (PSA flare). In this retrospective study, we analyzed the PSA flare after abiraterone treatment in patients with CRPC and correlated this phenomenon with PSA declines and clinical outcomes.

**Patients and Methods**

**Data Collection**

From March 2011 to August 2012, 103 consecutive patients with CRPC were included in the abiraterone compassionate use program at Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; at the time of their inclusion, these patients showed disease progression after having received at least a chemotherapeutic regimen including docetaxel. The compassionate use program was approved by the Romagna Ethics Committee; all patients gave their written informed consent before receiving abiraterone treatment.

Patients deemed eligible for this program had histologically confirmed adenocarcinoma of the prostate, evidence of metastases, progressive disease while receiving castration treatment using a gonadotropin-releasing hormone agonist with serum testosterone levels < 50 ng/dL, and had previously received at least 1 chemotherapeutic regimen including docetaxel. Abiraterone, 1000 mg daily in association with prednisone 5 mg twice daily, was administered continuously until evidence was noted of disease progression or unacceptable toxicity. All patients were maintained on a gonadotropin-releasing hormone agonist during abiraterone treatment. Baseline serum PSA levels were typically measured in the week before starting abiraterone treatment. The analysis of serum PSA levels was conducted in the Pieveistina Laboratory for all patients from Romagna included in this compassionate use program. Patients were evaluated every 4 weeks for serologic PSA response and safety. A computed tomographic scan was obtained every 3 months while abiraterone treatment continued. The Prostate Cancer Working Group 2 (PCWG-2) criteria were used to define response and progression.<sup>8</sup> PCWG-2 criteria require a minimum baseline threshold of PSA levels of 2.0. In patients with baseline PSA levels < 2.0, we considered radiologic progression alone as a criterion for disease progression and consequent discontinuation of abiraterone therapy.<sup>7</sup> Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.

**Statistical Analysis**

PSA response was defined as a decline in PSA level of at least 50%, confirmed 4 weeks after beginning abiraterone treatment.<sup>9</sup> Progression-free survival (PFS) was calculated from the start of abiraterone treatment until the first date of progression, death, or last follow-up. OS was calculated from the start of abiraterone treatment until death or last follow-up. Survival curves were estimated by the Kaplan-Meier method. The log-rank test was applied to compare survival between groups of patients according to early PSA changes. Cox regression analysis was used to determine univariate and multivariate hazard ratios (HRs) for selected potential predictors of PFS and OS. A P value of < .05 was considered statistically significant. Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC).

**Results**

From March 2011 to August 2012, a total of 103 patients with CRPC, median age 74 years (range, 48-87 years), received abiraterone after docetaxel alone (n = 61) or after docetaxel and at least 1 more line of therapy (n = 42). The characteristics of all patients are summarized in Table 1. The median follow-up was 16.8 months, with an estimated median PFS of 6.6 months (95% confidence interval [CI], 5.4-8.2 months) and an estimated median OS of 18.6 months (95% CI, 14.4-22.0 months).

**PSA Response and PSA Flare**

Of 103 patients, 43 (41.7%) had an immediate PSA response (without initial flare-up of PSA levels), whereas 9 (8.7%) patients had an initial PSA flare, and 1 case was not evaluable. A PSA level

| Table 1 | Patient Characteristics (N = 103) |
|-----------------|-----------------|-----------------|
| Characteristic | N (%) | N (%) |
| **Median age (range), years** | | 74 (48-87) |
| **ECOG performance status** | | |
| 0-1 | 94 (91.3) |
| 2 | 9 (8.7) |
| **Gleason score** | | |
| 6-7 | 37 (35.9) |
| 8-10 | 55 (53.4) |
| Unknown | 11 (10.7) |
| **Bone metastases** | | |
| Present | 88 (85.4) |
| Absent | 15 (14.6) |
| **Visceral metastases** | | |
| Present | 17 (16.5) |
| Absent | 86 (83.5) |
| **No. of previous chemotherapeutic regimens** | | |
| 1 | 61 (59.2) |
| 2 or more | 42 (40.8) |
| **Baseline PSA level** | | |
| Median (range), ng/mL | 32.5 (1-1834) |

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PSA = prostate-specific antigen.
decline ≥ 50% from baseline (PSA response) was obtained in 5 of 9 (55.6%) patients in the PSA flare group, whereas the remaining 4 patients achieved a transient reduction in PSA levels. The median age of the PSA flare group was 78 years (range, 63-82 years). Three patients (33.3%) had a Gleason score of 8 to 10, 8 patients (88.9%) had osseous disease, 3 (33.3%) patients had visceral metastases, and 3 (33.3%) patients had previously received docetaxel with at least 1 more line of therapy. The last therapy completed within 2 months before starting abiraterone was docetaxel/prednisone in 5 patients, oral cyclophosphamide in 1 patient, and estramustine phosphate in 1 patient. In the remaining 2 patients, abiraterone was started after late progression of disease while receiving docetaxel for 7 and 24 months, respectively. In 5 patients, the PSA peak of the flare phenomenon occurred after the first cycle, in 3 patients it occurred after 2 cycles, and in 1 patient the flare occurred after 3 cycles. The PSA flare lasted a median of 28 days (range, 28-112 days). The temporary PSA flare exceeded baseline values by a median of 19.7% (range, 5%-62.9%).

Survival

The median PFS of the 9 patients in the PSA flare group was 10.5 months (95% CI, 2.4-not reached). When compared with the 93 remaining evaluable patients treated with abiraterone without PSA flare, there was a trend toward a significant difference: 6.4 months (95% CI, 4.9-7.5) for the group with no PSA flares; P = .0999 (Figure 1). When compared with the 43 patients with an immediate PSA response, the median PFS was similar: 10.7 months (95% CI, 7.5-12.4) for the immediate PSA response group; P = .7019 (Figure 2). No difference in the median OS was recorded between patients with PSA flare and those without PSA flare (P = .7681) or those with an immediate PSA response (P = .2314).

We then compared the 5 patients in the PSA flare group who achieved a PSA response with those who achieved an immediate response; no difference was seen in the median PFS (P = .2529) and in the median OS (P = .3122).

A multivariate analysis was performed including the following variables: Gleason score (8-10 vs. < 7), Eastern Cooperative Oncology Group performance status (≥ 2 vs. 0-1), sites of metastases (visceral vs. not visceral), lines of previous therapies for CRPC including docetaxel (≥ 2 vs. 1), PSA response rate (< 50% vs. ≥ 50%), and PSA flare (no vs. yes). PSA response rate was the only predictor of PFS (HR, 4.4; 95% CI, 2.6-7.3; P < .0001) and OS (HR, 3.5; 95% CI, 1.7-7.1; P = .0004).

Discussion

Serum PSA levels are used in the management of patients with PC to monitor tumor response during hormonal therapy or chemotherapy, or both, in advanced disease. For some time, one of the obstacles to developing new therapies in PC was the absence of criteria to assess tumor response, with most patients exhibiting nonmeasurable bone-only disease. Although the debate continues as to whether a decline in the serum PSA level is a surrogate for OS in metastatic PC, a PSA level decline of at least 50%, confirmed at least 4 weeks after the start of treatment, has consensually been regarded as a criterion of response to treatment. The PSA flare is a well-known phenomenon consisting of an early and transient rise in serum PSA levels followed by a drop occurring in nearly 5% to 30% of patients receiving hormonal therapies with luteinizing hormone—releasing hormone analogues and in nearly 8% to 20% of patients treated with chemotherapy for CRPC. Abiraterone is a new hormonal therapy that has shown some benefit in the survival of patients with CRPC; PFS has been positively associated with the magnitude of PSA level decline. However, in those studies, serum PSA levels were monitored every 2 to 3 months, so the PSA flare phenomenon has not been investigated to date. In this report, we note for the first time that a proportion of 8.7% (9 of 103) patients with CRPC treated with abiraterone underwent an initial rise in serum PSA levels during the first 12 weeks of treatment, followed by a later drop in these levels. Five of these 9 (55.6%) patients ultimately reached the criterion of response, according to the consensus guidelines, whereas the remaining 4 (44.4%) patients had a transient stabilization. The clinical and disease characteristics of patients in the PSA flare group were not different from
PSA Flare on Abiraterone

the those in the other patients. Moreover, there was no suggestion that these patients with a postchemotherapy PSA flare syndrome with later response or stabilization were at higher risk of early progression with reduction of median PFS when compared with those who immediately achieved a response or stabilization. The median PFS duration after starting abiraterone therapy was 10.5, 10.7, and 6.5 months, respectively, in patients with an initial PSA flare followed by a PSA response or stabilization, in those with an immediate PSA response, and in those with no PSA flare including a PSA response or not. Thus, a PSA flare was associated with a survival close to that of patients with a PSA response. These data support the notion that PSA flare is a phenomenon related to tumor response. In clinical practice, it is important to recognize this phenomenon to avoid early discontinuation of abiraterone treatment because of PSA flare. Moreover, a consensus definition for PSA flare from the PCWG-2 would be recommended. Despite the limitations resulting from the retrospective nature of the analysis and the small number of patients, univariate/multivariate analyses were performed to evaluate potential predictors of PFS and OS: PSA response alone was able to predict either PFS or OS.

It is difficult to provide a biological interpretation of the early PSA flare after abiraterone treatment described in this report. A rapid PC cell destruction, an increased differentiation of PC precursors, or an enhanced PSA transcriptional efficiency induced by abiraterone might be assumed. In a recent work, no correlation was found between PSA flare after abiraterone treatment and baseline chromogranin A levels. In another recent work, no correlation was found between PSA flare after abiraterone treatment and bone flare as detected by 18F-fluorocholine positron emission tomography/computed tomography (unpublished personal data). It remains unclear why only a small proportion of these patients experience the PSA flare phenomenon and what the biological role in overall tumor control might be. Moreover, abiraterone is largely investigated in combination with other new biological agents: the PSA flare phenomenon should be considered and described to gain a better understanding of the biological interaction between these drugs. Translational prospective studies are required to understand in more depth the PSA flare phenomenon.

Conclusion

In this retrospective study, we reported the PSA flare in patients with CRPC treated with abiraterone. The PSA flare after abiraterone occurred in a number of patients (8.7%) treated with abiraterone. The clinical outcome of patients experiencing the PSA flare phenomenon correlated with that of those achieving an immediate PSA response. We believe that physicians should be aware of this PSA flare phenomenon during the first few months after the initiation of abiraterone treatment for CRPC. Because patients are commonly aware of their PSA results and their prognostic/predictive value, they should be informed of this possible PSA flare phenomenon.

Clinical Practice Points

- The PSA flare consists of an early and transient rise in serum PSA levels. Abiraterone has shown some benefit in the survival of patients with CRPC after docetaxel treatment, but in the pivotal trials the serum PSA levels were monitored every 2 to 3 months, so the PSA flare phenomenon has not been studied to date.
- We assessed the PSA flare phenomenon after abiraterone treatment in patients with CRPC and correlated this phenomenon with PSA declines and clinical outcomes.
- The PSA flare after abiraterone treatment occurred in 9 of 103 (8.7%) patients who received abiraterone after docetaxel.
- The median PFS of the patients who experienced the PSA flare was similar to that of patients achieving an immediate PSA response but was higher than that in those who did not have a PSA surge.
- Physicians should be aware of this effect to avoid early, and thereby inadequate, discontinuation of treatment.

Disclosure

UDG has received consultant fees and had an advisory role with Pfizer, GSK, Bayer, and Novartis.

References


