

Chromogranin A predicts outcome in prostate cancer patients treated with abiraterone

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Abstract

In this retrospective study, we evaluated the chromogranin A (CgA) baseline value as a predictor of clinical outcome in patients with metastatic castration-resistant prostate cancer (CRPC) treated with abiraterone 1000 mg per day, whose disease progressed after docetaxel chemotherapy. In the 48 evaluable patients, serum CgA level was normal when < 120 ng/ml (group A, $n = 16$), within three times the upper normal value (UNV) when between 120 and 360 (group B, $n = 16$), more than three times the UNV when ≥ 360 ng/ml (group C, $n = 16$). Decline in PSA level $\geq 50\%$ or more (PSA RR) was observed in 26 of 48 (54%) patients. PSA response rate did not correlate with the CgA groups. CgA levels more than three times the UNV predicted an early radiological progressive disease in eight of 11 cases (73%). The median progression-free survival (PFS) among the CgA groups A, B, and C was 9.2, 9.2, and 4.8 months respectively, $P = 0.0459$. The median overall survival (OS) among the CgA groups was 19.0, 18.8, and 10.8 months respectively, $P = 0.2092$. In the multivariate analysis, PSA RR (nonresponsive vs responsive) and CgA levels (group 3 vs groups 1 + 2) were predictors of PFS ($P = 0.0002$ and $P = 0.0047$ respectively), whereas PSA RR only was significantly associated with OS ($P = 0.0024$), while CgA levels remained of borderline significance ($P = 0.0919$). A serum CgA level more than three times the UNV predicted PFS and showed a trend vs OS prediction, independently from PSA response, in CRPC patients treated with abiraterone.

Key Words

- ▶ chromogranin A
- ▶ CgA
- ▶ castration-resistant prostate cancer
- ▶ CRPC
- ▶ abiraterone
- ▶ PSA
- ▶ bone flare

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Introduction

Metastatic castration-resistant prostate cancer (CRPC) is a leading cause of cancer-related mortality worldwide (Siegel *et al.* 2013). Unfortunately, despite advances in treatment, the prognosis remains poor (Petrylak *et al.* 2004, Tannock *et al.* 2004, de Bono *et al.* 2010). Abiraterone acetate is a selective inhibitor of androgen biosynthesis that potently and irreversibly blocks cytochrome P-450c17 (CYP17), resulting in virtually

undetectable serum and intratumoral androgens (Attard *et al.* 2009). Treatment with abiraterone improved survival of patients with metastatic CRPC who had already received docetaxel therapy and showed a trend toward improved overall survival (OS) of those who had not received previous chemotherapy (Fizazi *et al.* 2012, Ryan *et al.* 2013). A major limitation on abiraterone management is the lack of validated biomarkers of response to

therapy and the potential effect of PSA modulation that could impair its role as an indicator of response to therapy (de Bono *et al.* 2011, Burgio *et al.* 2014).

Chromogranin A (CgA) is an acidic glycoprotein that is commonly expressed by neuroendocrine cells and constitutes one of the most profuse components of secretory granules. CgA appears to be the most sensitive marker and is most frequently used for detecting neuroendocrine differentiation either at the tissue level or in the general circulation. The availability of such a specific circulating marker for the neuroendocrine component could allow us to easily detect and monitor neuroendocrine differentiation in prostate cancer patients (Berruti *et al.* 2005, Sciarra *et al.* 2009, Matei *et al.* 2012).

In this retrospective study, we evaluated baseline serum CgA levels as a predictor of clinical outcome in patients with metastatic CRPC treated with abiraterone.

Subjects and methods

Patients

This retrospective study included 55 consecutive metastatic CRPC patients progressing after docetaxel chemotherapy treated abiraterone and who had serum PSA and CgA levels performed at baseline. Seven patients were excluded from the analysis due to renal insufficiency and/or concomitant treatment with proton pump inhibitors that could influence serum CgA levels (Taplin *et al.* 2005). In the 48 evaluable patients, serum CgA level was considered normal, as reported by the kit for CgA, when <120 ng/ml (group A, $n=16$), within three times the upper normal value (UNV) when between 120 and 360 (group B, $n=16$), more than three times the UNV when ≥ 360 ng/ml (group C, $n=16$). Eligibility criteria for the use of abiraterone in CRPC required histological confirmation of adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology progressing on androgen deprivation. Patients received at least one chemotherapeutic regimen with docetaxel, but not more than two cytotoxic chemotherapy regimens for metastatic CRPC. Prior ketoconazole therapy was not permitted. Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status 0–2; adequate cardiac, renal, hepatic, and bone marrow function; normal serum potassium level; and ongoing androgen deprivation therapy with serum testosterone <50 ng/dl. The retrospective study was approved by the Institutional Review Board.

Treatment and evaluation

Therapy consisted of abiraterone acetate 1000 mg daily associated with prednisone 5 mg twice daily in a 28-day cycle. Treatment was given continuously until there was an evidence of either progressive disease (PD) or unacceptable toxicity. Before starting abiraterone treatment, patients underwent baseline blood sampling for PSA and CgA. Plasma CgA levels (in μg per liter) were measured in duplicate using a two-side 'sandwich' technique with two selected antibodies that bind to different epitopes of human chromogranin A (Epitope Diagnostics, Inc. – EDI Human Chromogranin A ELISA Kit, San Diego, CA, USA), following the manufacturer's instructions. The sensitivity is 2 $\mu\text{g}/\text{l}$. The inter-assay coefficients of variation of CgA assay were 7.3 and 3.1% respectively. The normal range reported by the kit for CgA was 0–120 ng/ml. Patients were evaluated monthly for serological PSA response and safety. A CT scan was performed every 3 months of abiraterone. Disease progression was defined according to PCWG2 criteria (Scher *et al.* 2008). Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.

Statistical analysis

A receiver-operating characteristic (ROC) curves were used to evaluate the diagnostic role of baseline serum CgA for determining the response to no response to treatment with abiraterone. The area under the ROC curve (AUC) was calculated.

Data were summarized by frequency for categorical variables and by median and range for continuous variables. Continuous variables were compared using the Wilcoxon test. Association between categorical variables was assessed using the Fisher's exact test, when appropriate. Differences were considered statistically significant when $P < 0.05$. The cutoffs for CgA in response to abiraterone were calculated through the AUC. Progression-free survival (PFS) was defined as the time elapsed between the date of the start of abiraterone and the date of PD or death or, if neither PD nor death occurred, the date of the last follow-up visit. OS was defined as the elapsed time between the start of abiraterone and the date of either death or the last follow-up in living patients at the time of analysis. Kaplan–Meier survival plots were generated on the basis of CgA groups and the curves were compared using log-rank test. A Cox-regression model was carried out with a univariable and multivariate approach. The following variables were included in the univariate

analysis: Gleason score (8–10 vs ≤ 7), Eastern Cooperative Oncology Group (ECOG) performance status (PS; ≥ 2 vs 0–1), line of therapy (≥ 3 vs 2), PSA response rate (PSA RR; < 50 vs $> 50\%$), and serum CgA level (group C vs groups A+B). Variables not fitting at univariate analysis were excluded for the multivariate model. Significance level from the univariate analysis for inclusion in the multivariate final model was more liberally set at a 0.1 level, according to Fagerland *et al.* (2008) and Fagerland & Hosmer (2013). All other significance levels were set at a *P* value of < 0.05 .

Results

Patients' characteristics

Between March 2011 and August 2012, 48 CRPC patients were considered evaluable for this study, with serum PSA and CgA levels measurement at baseline before starting abiraterone. The median serum CgA level was 235.5 ng/ml. Of the 48 evaluable patients, serum CgA level was considered normal in 16, 33% (CgA group A), elevated but within three times the UNV in 16, 33% (CgA group B), and elevated more than three times the UNV in 16, 33% (CgA group C). Characteristics of the 48 evaluable patients included in the study are summarized in Table 1.

Relationship between baseline CgA levels and response

The three patients with baseline liver metastases had increased levels of CgA (one case in CgA group B and two in CgA group C), while the six cases with lung metastases were distributed across the three CgA groups (two in CgA group A, three in CgA group B, and one in CgA group C). The CT response was assessed every 3 months of follow-up in 45 of 48 patients, while three cases experienced early clinical deterioration and did not perform the follow-up CT scan. Three month CT results were as follows: complete response ($n = 1$, 2%), partial response ($n = 7$, 15.5%), stable disease ($n = 25$, 55.5%), PD ($n = 11$, 25%), and not evaluable ($n = 1$, 2%). Therapy was interrupted in one case due to pulmonary thromboembolism and one due to not abiraterone-related infective diarrhea. The early PD at 3-month CT-scan occurred in one of 16 patients (7%) in CgA group A, two of 16 (13%) in CgA group B, and eight of 16 (50%) in CgA group C. Within the CgA group C, five of seven (71%) patients with CgA levels more than five times the UNV had early PD.

The three cases with early PD in CgA groups A and B had baseline bone lesions and experienced bone progression only, whereas of eight cases with early PD in the CgA group C, six had bone progression (five with baseline bone lesions), four liver progression (only one with baseline

Table 1 Clinical characteristics of patients at baseline

Characteristic	Overall <i>n</i> (%)	CgA < 120 group A <i>n</i> (%)	CgA ≥ 120 < 360 group B <i>n</i> (%)	CgA ≥ 360 group C <i>n</i> (%)	<i>P</i>
All patients	48	16 (33%)	16 (33%)	16 (33%)	
Median age (range) (years)	73 (57–90)	72 (57–86)	75 (63–87)	73 (61–90)	0.5609
ECOG performance status					
0–1	45 (94%)	16 (100%)	14 (87.5%)	15 (94%)	0.4076
2	3 (6%)	0	2 (12.5%)	1 (6%)	
Gleason score					
6–7	20 (42%)	7 (44%)	7 (44%)	6 (38%)	0.9711
8–9	27 (56%)	9 (56%)	9 (56%)	9 (56%)	
Unknown	1 (2%)	0	0	1 (6%)	
Bone metastasis					
Absent	10 (21%)	4 (25%)	3 (19%)	3 (19%)	1.0000
Present	38 (79%)	12 (75%)	13 (81%)	13 (81%)	
Visceral metastasis					
Absent	39 (81%)	14 (87.5%)	12 (75%)	13 (81%)	0.8953
Present	9 (19%)	2 (12.5%)	4 (25%)	3 (19%)	
No. of previous chemotherapeutic regimens					
One	21 (44%)	8 (50%)	9 (56%)	4 (25%)	0.1690
Two or more	27 (56%)	8 (50%)	7 (44%)	12 (75%)	
Baseline PSA					
Median (range) (ng/ml)	32.5 (1–1501)	17.3 (1.5–1501)	35.0 (1–1435)	35.4 (5–1083)	0.9172
Baseline CgA					
Median (range) (ng/ml)	235.5 (22–1000)	83 (22–118)	235.5 (125–344)	579 (382–1000)	< 0.0001

CgA, chromogranin A; ECOG, Eastern Cooperative Oncology Group.

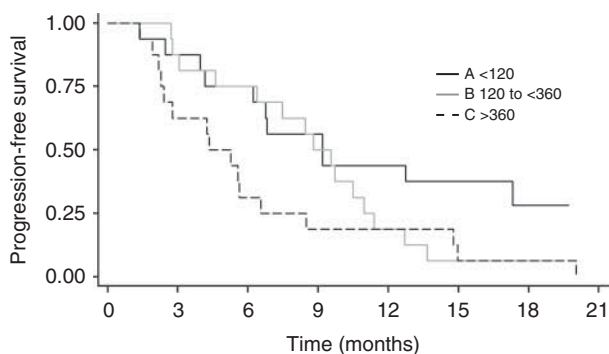


Figure 1
Kaplan–Meier plots illustrating progression-free survival (PFS) according to CgA groups.

liver lesions), two lung progression (one with baseline lung lesions), and one with nodal progression (baseline nodal disease only). The ROC curves of CT response (CR, PR, SD vs PD) registered an area (AUC) of 0.81 ± 0.07 .

All 48 patients were evaluable for PSA response. Decline in PSA level of 50% or more was observed in 26 of 48 (54%) patients. PSA decline $\geq 50\%$ did not correlate with the CgA groups: ten PSA response occurred in CgA group A, eight in CgA group B, and eight cases in CgA group C. The AUC for the PSA response was 0.57 ± 0.08 , suggesting that baseline serum CgA is a poor marker of the decline in PSA.

Outcome prediction

The median follow-up was 21.7 months (range, 1–28.5). In all 48 patients, the median PFS time from baseline was 7.1 months (95% CI 5.3–9.5), while the median OS time from baseline was 17.6 months (95% CI 11.8–21.9). At the time of analysis, six patients (12.5%) were considered free of progression, whereas 30 (62.5%) patients had died.

A statistical significant difference was reported in the median PFS among the CgA groups A, B, and C: 9.2 months (95% CI 4.1–...) vs 9.2 months (95% CI 4.6–10.9) vs 4.8 months (95% CI 2.3–6.5) respectively, $P=0.0459$ (Fig. 1). A trend toward a decreased in the median OS was observed among the CgA groups: 19.0 months (95% CI 9.6–...) vs 18.8 months (95% CI 11.8–...) vs 10.8 months (95% CI 3.4–17.7), respectively, $P=0.2092$ (Fig. 2). In the multivariate analysis, PSA RR and CgA levels were predictors of PFS (HR=3.8, 95% CI 1.9–7.6, $P=0.0002$ and HR =2.7, 95% CI 1.3–5.2, $P=0.0047$ respectively) (Table 2), while PSA RR only was significantly associated with OS (HR=3.2, 95% CI 1.5–6.9, $P=0.0024$), whereas CgA levels remained of borderline significance (HR=1.9, 95% CI 0.9–4.1, $P=0.0919$) (Table 3).

Discussion

Serum CgA levels are elevated in 15–48% of patients with prostate cancer, depending on the clinical stage and grading (Deftos *et al.* 1996, Kimura *et al.* 1997, Berruti *et al.* 2000). Elevated serum CgA levels have correlated with the amount of CgA-positive prostate tumor cells and may reflect neuroendocrine differentiation of prostate cancer (Angelsen *et al.* 1997). Neuroendocrine cells in the prostate are not regulated by androgens and are resistant to hormonal therapies. In the high serum CgA, which would have more neuroendocrine cells with less androgen receptors, so we postulated that patients with CRPC associated with high serum CgA levels may show resistance to treatment with abiraterone and a poor prognosis.

In the present study, we analyzed retrospectively 48 consecutive evaluable metastatic CRPC patients progressing after docetaxel chemotherapy treated abiraterone and who had both serum PSA and CgA levels performed at baseline. Our results showed that serum CgA levels elevated more than three times the UNV are able to predict PFS of CRPC patients treated with abiraterone and can contribute to predict early PD within 3 months in 50% of cases. To our knowledge, this is the first study that evaluated the role of CgA for outcome prediction in patients with CRPC treated with abiraterone.

CgA is recognized as a useful predictive marker in patients with prostatic cancer with lower PSA levels (Isshiki *et al.* 2002, Conteduca *et al.* 2014). However, in our experience, the lack of correlation between low PSA levels and high CgA values may be expression of a selection of patients with far advanced CRPC with a neuroendocrine differentiation in a context of a

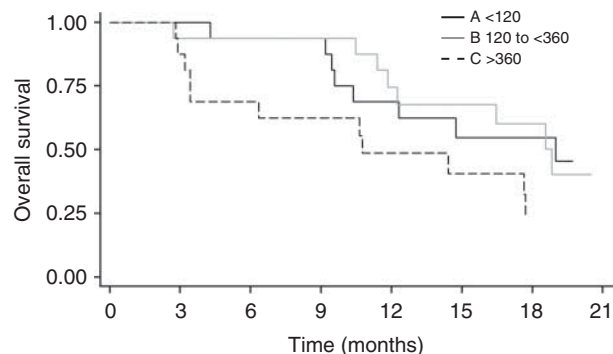


Figure 2
Kaplan–Meier plots illustrating overall survival (OS) according to CgA groups.

Table 2 Univariate and multivariate Cox regression analyses for PFS in patients with castration-resistant prostate cancer treated with abiraterone

Parameters	No. of patients	Univariate analysis PFS risk from baseline			Multivariate analysis PFS risk from baseline		
		HR	95% CI	P	HR	95% CI	P
Gleason score (8–9 vs 6–7)	48	0.8	0.4–1.5	0.4691			
No. of previous chemotherapeutic regimens (≥ 2 vs 1)	48	1.5	0.8–2.8	0.2104			
ECOG performance status (2 vs 0–1)	48	0.8	0.2–2.5	0.6743			
PSA decline (<50 vs $\geq 50\%$)	48	3.1	1.6–5.9	0.0007	3.8	1.9–7.6	0.0002
Baseline CgA levels (group 3 vs groups 1–2)	48	2.0	1.1–3.8	0.0304	2.7	1.3–5.2	0.0047

PFS, progression-free survival; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group.

heterogeneous tumor volume including a rich component with PSA expression. In the multivariate analysis, PSA RR and CgA levels were able to predict PFS ($P=0.0002$ and $P=0.0047$ respectively), while PSA RR only was significantly associated with OS ($P=0.0024$), whereas CgA levels remained of borderline significance ($P=0.0919$). Instead, PSA decline $\geq 50\%$ did not correlate with the CgA groups. The AUC for the PSA response was 0.57, suggesting that baseline serum CgA level is a poor marker of the declines in PSA level of 50% or more. While the ROC curves of CT response registered an area of 0.81 that is in line with the capacity of high CgA levels to predict early PD within 3 months in 50% of cases. Thus high CgA levels appeared to be the expression of tumor resistance to abiraterone. Elevated serum CgA levels usually correlate with the amount of neuroendocrine differentiation in prostate tumor (Angelsen *et al.* 1997). Emerging evidence suggests that the acquisition of epithelial–mesenchymal transition and cancer stem cell phenotype are associated with the development of neuroendocrine differentiation in CRPC, further contributing to resistance to hormonal therapies (Conteduca *et al.* 2014).

Despite a lack of correlation between baseline serum CgA levels with PSA response, the prediction of PFS could be related to the fact that serum CgA levels are an expression of a subclone of prostate cancer cells with neuroendocrine differentiation that could represent a minority of the tumor volume; this has an impact on overall clinical progression without affecting PSA response, which is related to the activity of abiraterone on the non-neuroendocrine component.

The small sample size and the retrospective nature of the analysis were the major limitations of our study. The interpretation of PFS is difficult in a retrospective study, even if there was a high compliance with the PSA and CT assessments. Moreover, we excluded cases with known factors that could influence serum CgA levels (renal insufficiency and/or concomitant proton pump inhibitors), but we cannot exclude that other concomitant medications, frequently used in an elderly patient population like that with CRPC, could have a smaller but significant impact on the CgA values (Taplin *et al.* 2005). The CgA group classification used in the present study was based on fairly arbitrary thresholds; nevertheless

Table 3 Univariate and multivariate Cox regression analyses for OS in patients with castration-resistant prostate cancer treated with abiraterone

Parameters	No. of patients	Univariate analysis OS risk from baseline			Multivariate analysis OS risk from baseline		
		HR	95% CI	P	HR	95% CI	P
Gleason score (8–9 vs 6–7)	48	0.8	0.4–1.6	0.4969			
No. of previous chemotherapeutic regimens (≥ 2 vs 1)	48	1.8	0.8–3.9	0.1597			
ECOG performance status (2 vs 0–1)	48	1.2	0.3–5.1	0.8066			
PSA decline (<50 vs $\geq 50\%$)	48	3.3	1.5–7.0	0.0023	3.2	1.5–6.9	0.0024
Baseline CgA levels (group 3 vs groups 1–2)	48	1.9	0.9–4.1	0.0853	1.9	0.9–4.1	0.0919

OS, overall survival; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group.

more optimized thresholds might lead to a better performance by serum CgA levels as biomarker. Despite these limitations, our results suggest a potential role of serum CgA in the management of CRPC patients treated with abiraterone. Serum CgA is a simple, reproducible, and low-cost biomarker, which may be a useful outcome predictor and could offer complementary information with respect to PSA. Moreover, abiraterone is administered until progression, so it appears fundamental to predict early progression rather than the tumor response to therapy. In our experience, CgA levels more than three times the UNV predicted an early radiological PD in eight of 11 cases (73%).

In previous studies, CgA values were not substantially affected by either endocrine therapy or chemotherapy. The administration of a somatostatin analog in CRPC patients was able to reduce plasma CgA values consistently in a few cases, but neither baseline CgA nor octreoscan could identify tumor responders (Kalkner *et al.* 2006). PI3K/AKT/mTOR signaling pathway contributes to transition to androgen-independent disease and neuroendocrine differentiation (Carver *et al.* 2011, Burgio *et al.* 2012, Conteduca *et al.* 2014). Thus, targeting of PI3K/AKT/mTOR may represent a promising therapy for CRPC with neuroendocrine differentiation. PI3K and dual PI3K/mTOR inhibitors are currently investigated in combination with abiraterone in metastatic CRPC, and the effect on the neuroendocrine component will be crucial for the success of these clinical trials (Conteduca *et al.* 2014).

In conclusion, elevated plasma CgA levels are frequently observed in CRPC patients after docetaxel. A plasma CgA level more than three times the UNV predicted PFS and showed a trend vs OS prediction, independently from PSA decline, in CRPC patients treated with abiraterone. The integrated use of PSA response and baseline CgA levels could potentially lead to a significant improvement in outcome prediction of these patients. Further larger studies should investigate serum CgA levels as a potential biomarker for outcome prediction in CRPC treated with abiraterone.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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