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Prostate-specific antigen growth rate constant after first-line cytotoxic chemotherapy in metastatic castration-resistant prostate cancer: A monoinstitutional experience

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Abstract

Objective: Validation in clinical practice, after first-line chemotherapy (CT) of metastatic castration-resistant prostate cancer (PC), of prostate-specific antigen growth rate constant logarithm (PSA-G), calculated by a formula developed by Stein et al. in comparison with PSA decrease (PSA-D), calculated as recommended by PCWG2.

Patients and methods: This study is a retrospective monoinstitutional assessment of PSA-G and PSA-D after 12 weeks from the beginning of first-line cytotoxic CT in 49 patients with metastatic castration-resistant PC treated from 2006 to 2011, and whose pre-CT PSA and post-CT PSA determinations have been measured at specific time points. The 12-week PSA was measured at 80 to 91 days from the beginning of CT.

Results: PSA-G exhibited a significant correlation with overall survival by Mann-Whitney *U* test and by linear regression, whereas PSA-D did only at the first test. After multivariate analysis, PSA-G was the only posttreatment measure to predict overall survival.

Conclusion: PSA-G appears a reliable surrogate end point after first-line cytotoxic CT outside of clinical trials. A cutoff value of PSA-G post-CT higher than −2.4 could be considered suggestive for moving to another treatment. © 2014 Elsevier Inc. All rights reserved.

Keywords: Prostate cancer; Growth rate constant; Chemotherapy; Surrogate end point

1. Introduction

In Europe, prostate cancer (PC) is the most common nonskin cancer among men, with 382,300 new cases and 89,300 deaths in 2008 [1]. Death from PC occurs almost exclusively in the last stage of the disease, the metastatic castration-resistant PC (mCRPC) [2]. Since 2004, many drugs have been approved for the treatment of mCRPC, because they have increased overall survival (OS) in randomized prospective trials [3–8].

However, the assessment of activity of new drugs for mCRPC remains difficult, due to poor performance of surrogate end points (SEs) of OS. The decrease in prostate-specific antigen (PSA), or PSA decrease (PSA-D), has been initially tested in prospective trials, but it was not a reliable SE after vaccine therapy and targeted therapies, whereas in trials of cytotoxic chemotherapy (CT) PSA-D resulted in controversial findings [9,10]. Though PC Working Group-2 (PCWG2) has proposed some rules to address this issue, suggesting to base decisions concerning treatment changes on measurements of progression/delay [11], the absence of SEs and validated measures of response and progression complicates decision making after first-line CT.

In this context, measurements related to the kinetics of the PSA, which can be approximated to cancer cells kinetics [12], have been developed [13]. In a retrospective analysis of PSA kinetics in patients with mCRPC of 5 studies with different agents, carried out from 1996 to 2010 at the National Cancer Institute in Bethesda, some kinetic

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parameters were calculated for estimating the growth rate and the regression rate of mCRPC, based on PSA measurements. The authors concluded that the growth rate constant (g), expressed as log g (PSA growth rate constant [PSA-G]), was correlated with OS while the decay rate constant did not. PSA-G resulted from an equation that took into account regression and cell growth, which occur simultaneously during cancer treatment. In mCRPC, the regression portion of the curve did not predict survival, whereas the growing fraction did. PSA-G is expressed in logarithmic form, and it is reported as a negative number. If g value is 0.011214208 days-1, it follows that PSA-G $= \log_{10} -1.9502$, and is reported as -1.95. Its absolute value correlates with the slowness of neoplastic proliferation, so that more negative values are associated with slower cell growth of mCRPC. PSA-G predicted OS in all 5 examined clinical trials regardless of the type of systemic treatment [14]. The advantages of PSA-G over PSA doubling time (PSADT) are significant: it does not require measurements pretherapy, it is often calculable even in patients with a PSA response to treatment, and it is informative, about 12 weeks before calculating the posttreatment PSADT.

To date, clinical reports about the feasibility of PSA-G outside clinical trials are not available. The purpose of this study is to perform a retrospective evaluation of PSA-G and PSA-D at 12 weeks in patients treated with CT for mCRPC and their correlation with OS.

2. Patients and methods

Patients were selected among men with mCRPC, who were treated at the division of Medical Oncology of "G. Borea" Hospital in Sanremo, Italy, from March 2006 to January 2011. To be included in this study, the patients must have received at least 1 cycle of first-line CT and should have at least 4 determinations of serum PSA in the first 12 weeks after the start of CT, with the last at least in the range of 80 to 91 days after the day of beginning CT. Date of death had to be reported in their clinical record. Patients with a median OS less than 6 months from the first course of CT were excluded. OS was measured from the first cycle of CT to death or last censoring. Finally, every patient should have signed a consensus form about the management of his clinical record for research purposes.

Determinations of serum PSA were performed at the "Laboratorio Analisi" department of the "G. Borea" Hospital, by chemoluminescence assay. The upper value of normal range was 4 ng/ml.

The computation of g was performed using the Excel spreadsheet supplement, by Stein et al. [14] and was expressed as log g (PSA-G). To calculate PSA-related measurements, the first blood test should be performed on the day of the beginning of first-line CT, or a maximum of 2 weeks before; a second and a third sample for serum PSA determination were collected at the fourth, seventh, or tenth week, before the corresponding CT cycle. The forth, and last, value was the PSA at 12 weeks, at 80 to 91 days after the start of CT. In the event that the PSA reduction after CT was so large that we could not recalculate PSA-G, we used PSA-nadir in place of the third value of PSA and, as the last PSA value, the first post-nadir PSA that made it possible to calculate PSA-G.

The calculation of PSA-D has been done by expressing PSA at week-12 as the percentage of the baseline PSA. A reduction of 30% or more was classified as a serologic response, whereas an increase $>25\%$ as a serologic progression, with the intermediate values configuring a stable disease [11]. It was also expressed as a continuous variable, as PSA response rate.

PSA nadir and PSA time-to-nadir after CT were reported, selecting the lower value of PSA after CT and before the further serologic progression.

Cases were grouped in 2 different subgroups around the median value of PSA-G. The analyses were done, including all the selected patients at January 27, 2012.

A correlation analysis was performed between PSA-G and other prognostic factors at the time of first-line CT (performance status, hemoglobin, baseline PSA, and PSADT) and PSA nadir, and a correlation coefficient was calculated for every comparison. A similar analysis was repeated for PSA-D.

Furthermore, a multivariate analysis was undertaken with the aim to test the role of PSA-G and PSA-D on OS; it included performance status, hemoglobin, baseline PSA, PSA nadir, PSA time-to-nadir, and docetaxel vs. other CT. Multivariate analysis was performed with Cox proportional

Table 1
Characteristics of patients

Number	49
Age (range)	68 (53–82)
Comorbidities	1 (0–4)
Gleason score (range)	8 (5–9)
Karnofsky PS	
100%	38
80%–90%	11
Median PSA (ng/ml; range)	55 (3.51–587)
Hemoglobin (g/dl)	13.5 (10.2–15.6)
Site of disease	
Prostate	23
Nodes	20
Bone	43
Other sites	7
Primary treatment	
Surgery	12
Radiotherapy	6
Hormonal therapy	31
First-line CT	
Docetaxel based	38
Other	11
Median time from diagnosis to CRPC (months)	28.58
Median time from CRPC to CT (months)	7.85
PSADT at the time of CT (months)	2.63

PS = performance status.

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