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Prostate-specific antigen doubling time before onset of chemotherapy as a predictor of survival for hormone-refractory prostate cancer patients

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Background: We evaluated the possible use of prostate-specific antigen doubling time (PSA-DT) before chemotherapy initiation as a surrogate marker of survival in hormone-refractory prostate cancer (HRPC) patients.
Patients and methods: Data from 250 consecutive metastatic HRPC patients treated with chemotherapy between February 2000 and November 2006 were retrospectively analysed. At least three PSA assays were required within 3 months before chemotherapy. PSA-DT was calculated as ln 2 divided by the slope of the log PSA line, and the difference between two log PSA levels was divided by the time interval. The primary endpoint was overall survival (OS). Survival rates according to PSA-DT were stratified on chemotherapy regimen. Multivariate Cox regression analysis was performed to isolate the impact of PSA-DT on OS, controlling for associate prognostic covariates.
Results: Patients received docetaxel- (82%) or mitoxantrone-based chemotherapy. The median PSA-DT was 45 days (range 4.7–1108 days). There were 174 deaths (70%). The median survival was 16.5 months (95% confidence interval [CI] = 12.5–20.5) and 26.4 months (95% CI = 20.3–32.4) for patients with a PSA-DT < 45 and ≥45 days, respectively. In the multivariate setting, the adjusted hazard ratio (HR) was 1.39 (95% CI = 1.03–1.89; $P = 0.04$), stratified by chemotherapy regimen.
Conclusion: A short PSA-DT before onset of chemotherapy in HRPC patients was associated with an increased risk of death. This could be useful as a stratification parameter in trials with new drugs in a metastatic setting.
Key words: chemotherapy, hormone-refractory prostate cancer, overall survival, predictive factor, prostate-specific antigen doubling time

introduction

Prostate cancer is currently the most frequent malignancy in men and is responsible for the second highest number of cancer-related deaths after lung cancer. The American Cancer Society estimates that 232 000 new cases of prostate cancer were diagnosed in the United States during 2005 and more than 30 000 men will die of metastatic disease [1]. Around half of all patients are metastatic at the initial diagnosis, and nearly 50% of those who present with an initial localized disease will develop subsequent metastases. Androgen deprivation therapy allows a response rate of 80–90% [2]. Those remissions last 2 or 3 years, but almost all metastatic prostate cancer patients evolve towards an androgen-independent state resulting in death due to widespread metastases [3].

For a long time, prostate cancer has been considered as a chemoresistant disease [4]. Two major randomized trials modified our chemotherapy procedure in hormone-refractory prostate cancer (HRPC) patients [5, 6]. These studies compared docetaxel–estramustine with or without prednisone or docetaxel–prednisone regimens with the previous standard (mitoxantrone–prednisone combination). The authors demonstrated a significant advantage of docetaxel-based regimens in terms of overall and progression-free survival. These results led us to consider a docetaxel-based regimen as the reference treatment in the management of HRPC patients, and we have been using this since 2004. A phase II randomized study evaluated the crossover impact on survival of HRPC patients [7].

The main issue with the evaluation of response to chemotherapy for HRPC patients is due to the predominance of bone metastases, which are considered to be evaluable but non-measurable lesions (non-target). The level of prostate-specific antigen (PSA) is related to tumour growth and

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has a positive correlation with tumour burden [8]. A decrease of more than 50% in the PSA level as compared with the baseline value has been proposed as a biological response criterion [8]. A significant relationship has been established between this decrease and an improvement in survival, justifying the use of this criterion to identify potentially effective drugs. Nevertheless, this cut-off did not met the criteria for surrogacy in a recent retrospective analysis of docetaxel-treated HRPC patients [9]. Reliable surrogate endpoints for survival are being investigated in order to reduce the time required to assess the efficacy of a new treatment and appropriate selection of patients for clinical trials. New biological variables such as albumin, alkaline phosphatase and lactate dehydrogenase have been validated and included in nomograms for HRPC patients [10]. For instance, the rate of increase in PSA has been shown to correlate with the prostate cancer-specific mortality following primary therapy: patients presenting with a rapid increase in PSA [i.e. a short PSA doubling time (PSA-DT)] had a higher risk of death than those with a slower increase [11–15]. In order to confirm these findings, we analysed the PSA-DT before initiation of chemotherapy in metastatic HRPC patients as a surrogate endpoint for overall survival (OS).

methods

study population

We retrospectively analysed data from consecutive metastatic HRPC patients who had received docetaxel- or mitoxantrone-based chemotherapy in five French centres (Georges Pompidou European Hospital, Curie Institute and Cochin Hospital in Paris, François Baclesse Centre, Caen and Antoino-Lacasagne Centre, Nice). At least three consecutive PSA determinations had to be available within 3 months before the start of chemotherapy. To be eligible for this analysis chemo-naïve patients had to fail both androgen blockade and anti-androgen withdrawal, to present an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 and a castrate serum testosterone level.

The database was declared to the appropriate French authorities supervising individual computerized data files (Commission Nationale Informatique et Liberté).

PSA doubling time evaluation

The PSA-DT was estimated in patients with rising PSA before the onset of chemotherapy according to the formula: $t \times \log_e(2)/[\log_e(\text{PSA2}) - \log_e(\text{PSA1})]$ where t is the time between two consecutive PSA determinations (PSA1 and PSA2) [16]. This was made possible because all PSA assays for each patient were performed in the same laboratory. More complex models able to estimate PSA-DT have been described in the literature [17].

statistical analysis

The primary endpoint was OS defined as the time interval between the start of chemotherapy and death or last follow-up for living (censored) patients. The OS rates according to PSA-DT categories were estimated using the Kaplan–Meier method and compared using a stratified log-rank test. Reduction in the risk of death and hazard ratios (HRs) were estimated with a 95% confidence interval (CI) at the univariate analyses. Because patients were not randomly assigned to chemotherapy and treatments were previously shown as different in terms of survival, regression and log-rank analyses were stratified by chemotherapy regimen. A multivariate Cox proportional hazard regression analysis was used as the main statistical method, controlling for explanatory covariates that have been shown to be prognostic and therefore, could confound the core analysis [18]. These variables included age, PSA baseline, hormone sensitivity interval, Gleason score, haemoglobin, number of metastatic sites and ECOG PS. The stepwise backward elimination strategy was used in order to better estimate the impact of PSA-DT on OS as the backbone of the multivariate analysis. The PSA-DT was expressed in days and analysed as a binary variable (short and long PSA-DT) according to the median value. The hormone sensitivity interval was calculated as the difference between two chronological moments: the start of hormonal therapy and the start of chemotherapy (when patients were considered as hormone-refractory), expressed in days. The Fischer test and Student's t-test were used to estimate differences between PSA-DT categories on demographic, clinical and biological categorical or quantitative variables, respectively. All statistical tests were two-sided and assessed for significance at the 0.05 level. No statistical adjustment was performed for the multiplicity of tests. The relational database was created using FileMaker Pro™ 8.5 (FileMaker Inc, CA, USA) software. The statistical analysis was performed by Eugeniu Banu using SPSS™ 15 (SPSS Inc., Cary, NC, USA) and EpiInfo 2000 version 3.2.2 (Centers for Disease Control, Atlanta, GA, USA).

results

patient characteristics

Data from 250 metastatic HRPC patients who had received chemotherapy between February 2000 and November 2006 were analysed. Chemotherapy consisted of docetaxel- or mitoxantrone-based regimens in 204 (82%) and 46 (18%) of patients, respectively. The median time interval between two consecutive PSA readings before the start of chemotherapy (for PSA-DT estimation) was 22 days (95% CI = 3–90 days). The median PSA-DT was 45 days (range 4.7–1108). Two groups of patients were defined: those with a short PSA-DT < 45 days (n = 125) and those with a long PSA-DT ≥ 45 days (n = 125). Patient characteristics according to PSA-DT groups are summarized in Table 1. There were significant differences between some baseline characteristics such as hormone-sensitivity interval, age and PSA level ($P < 0.02$).

overall survival

At the time of analysis 174 (70%) patients had died, of whom 88 (70%) were in the short PSA-DT group and 86 (69%) in the long PSA-DT group. The median OS for the entire cohort was 20.2 months (95% CI = 16.7–23.7). Docetaxel-based regimens demonstrated a significant survival benefit over mitoxantrone: median OS of 21.3 months (95% CI = 17.5–25.1) and 13.8 months (95% CI = 5.9–21.6), respectively. As specified in the statistical design, stratified survival analyses were performed thereafter according PSA-DT. The median and 2-year OS rates were 16.5 months (95% CI = 12.5–20.5) and 32% in the short PSA-DT group and 26.4 months (95% CI = 20.3–32.4) and 55% in the long PSA-DT group, respectively ($P = 0.04$; log-rank test, $P = 0.004$ Breslow–Gehan test; Table 2, Figure 1.) The unstratified and stratified HRs according to chemotherapy regimen were 1.40 (95% CI = 1.04–1.89) and 1.37 (95% CI = 1.01–1.84), respectively, allowing a significant reduction in the risk of death for patients presenting with a longer PSA-DT ($P = 0.04$, Cox regression; Table 3). The median OS for patients treated with

Table 1. Patient characteristics according to PSA doubling time

Characteristic	PSA-DT <45 days (n = 125)		PSA-DT ≥45 days (n = 125)		P
	n	%	n	%	
PSA-DT (days)					0.0001
Median	25.7	87.7			
Range	4.7–44.5	45.2–1108			
Age (years)					0.25
Median	67.4	69.3			
Range	50.7–85.5	49.5–90.9			
Baseline PSA (ng/ml)					0.002
Median	98.8	63			
Range	4–3720	4.1–1840			
Haemoglobin (g/dl)					0.50
Median	12.6	12.5			
Range	7.8–15.1	8–17			
ECOG PS					0.10
0	58	46.4	73	58.4	
1	53	42.4	37	29.6	
2	14	11.2	15	12	
Gleason score					0.25
2–4	2	6	1	0.8	
5–7	56	44.8	71	56.8	
8–10	67	53.6	53	42.4	
Hormone-sensitivity interval (months)					0.03
Median	33.9	45			
Range	3–204.4	2.8–215.6			
No. of metastatic sites					0.09
1	77	61.6	85	68	
≥2	48	38.4	40	32	
Type of metastases					0.18
Bone	117	93.6	113	90.4	
Lymph nodes	47	37.6	43	34.4	
Visceral	18	14.4	9	7.2	
Chemotherapy regimen					0.25
Docetaxel-based	98	78.4	106	84.8	
Mitoxantrone-based	27	21.6	19	15.2	

n, number of patients; P, statistical P-value; PSA-DT, prostate-specific antigen doubling time; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Overall survival according to PSA doubling time

Survival parameter	PSA-DT <45 days (n = 125)	PSA-DT ≥45 days (n = 125)
Deaths, n (%)	86 (69)	88 (70)
OS (months)		
Median (95% CI)	16.5 (12.5–20.5)	26.4 (20.3–32.4)
1-year OS, % (95% CI)	62 (53–70)	80 (72–87)
2-year OS, % (95% CI)	32 (23–41)	55 (45–64)
3-year OS, % (95% CI)	22 (14–30)	33 (24–43)

n, number of patients; PSA-DT,prostate-specific antigen doubling time; OS, overall survival; CI, confidence interval.

docetaxel were 26.2 months (95% CI = 18.1-34.3) and 17.8 months (95% CI = 12.1–23.4) for PSA-DT ≥45 days and <45 days, respectively. The associated HR was 1.27 (95% CI, 0.90–1.81), P = 0.17.

The univariate analyses for pre-defined variables showed that ECOG PS, haemoglobin, hormone sensitivity interval, baseline PSA and PSA-DT were significantly associated with the risk of death (Table 3), whereas age, number of metastatic sites and Gleason score were not predictive of survival. In the multivariate analysis by Cox regression modelling, ECOG PS, haemoglobin and PSA-DT remained significantly predictive of risk of death (Table 3, Figure 1, stratified by chemotherapy regimen. Despite their statistical significance, the impact on survival for two covariates (hormone sensitivity interval and baseline PSA) was negligible (associated HR = 1.00, 95% CI = 1.00–1.01, regression coefficient < 0.001, P-value < 0.005). Including the hormone sensitivity interval and baseline PSA in the multivariate analysis (with haemoglobin, ECOG PS and PSA-DT as covariates), as expected, has no impact on the results, but this degraded the overall goodness-of-fit of the model. The interaction term between PSA-DT categories and ECOG PS was found to be statistically significant in the multivariate setting. As demonstrated, the risk of death was

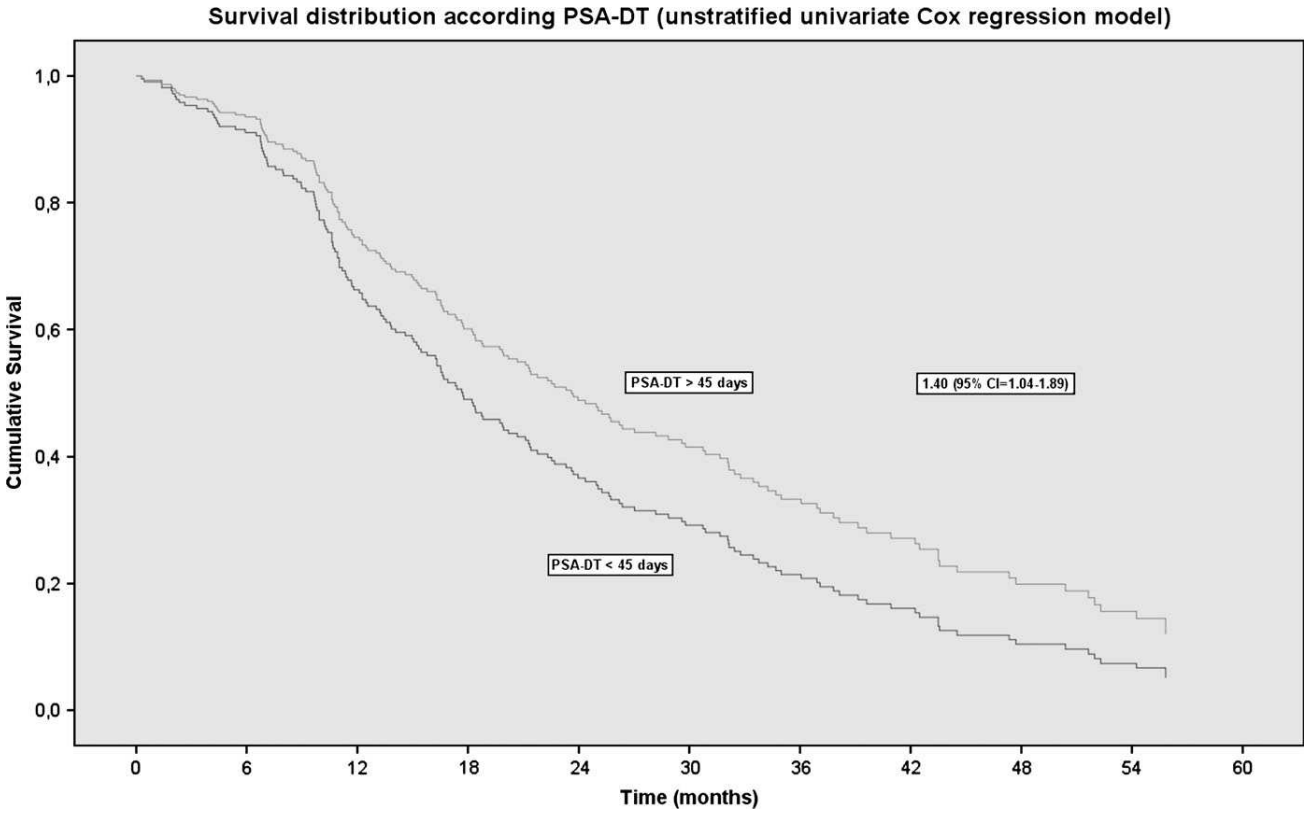

Figure 1. Survival distribution according to PSA-DT, multivariate Cox regression model.

Table 3. Univariate and multivariate survival analyses stratified for chemotherapy regimen

Covariate	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
PSA-DT	1.37	1.01–1.84	0.04	1.39	1.03–1.89	0.03
Haemoglobin	0.80	0.72–0.90	0.0001	0.85	0.76–0.95	0.004
ECOG PS	2.17	1.74–2.72	0.0001	2.02	1.61–2.54	0.0001
Gleason score	1.08	0.95–1.23	0.25			
Age	1.01	0.99–1.03	0.45			
PSA baseline	1.00	1.00–1.00	0.0001			
Number of metastatic sites	1.19	0.92–1.55	0.19			
Hormone sensitivity interval	1.00	1.00–1.00	0.005			

HR, hazard ratio; CI, confidence interval; PSA-DT, prostate-specific antigen doubling time; ECOG PS, Eastern Cooperative Oncology Group performance status; PSA, prostate-specific antigen.

significantly higher for patients having an ECOG PS of 1 or 2 and a PSA-DT < 45 days. The interaction term between chemotherapy regimen and PSA-DT categories was not statistically significant.

discussion

Data presented here represent a retrospective review of 250 metastatic HRPC patients who received docetaxel- or mitoxantrone-based chemotherapy. The analysis showed that patients with a short PSA-DT (<45 days) before the onset of chemotherapy were at a higher risk of death, regardless of the chemotherapy regimen. To our knowledge, this is one of the first reports to investigate the role of PSA-DT as a predictive factor of survival in metastatic HRPC.

PSA levels present great variability among patients; this is explained by different PSA expression by prostate cancer cells and tumour cell heterogeneity [19]. The interpretation of PSA values is further complicated by the fact that some patients who demonstrate increased values after initial treatment will not evolve towards clinical relapse and also that PSA-DT may change between disease states over time [20, 21]. One study showed that PSA-DT may be a useful tool in the management of untreated prostate cancer patients with a good prognosis,

and that PSA-DT varied widely, ranging from less than 2 years (14%) to more than 10 years (33%) [22]. Results from several studies have highlighted the interest in PSA-DT for the monitoring of prostate cancer at each step of the disease. Recently, a relationship between PSA-DT and survival was demonstrated by multivariate analysis for patients treated with radical prostatectomy and adjuvant hormonal therapy [23]. After primary treatment consisting of radical surgery or radiotherapy, a PSA-DT below 3 months was significantly associated with cancer-specific survival in non-metastatic patients, whereas the treatment received was not correlated [24]. Thereafter, the use of PSA-DT has been proposed as a means of estimating the aggressiveness of the disease and differentiating between the local (pelvic) and metastatic risk of disease progression [25]. Several reports have demonstrated the usefulness of PSA-DT as a predictor of biochemical recurrence [26, 27]. In a study of 249 patients, a significant decrease in PSA-DT was observed when patients went through hormone-naïve to hormone-refractory status, identifying several stages of the HRPC period [17]. When PSA-DT was compared between untreated hormone-naïve and HRPC patients, values were approximately 10 times greater in untreated patients [12]. This comparison showed a wide difference in terms of PSA-DT, allowing an estimation of the tumour growth rate. The definition of a threshold value for PSA-DT is actually a major concern and needs to be considered differently according to the stage of the disease in establishing nomograms. In HRPC patients, PSA-DT was shorter in patients who showed bone progression rather than in patients with local relapse and/or lymph node metastases. Patients showing a longer DT (>80 days) had a better overall prognosis than those with shorter DTs [12]. The value of PSA-DT has been correlated with the objective response to chemotherapy in metastatic HRPC patients: the median PSA-DT was 238, 224 and 113 days in patients presenting with a partial response, stable and progressive disease, respectively (Wilcoxon test, $P = 0.002$) [15]. More recently, a PSA-DT of 70 days has been found to be the cut-off value associated with significant survival differences between identified strata (11 vs 19 months, HR = 1.79) [28]. In this report, the PSA-DT cut-off was identified by multiple chi-square tests according to minimal *P*-value. In our study, the cut-off of 45 days was the median PSA-DT value. The relative increase in the risk of death was slightly lower for our patients (HR = 1.39). In the Semeniuk *et al.* study [28] the multivariate survival analysis was not adjusted for ECOG PS, a well-known prognostic variable in large phase III studies. A higher PSA-DT cut-off was previously described in a small cohort of patients [11].

Moreover, HRPC patients with a short PSA-DT had a poorer life expectancy [12]. Our study demonstrated that PSA-DT was a valuable tool capable of selecting high-risk patients after failure of endocrine therapy and before initiation of chemotherapy. The potential usefulness of PSA-DT is to provide reliable data at successive steps of the disease. It could be used to guide therapeutic strategy in patients managed conservatively with watchful observation, to select high-risk patients after primary therapy or after failure of endocrine therapy, to assess prognosis after relapse and to evaluate the efficacy of cytotoxic drugs in HRPC patients.

Could we define a true surrogate endpoint in prostate cancer using PSA-DT? According to the Prentice criteria, a surrogate endpoint has to be a prognostic factor, and when a patient achieves a surrogate endpoint the time to prostate cancer-specific mortality has to be independent of the treatment received [29].

conclusions

This retrospective analysis shows that a short PSA-DT before chemotherapy initiation in HRPC patients is associated with an increased risk of death. Our results were statistically significant using a multivariate regression model, and showed that patient-related predictive factors such as ECOG PS or haemoglobin remained crucial. The sole disease-related covariate associated with OS was the PSA-DT. It directly interacted with ECOG PS, as demonstrated by a borderline relationship at interaction terms.

We identified a high-risk subset of patients with an aggressive disease. PSA-DT could be used to stratify HRPC patients in order to avoid some potential imbalances between baseline covariates in the design of future clinical trials.

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