Progression after docetaxel–based chemotherapy in androgen–independent prostate cancer

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OBJECTIVE
To assess the clinical pattern of progression and prostate–specific antigen doubling time (PSA-DT) after exposure to docetaxel–based chemotherapy in patients with androgen–independent prostate cancer (AIPC).

PATIENTS AND METHODS
Fifty-five patients received docetaxel–based chemotherapy; data were collected retrospectively from three different departments. Progression was known in 44 (79%) and the PSA-DT was available in 33 patients.

RESULTS
Of the 29 patients with soft-tissue and soft-tissue plus bone metastases, 22 (76%) developed soft-tissue progression. Among the 35 patients with bone and bone plus soft-tissue metastases, 27 (77%) had osseous progression. There was no difference between the PSA-DT at progression before and after docetaxel–based therapy (mean 3.1 vs 2.7 months, \( P = 0.592 \), Student’s t-test). However, the median (range) PSA-DT at progression after docetaxel–based therapy was 0.84 (0.3–4) months in patients with a PSA response, significantly shorter than the median of 3.1 (0.3–12) months of patients with no biochemical response (\( P = 0.002 \), Student’s t-test). The PSA-DT dynamics at progression had no effect on survival (\( P = 0.63 \), log-rank test).

CONCLUSION
The pattern of progression after docetaxel-based chemotherapy is predominantly osseous in patient with bone metastases and mostly soft-tissue in those with soft-tissue disease. Progression after docetaxel–based chemotherapy in AIPC does not modify the PSA-DT before docetaxel. Evaluation of a larger population is needed to assess the clinical relevance of PSA dynamics after docetaxel therapy.

KEYWORDS
PSA doubling time, androgen–independent prostate cancer, docetaxel

INTRODUCTION
Docetaxel–based chemotherapy (DBC) can provide significantly prolonged survival and palliative benefits in patients with androgen-independent prostate cancer (AIPC) [1,2]. As the benefits are short-term, this has created a further legitimate demand for additional systemic chemotherapy [3]. Previously, bone-targeted therapy increased the survival of patients who did not progress after a combination regimen not including docetaxel [4]. Therefore, it is essential to recognize the clinical characteristics of progression after DBC to define a potential additional approach to extend the therapeutic effect of this regimen in AIPC.

The PSA doubling time (PSA-DT) was determined to be a predictive factor for aggressive prostate cancer in cases of localized disease, biochemical progression, and androgen–dependent and –independent states after hormonal therapy. Men with AIPC and a PSA-DT of ≤70 days had a significantly shorter survival time than men with a PSA-DT of >70 days [5–8]. However, there are no data on PSA-DT and its prognostic value for progression after DBC in AIPC. Thus we assessed the clinical pattern of progression and PSA-DT after exposure to DBC in patients with AIPC.

PATIENTS AND METHODS
Data were retrieved from the charts of 55 patients who received DBC from August 1999 to December 2005 in three different centres. The treatment protocols included: docetaxel 60–70 mg/m² with estramustine 280 mg three times daily on days 1–5 every 21 days (33 patients); docetaxel 35 mg/m² on day 1 with estramustine 280 mg three times daily on days 1–3, given weekly for 3 weeks every 4 weeks (one patient); docetaxel 75 mg/m² on day 1 with prednisone 5 mg twice daily every 21 days (14 patients) and docetaxel 75 mg/m² on day 1 (seven patients) [1,2,8]. Dexamethasone preceded DBC in all the patients. All patients were evaluated for biochemical response and only 36 for soft-tissue response.

The results were assessed using the chi-square test to compare variables, Student’s t-test to compare PSA-DT, Kaplan-Meier analysis to calculate survival estimates and the log-rank test to compare survival times. The PSA response and progression were defined according to the criteria of Bubley et al. [9], while the objective response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) [10]. We calculated the PSA-DT using the first two values indicating progression, as:
RESULTS

The mean (range) patient age was 67 (43–82) years, the Eastern Cooperative Oncology Group performance status 1 (0–3) and the baseline PSA level 83.6 (0.06–1967) ng/mL. The disease involved bone in 43 (78%) patients, lymph nodes in 28 (51%), prostate in 10 (18%), liver in six (11%) and lung in one (2%). Overall, there was soft-tissue disease in 36 (65%) patients.

Previous therapy before DBC included radiation therapy in 31 patients (56%), other than docetaxel-based regimens in 17 (31%), adrenal suppression in 18 (33%) and diethylstilbestrol in 13 (24%).

There was a biochemical response in 26 of 55 (47%) patients (95% CI 33.6–61.2). Using RECIST there was a partial response in 10 of 36 (28%; 95% CI 14.2–45.1) and stable disease in 15 of 36 (42%; 95% CI 25.5–59.2).

Table 1 shows the data of the RECIST progression sites in 44 (79%) patients; among the 11 remaining, two are still responding, three had biochemical progression only and six had no information about their progression. Of the 29 patients with soft-tissue and soft-tissue plus bone metastases, 22 (76%) developed soft-tissue progression. Among the 35 patients with bone and bone plus soft-tissue metastases, 27 (77%) had osseous progression. The survival of all the patients was 15.2 months.

The PSA-DT data at progression was available in 33 patients, there was no difference in PSA-DT at progression before and after DBC (median 1.99 vs 2.1 months, mean 3.1 vs 2.7 months, respectively, P = 0.592, Student’s t-test), although some of the patients had a large increase in PSA-DT at progression after DBC (Fig. 1). However, the median (range) PSA-DT at progression after docetaxel-based therapy was 0.84 (0.3–4) months in patients with a PSA response, significantly shorter than the median of 3.1 (0.3–12) months in those with no biochemical response (P = 0.002, Students’ t-test). In addition, a shorter PSA-DT at progression was significantly more common in patients who had a PSA response (16 of 17, 94%) than in those with no PSA response to DBC (six of 15, 40%; P = 0.004, chi-square).

The PSA-DT dynamics at progression (shorter or longer than before DBC) had no effect on survival (P = 0.63, log-rank test). The survival time was similar (19.7 months) in patients with either an increased or decreased PSA-DT comparing values before and after DBC. We did not confirm that a PSA-DT of <70 days indicates a high risk of death; the median survival of those in whom docetaxel failed and with a PSA-DT of ≤2.3 months was 19.4 months, similar to those with a PSA-DT of >2.3 months (19.0 months, P = 0.877) [5].

DISCUSSION

Hormone-refractory lethal metastatic prostate cancer is a heterogeneous group of diseases with genotypic and phenotypic diversity among patients and within the same patient [11,12]. Despite the heterogeneity, we showed that progression after DBC is predictable. Progression tended to occur at the disease sites present before DBC. We confirmed that patients with bone metastases only predominantly progressed in osseous sites [13]. However, patients with solely soft-tissue disease tended to progress in soft-tissue sites, while patients with mixed sites progressed in both. To date, with the earlier administration of DBC, even in biochemical-only progression, it is conceivable that the heterogeneity reported in autopsy studies before the use of docetaxel might differ, leading to more predictable clinical behaviour. Understanding the heterogeneity of AIPC might guide the development of future treatments, as those tailored to a particular disease site, at a certain time, might not affect other sites in the same organ, or other organs, or the same tumour at a another time [11,12]. Our data suggest that osseous disease is the appropriate target for evaluating bone-targeted therapy, along with DBC in AIPC. Other systemic therapeutic approaches should be integrated with docetaxel in patients with soft-tissue disease.

FIG. 1. The percentage change in PSA-DT before and after DBC.

Regardless of the heterogenicity in AIPC, PSA dynamics, e.g. PSA velocity, PSA response duration and PSA-DT, have emerged recently as potential predictive factors for survival in AIPC [5,14–17]. There are limited data on PSA-DT in AIPC; it was proposed as an auxiliary endpoint for antiandrogen and other chemotherapy than DBC in AIPC with soft-tissue disease [18]. Previously, patients with AIPC in whom second hormonal therapy with antiandrogen or other than DBC failed, progressed with significantly shorter PSA-DT than those who responded to these agents (Table 2) [17,18]; in the present study we showed the opposite. Those with a PSA response to DBC had a significantly shorter PSA-DT than those with no biochemical response (Table 2). Several factors could account for these contradictory results. The patients who received the other than DBC included only those with soft-tissue disease [17]; these men might have a different biology from patients with osseous metastases [13]. This difference in PSA-DT might also reflect a biological effect of docetaxel in AIPC. We also showed that the failure to respond to DBC tended to be associated with a lower PSA-DT than before DBC, and that the PSA-DT at progression was not associated with survival. We did not confirm that a PSA-DT of <70 days at progression constitutes a high risk for survival. These findings must be further evaluated on a larger scale.
For many years chemotherapy failed to provide clinical benefits for patients with AIPC [19]. Only recently has docetaxel given a significant survival advantage in this disease [1,2]. As a result, several issues have emerged. It is unknown why docetaxel is the only currently active drug to-date in AIPC. In addition, it is unclear why docetaxel retains efficacy when given intermittently or after previous failure of docetaxel [3,20–22]. Thus, additional information about the biological mechanism of failure to respond to docetaxel in AIPC, the characteristics of docetaxel-independent AIPC and the PSA dynamics in AIPC is needed for further progress in the care of these patients.

CONFLICT OF INTEREST

None declared.

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Abbreviations: AIPC, androgen-independent prostate cancer; PSA–DT, PSA doubling time; DBC, docetaxel-based chemotherapy; RECIST, Response Evaluation Criteria in Solid Tumors.