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Short Communication

The interval from the last cycle of docetaxel-based chemotherapy to progression is associated with the efficacy of subsequent docetaxel in patients with prostate cancer

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ABSTRACT

There is currently no standard treatment after first-line docetaxel-based chemotherapy for patients with castration-refractory prostate cancer (CRPC). Some patients are likely to discontinue first-line docetaxel-based chemotherapy because of either completed treatment or the occurrence of manageable side-effects. The aim of this study was to determine whether a rechallenge with docetaxel might be appropriate in patients with CRPC previously treated with docetaxel.

Between December 2004 and July 2009, 39 patients diagnosed with metastatic cancer prostate at the Institut Gustave Roussy were administered subsequent docetaxel after front-line docetaxel-based chemotherapy. The medical records of these patients were extracted from the database. The PSA response rate (PSA decline $\geqslant$30% and $\geqslant$50%), progression-free survival (PFS) and overall survival (OS) of patients receiving docetaxel as a subsequent line of therapy were evaluated using consensus criteria. The effect of pre-treatment variables on efficacy was studied.

A PSA decline $\geqslant$30% and $\geqslant$50% was observed in 64% and 38% of patients, respectively, median PFS was 4.3 months [confidence interval (CI) 95%: 3.6–4.9] and median OS was 15.8 months (CI 95%: 11.7–20.3) in 39 patients who received subsequent docetaxel. The interval between the last cycle of first-line docetaxel and progression [median: 3.0 months; range: 1–30 months] was associated with PFS: median PFS was 3.4 months (CI 95%: 2.6–4.1) and 6.3 months (CI 95%: 3.0–5.6), respectively, in patients with an interval <3.0 months and an interval $\geqslant$3.0 months, ($p = 0.04$). Tolerance of re-treatment with docetaxel was acceptable with no toxicity-related death.

Re-treatment with subsequent docetaxel in patients with CRPC pretreated with first-line docetaxel is safe and demonstrates some activity. The interval from the last cycle of first-line docetaxel-based chemotherapy to progression is associated with the efficacy of subsequent docetaxel.

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1. Introduction

Prostate cancer is the most commonly diagnosed cancer in men in the Western world and is the second leading cause of male cancer deaths.[1] Although androgen-deprivation therapy remains the mainstay of treatment for metastatic disease, patients eventually progress to a castration-refractory state also termed 'castration-refractory prostate cancer' (CRPC). Docetaxel-based chemotherapy (DBC) is currently the standard therapy for CRPC.[2–4] There is currently no standard treatment for patients failing first-line DBC.

Some patients are likely to discontinue first-line DBC because of either completed treatment or the occurrence of manageable side-effects. Completed treatment and adverse events were the reasons for stopping treatment in 46% and 11% of patients, respectively, in the TAX 327 study.[3] There is an important distinction between patients exhibiting truly docetaxel-resistant disease and those previously exposed to docetaxel and who then exhibit progression, but may still have docetaxel-sensitive disease. In this group of patients, a rechallenge with docetaxel could be appropriate if progression occurs after a reasonably long interval.

The aim of this study was to determine whether a rechallenge with docetaxel might be appropriate in patients with CRPC previously treated with docetaxel.

2. Patients and methods

2.1. Eligibility

Patients with CRPC evaluated in our centre between January 2004 and July 2009 were identified from our institutional database. All patients who met the following criteria were included in our cohort: (a) histologically confirmed diagnosis of a prostate cancer, (b) original treatment of CRPC with DBC, (c) achievement of a partial response or stable disease after front-line therapy as defined by the PSA Working Group,[5] (d) confirmation of a relapse by clinical, biochemical or radiographic assay and (e) subsequent treatment with DBC.

2.2. Response criteria and toxicity assessment

Toxicity was defined using the National Institute common Toxicity Criteria version 3.0. The efficacy outcomes were defined according to the guidelines of the Prostate-Specific Antigen Working Group.[5] Overall survival (OS) was calculated from the time of treatment initiation to death. Progression-free survival (PFS) was calculated according to the guidelines of the Prostate-Specific Antigen Working Group.[5]

2.3. Statistical analysis

Descriptive statistics were used to analyse patient characteristics (median, 95% confidence intervals; 95% CI). PFS and OS were calculated using the Kaplan–Meier method and compared by the logrank test. A p value of <0.05 was considered statistically significant for all comparisons.

3. Results

3.1. Patient characteristics

Patient characteristics are listed in Table 1. Among the 61 patients who had received first-line DBC (63%), 39 had received subsequent DBC from January 2004 to July 2009. Median PFS after first-line docetaxel-based chemotherapy was 7.8 months (CI 95%: 5.9–9.8 months) and the median interval from the last cycle of DBC to progression was 3.0 months (range: 1–30 months).

3.2. Efficacy

Among the 39 patients, 25 (64%) had achieved a PSA decline $\geqslant$30% from the baseline PSA level and 15 (38%) had achieved

Table 1 – Baseline characteristics.

Baseline characteristics	N = 39
Age at subsequent docetaxel treatment, median (years)	68 (45–76)
Previous chemotherapy regimen	N = 39
Docetaxel alone	N = 29 (74%)
Docetaxel + estramustine	N = 10 (26%)
Number of cycles of docetaxel as front-line, median	N = 39 9 (4–10)
Front-line docetaxel response	N = 39
PSA decline $\geqslant$50%	35 (90%)
SD	4 (10%)
Median PFS after front-line docetaxel (months)	7.8 (CI 95%: 5.9–9.8)
Interval between last cycle of docetaxel and progressive disease median (months)	3.0 (1–30)
Subsequent docetaxel	N = 39
2nd line	10 (26%)
3rd line	26 (67%)
$\geqslant$4th line	3 (7%)
Docetaxel regimen at reintroduction	N = 39
Docetaxel alone	23 (60%)
Docetaxel + estramustine	16 (40%)
Median number of cycles of subsequent docetaxel	5 (2–10)
Serum PSA before subsequent docetaxel, median (ng/ml)	204 (2–4839)
Median PSA doubling time before subsequent docetaxel (months)	1.7 (0.5–17.6)
PSA response	N = 39
PSA decline $\geqslant$50%	N = 15 (38%)
PSA decline $\geqslant$30%	N = 25 (64%)
Cause of docetaxel withdrawal	N = 39
Progressive disease	20 (51%)
Surveillance	14 (36%)
Toxicity	5 (13%)
Progression-free survival, median	4.3 months (CI 95%: 3.6–4.9)
Overall survival, median	16.0 months (CI 95%: 11.7–20.3)

a PSA decline ⩾50%. Five of 39 patients had experienced a serum PSA rise during the first 8 weeks of chemotherapy, followed by a subsequent decline in serum PSA. This phenomenon, described as the surge syndrome, frequently occurs in this setting.[6]

The median PFS for the cohort was 4.3 months (CI 95%: 3.6–4.9). When patients were stratified according to their interval since the last cycle of DBC (<3 months versus ⩾3 months), a statistically significant difference was observed for PFS. Median PFS after subsequent DBC was 3.4 months (CI 95%: 2.6–4.1 months) and 6.3 months (CI 95%: 3.0–5.6 months), respectively, in patients with an interval of <3.0 months and an interval of ⩾3.0 months ($p = 0.04$).

The median OS was 15.8 months (CI 95%: 11.7–20.3 months). Median OS after subsequent DBC was 12.8 months (CI 95%: 12.3–13.3 months) and 19.4 months (CI 95%: 11.8–27.0 months), respectively, in patients with an interval <3.0 months and an interval ⩾3.0 months ($p = 0.04$).

3.3. *Toxicity*

Two patients (5%) had required hospitalisation for neutropaenic fever. Five of 39 (13%) had stopped treatment due to toxicity. No treatment-related death was reported with re-treatment. The most frequent side-effects were neutropaenia (21%), anaemia (18%) and asthaenia (15%).

4. Discussion

Re-treatment with docetaxel is a current option for patients who have stopped first-line DBC for surveillance or toxicity. In this study, we report on the efficacy of subsequent docetaxel in patients previously treated with front-line DBC. We observed that 64% and 38% of these patients obtained a PSA decline ⩾30% and ⩾50%, respectively. The high percentage of PSA response may have been due to patient selection in this retrospective study. To better identify patients who were more likely to have benefited from re-treatment with docetaxel, we assessed the effect of several pre-treatment variables on efficacy. We considered that the time since the last first-line DBC cycle to progression ⩾3.0 months could have an impact on outcome. It could be an attractive criterion when considering subsequent DBC. No preclinical data are currently available to explain this finding.

Very few studies addressing the efficacy of subsequent DBC have been published. A phase II trial reported a response rate of 18% and a median PFS of 3 months in 34 patients who were refractory to docetaxel (progression during or within 45 days after first-line docetaxel-based chemotherapy) and who received a combination of carboplatin and docetaxel in the second-line setting.[7] Bevacizumab seems to be another drug of interest in CRPC: a retrospective study reported a major PSA response in 55% of patients treated with bevacizumab and docetaxel, who eventually progressed after first-line DBC and 4 of 20 achieved a PSA response in the second-line setting whereas they were previously unresponsive to docetaxel alone.[8]

Safety must be taken into account while considering second-line chemotherapy for patients with CRPC. Re-introduction of docetaxel is safe since no treatment-related death was observed and only 13% of patients stopped chemotherapy for toxicity.

Although the size of this cohort is limited, these data show that the re-introduction of docetaxel is a reasonable option for patients who fail under first-line DBC. Nevertheless, these findings should be confirmed in other retrospective and prospective data sets.

Conflict of interest statement

The authors disclose any financial and personal relationships with other people or organisations that could inappropriately influence this study.

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