Preliminary results of the Prostacox phase II trial in hormonal refractory prostate cancer

Baptiste Albouy, Jean-Marc Tourani*, Patrick Allain†, Frederic Rolland‡, Frederic Staerman§, Pascal Eschwege¶ and Christian Pfister

*Departments of Urology, Rouen University Hospital, Rouen, §Reims University Hospital, Reims and ¶Kremlin-Bicêtre University Hospital, Kremlin-Bicêtre; and Departments of Oncology, *Poitiers University Hospital, Poitiers, †Maurice Tubiana Center, Caen, ‡Nantes University Hospital, Nantes, France*

Accepted for publication 16 March 2007

Type of Study – Therapy (case series)
Level of Evidence 4

OBJECTIVES

To assess in a phase II open multicentre study the efficacy and tolerance of docetaxel administered every 14 days combined with celecoxib, in patients with hormone-refractory prostate cancer (HRPC), and to test the hypothesis that this therapeutic combination would improve overall survival.

PATIENTS AND METHODS

In all, 48 patients were included with a mean age of 70.4 years and Gleason score of 7.5, all had a satisfactory Karnofsky performance-status score of 92% and a metastatic bone site was measurable in 77%. The mean delay between initial diagnosis and docetaxel administration was 45 months, with a median PSA level increase of 54.8 ng/mL. The therapeutic schedule was: docetaxel (50 mg/m^2) administered every 14 days (one cycle of two injections at 2 week intervals (Day 1 = Day 28) with a total of six cycles) and simultaneously a daily oral fixed dose of celecoxib (800 mg).

RESULTS

In all, 237 cycles of docetaxel were administered with a dose reduction in 23 patients at the beginning of a cycle (day 1) and 36 in the middle of a cycle (day 14). The haematological toxicity included anaemia grade 1–2 (78%) and only 10% neutropenia grade 3–4. However, there was only a 15% improvement of pain intensity. The response rate for the total PSA level was 45.5 (30.4–61.1)%, the mean time to progression was 9.3 months and the tumour-response rate was 26.3%. In all, 75% of patients had an overall survival of >14.6 months.

CONCLUSION

Our results confirm the usefulness of docetaxel for HRPC treatment and show a significant reduction of haematological toxicity with bi-weekly docetaxel administration combined with celecoxib.

KEYWORDS

prostate cancer, hormone refractory, docetaxel, bi-weekly, celecoxib.

INTRODUCTION

Prostate cancer continues to be the most lethal malignancy diagnosed in American men and the second leading cause of male cancer mortality, with 220 000 cases and 29 000 deaths annually in the USA [1,2]. Over 60 years ago, Huggins and Hodges [3] discovered androgen deprivation as an effective first-line therapy for metastatic prostate cancer. Although this therapeutic approach frequently leads to significant cancer control lasting for 2–3 years, it ultimately progresses to a hormone-refractory prostate cancer (HRPC) status resulting in significant morbidity and death [4,5]. Multiple mechanisms of androgen independence have been reported, including amplification of the androgen receptor as well as signal transduction pathways that completely bypass the androgen receptor [6]. In 2004, two landmark studies reported a survival advantage in patients with HRPC following docetaxel chemotherapy, which set a new standard of care for this disease. Chemotherapy can reduce serum PSA levels in patients with HRPC and should relieve pain in 35% of patients [7,8]. However, the survival benefits are limited, suggesting that a rationally designed therapeutic approach is required [9,10].

At the end of the 1970s, researchers found elevated concentrations of prostaglandins present in cancer tumours, which suggest that arachidonic acid metabolites might play a role in carcinogenesis [11]. It was therefore suggested that the over-expression of cyclooxygenase-2 (COX-2) could play a significant role in apoptosis inhibition or an alteration in cellular cycle regulation in the epithelial cells of the gastrointestinal tract [12]. Some authors have investigated the possible role of a COX-2 inhibitor in prostate cancer cell apoptosis induction, in an attempt to reduce tumour growth and improve the potential effect of chemotherapy drug efficacy [13].

The aim of this multicentre phase II trial (called Prostacox) was to evaluate the efficacy and tolerance docetaxel every 2 weeks combined with celecoxib daily, in patients with HRPC. The primary endpoint was a reduction in serum PSA levels by at least half. The secondary endpoints were predefined as objective tumour response according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, an improvement in quality of life (QoL) using an analogue scale-pain evaluation, and finally overall survival.

PATIENTS AND METHODS

Five university hospital centres participated in this non-randomized, open-label, docetaxel

Variable	Value
Number of eligible patients	48
Median (range):	
Age, years	70.4 (48–90)
Gleason score	7.5 (5–10)
KPS score, %	92 (60–100)
Previous treatment, %	
Prostatectomy	33
Radiotherapy	40
Hormone therapy	100
Median (range) time between diagnosis and first perfusion, months	54.10 (2.3–148.4)
Bone metastases, %	77
Evidence of progression at entry, %	
Bone scan	56
Increase in measurable lesions	33
Increase in non-measurable lesions	17
Increased PSA level	88

TABLE 1
The patients' baseline characteristics

combined with celecoxib phase II trial. All eligible patients had histologically confirmed adenocarcinoma of the prostate, with clinical or radiological evidence of refractory cancer to standard therapy (maximum androgen blockade). Disease progression with confirmation of an increase in the PSA level, on three consecutive measurements according to American Society of Clinical Oncology (ASCO) criteria, was required for inclusion in the study. In all, 77% of patients had metastatic disease confirmed by CT and/or bone scanning.

No treatment with cytotoxic agents (including mitoxantrone and estramustine), or radioisotopes (strontium), or zoledronic acid was administered prior to patient inclusion in the study. Corticosteroid treatment except chemotherapy premedication was prohibited. Pain, analgesic intake and QoL were assessed at baseline: a pain visual analogue scale was self-recorded weekly, whereas a medication questionnaire was completed at each chemotherapy session. All patients provided written informed consent, and the study was approved by the local Hospital Ethics Committee in accordance with the international standards of good clinical practice. Independent data and safety monitoring were also considered for our study.

Patients, enrolled in this prospective trial, received 50 mg/m^2 docetaxel (Taxotere®, Sanofi-Aventis), in 1-h i.v. infusions, on day 1 then every 14 days. Six cycles were planned and anti-emetic medication was prescribed according to local standard protocol, as well as 8 mg dexamethasone premedication (12 and 1 h before chemotherapy administration). Simultaneously, 800 mg/day of celecoxib (Celebrex®, Pharmacia-Pfizer) was given orally to the patients throughout the chemotherapy cycle.

Professor Pfister was responsible for the study design in collaboration with Sanofi-Aventis personnel. The protocol was completed after being reviewed by the other co-authors, Profs. Tourani, Staerman, Drs Allain, Rolland, Eschwege and Albouy. The data were collected and maintained by Rouen Clinical Research Unit personnel. The authors dealt with all questions regarding management of the study and the independent statistical analysis performed.

A two-steps Simon minima-maxima analysis was used with a $P = 20\%$ maxima effectiveness (13 patients required) and a $P = 40\%$ minima efficacy (30 patients required). Kaplan–Meier curves were used to estimate rates of overall survival and progression-free survival. Survival was defined from the date of randomization to the date of death from any cause or censored at the date of the last contact. Progression-free survival was defined as the time from randomization to the first occurrence of objective or PSA progression or death from any cause. The general chi-square test was used to compare rates of response (objective and PSA) and adverse events; $P = 0.05$ was considered statistically significant.

RESULTS

From January 2003 to November 2004, 48 patients, median (range) age 70.4 (48–90) years, were included in the present study. The median (range) delay between initial prostate cancer diagnosis and treatment with docetaxel combined with celecoxib was 45 (2.3–148.3) months. The baseline characteristics of the patients showed that 33% had had radical surgery and 40% prostate radiotherapy before hormonal treatment, which was received by all patients until HRPC status. The median Gleason score was 7.5 (5–10) and the Karnofsky performance status (KPS) score was satisfactory (mean 92%) (Table 1). On three consecutive measurements, according to ASCO criteria, there was a mean (median, range) PSA level increase of 272 (54.8, 6–3992) ng/mL. Bone metastatic localization was found in ≈80% of cases, with a single metastatic site in 31 patients.

TREATMENT

Due to adverse events and/or KPS score, chemotherapy was administered in 48 patients with a total of 237 cycles: 33 patients (70%) received six cycles as previously scheduled, one received four cycles, nine received three cycles, three received two cycles and two received only one cycle. The mean number of cycles per patient was 4.9. At day 1, with docetaxel administration, 23 dose reductions occurred, i.e. a reduction of 50 to 40 mg/m^2 between day 14 of the previous cycle and day 1 of the current cycle. Similarly, at day 14 of a treatment cycle, 36 dose reductions occurred, i.e. a 30% reduction of 50 to 40 mg/m^2.

The relative dose intensity was defined as the ratio between dose intensity received vs dose intensity scheduled in our protocol. For the 237 cycles administered, the mean value was 98% per cycle and 97% per patient, which confirmed satisfactory compliance. By contrast, administration of celecoxib (800 mg daily) was discontinued in 45% of patients, possibly due to daily oral administration and poor compliance in this aged population, rather than COX-2 inhibitor side-effects.

EFFICACY AND QOL

The primary endpoint was the reduction in serum PSA levels of at least half, as well as objective CT and/or bone scanning tumour

FIG. 1. PSA level response curve for the Prostacox phase II trial patients.

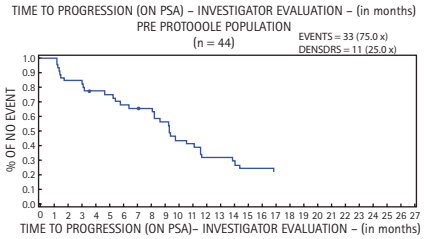

FIG. 2. Kaplan–Meier overall survival curve for the Prostacox phase II trial patients.

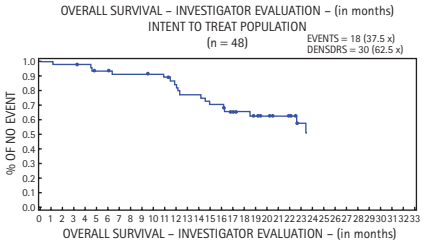

TABLE 2 Toxicity of chemotherapy per cycle

	NCI Common Toxicity Criteria grade				
Toxicity, n (%)	0	1	2	3	4
Haematological					
Anaemia	29 (12.24)	185 (78.06)	20 (8.44)	1 (0.42)	2 (0.84)
Leukopenia	236 (99.58)	0	1 (0.42)	0	0
Neutropenia	139 (58.65)	54 (22.78)	31 (13.08)	11 (4.64)	1 (0.42)
Thrombocytopena	235 (99.16)	2 (0.84)	0	0	0
Anorexia	232 (97.89)	2 (0.84)	3 (1.27)	0	0
Non-haematological					
Nausea/vomiting	217 (91.56)	18 (7.59)	1 (0.42)	1 (0.42)	0
Diarrhoea	220 (92.83)	13 (5.49)	3 (1.27)	1 (0.42)	0
Constipation	231 (97.47)	5 (2.11)	1 (0.42)	0	0
Fatigue	173 (73)	57 (24.05)	5 (2.11)	2 (0.84)	0
Stomatitis	236 (99.58)	1 (0.42)	0	0	0
Myalgia	234 (98.73)	3 (1.27)	0	0	0
Alopecia	184 (77.64)	45 (18.99)	8 (3.38)	0	0
Lacrymal side-effects	232 (97.89)	5 (2.11)	0	0	0
Peripheral neuropathy	230 (97.05)	7 (2.95)	0	0	0
Pneumonitis	235 (99.16)	0	2 (0.84)	0	0
Fluid retention	236 (99.58)	0	1 (0.42)	0	0

response. Secondary endpoints were defined as an improvement in the QoL by a reduction in pain and we also tested the hypothesis that this therapeutic combination would improve overall survival.

In all, 20 of 48 patients had a reduction in serum PSA levels of at least half at follow-up, confirmed 4 weeks later. There was a tumour response rate of 26.3% (median time 2.2 months), with a median (range) time to progression of 9.3 (8–11.5) months (Fig. 1). For the patients' QoL, there was a significant improvement of pain (visual analogue scale and medication questionnaire) in only 15% of patients, with pain intensity and KPS score remaining stable in more than half of the population. Overall survival was estimated at >14.6 months in 75% of patients (Fig. 2).

ADVERSE EVENTS

The incidence of grade 3 and 4 neutropenia was low (10% of cycles) and there was no febrile neutropenia. However, anaemia often occurred, 86.5% of cycles had grade 1–2 anaemia, but there was no clinical consequence (Table 2). When considering the maximal grade haematological toxicity per patient, according to the National Cancer Institute (NCI) Common Toxicity Criteria, there was: for neutropenia, 29% grade 1, 27% grade 2, 17% grade 3; for leucopenia, 33% grade 1, 33% grade 2, 9% grade 3; and for anaemia, 75% grade 1, 13% grade 2, 4% grade 3.

We also assessed non-haematological side-effects: anorexia, diarrhoea, nausea/vomiting, constipation, fatigue, stomatis, myalgia, alopecia, lacrymal side-effects, peripheral neuropathy, pneumonitis, and fluid retention Alopecia and fatigue were the most frequently reported adverse events (only 20–25% of patients), but were not considered as an obstacle to treatment. Finally, grade 3 and 4 non-haematological adverse events remained exceptional (<1%) (Table 2).

DISCUSSION

For many years, the treatment of metastatic prostate cancer has been only palliative. Although androgen deprivation remains an effective first-line therapy, the benefits of this treatment for cancer control only lasts for 2–3 years with a subsequent progression to HRPC [5]. The benefits of mitoxantrone combined with corticosteroids have been reported in randomized trials; however, this approach has not improved overall survival [14]. Various phase II studies, using docetaxel chemotherapy, have also shown good PSA responses in up to half of patients [15,16]. Petrylack *et al.* [8] reported an improvement in median survival of nearly 2 months, with docetaxel and estramustine as compared with mitoxantrone and prednisone. Tannock *et al.* [7] reported an improvement in median survival, pain evaluation, serum PSA level and QoL, when docetaxel combined with prednisone was administered every 3 weeks. More recently, Oudard *et al.* [17] showed the advantages of docetaxel-estramustine-prednisone regimens vs mitoxantrone-prednisone in a randomized phase II trial. Those data showed that a rate of PSA decline of half or more and the median time to PSA progression was five times longer with docetaxel. Furthermore, in those studies docetaxel was administered every 3 weeks. Also, the objective of the present multicentre phase II trial was to evaluate, for the first time to our knowledge, the efficacy of and tolerance to combined docetaxel every 2 weeks with daily celecoxib.

With an overall survival of 14.6 months in 75% of patients, a tumour response rate of 26.3% with a median time to progression of 9.3 months, the present results are comparable to review data recently published by Collins *et al.* [18], which confirm the effectiveness of docetaxel in metastatic HRPC. However, the characteristics of the present patients were quite different compared with previous reports. In the present series, most patients had symptomatic bone metastases, a

high serum PSA level, and in particular had not previously received cytotoxic agents (mitoxantrone, estramustine) and also had a longer period between diagnosis and initial chemotherapy administration. Berry *et al.* [19] assessed the QoL and pain in advanced-stage prostate cancer. Those authors reported no statistically significant differences in pain palliation between docetaxel and estramustine vs mitoxantrone and prednisone. Similarly, in the present series there was poor clinical benefit, with a pain palliation improvement in only 15% of patients (analogue scale and medication questionnaire) and a stable KPS score in more than half of the population.

By contrast with Canadian and CALGB 9182 trials [20], which reported severe haematological toxicity with an incidence of grade 3–4 granulocytopenia of almost half, in the present series there were less adverse events with grade 3 and 4 neutropenia occurring in only 10% of cycles (Table 2). Moreover, for the NCI grade haematological toxicity per patient, we also found that most patients had grade 1 neutropenia (29%), leucopenia (33%) and anaemia (75%) as well. These significant results could probably be explained by the following factors: the particular chemotherapy administration schedule (docetaxel every 2 weeks) and absence of estramustine and celecoxib association. In fact, different studies in metastatic breast cancer suggested the safety and efficacy on tumour response with bi-weekly docetaxel administration [21]. Karavasilis *et al.* [22] also concluded that bi-weekly administration of low-dose docetaxel (30 mg/m^2) in patients with HRPC could be considered an effective nontoxic therapeutic option. Moreover, Efstathiou *et al.* [23] reported a higher symptomatic improvement with bi-weekly docetaxel, in association with estramustine and zoledronic acid; 45% of the 49 assessable patients had a PSA response, the median time to progression was 4.4 months and overall survival was 13.3 months. By contrast, they reported more haematological toxicity than in the present series, suggesting that these data could be discussed in relation to the use of estramustine and zoledronic acid vs celecoxib combination.

A PSA level decrease can be obtained with daily continuous dexamethasone, unfortunately with no antitumour activity in patients with HRPC [24]. Regarding COX-2 and prostate cancer, different studies have confirmed that celecoxib could possibly inhibit rising PSA levels in men who have had treatment for prostate cancer. Questions still remain as to whether or not these effects will correlate with an actual decrease in clinical recurrence of prostate cancer [25]. Furthermore, several concerns exist about the safety of using selective COX-2 inhibitors in an older population. It is encouraging that in the present patients there were no significant adverse events using celecoxib, especially cardiovascular toxicity [26]. The combination of docetaxel with celecoxib could possibly explain the significant reduction of chemotherapy haematological toxicity. However, it remains difficult to ascertain the celecoxib benefit in this setting, when nearly half of the patients discontinued medication because of poor compliance.

In conclusion, the establish efficacy of docetaxel and the uncertain overall benefit of estramustine, might suggest new docetaxel combination development and evaluation. We suggest that, the clinical results of bi-weekly docetaxel administration combined with celecoxib in the management of patients with HRPC warrants further confirmation in a larger randomized phase III trial.

ACKNOWLEDGEMENTS

The authors thank Richard Medeiros, Rouen University Hospital Medical Editor, for his valuable advice in editing the manuscript and Julien Blot, Rouen University Hospital Clinical Research Unit for the management of multicentre data collection.

CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Brawley OW, Knopf K, Thompson I.** The epidemiology of prostate cancer part II: the risk factors. *Semin Urol Oncol* 1998; **16**: 193–201
2 **Jemal A, Tiwari RC, Murray T *et al.*; American Cancer Society.** Cancer statistics, 2004. *CA Cancer J Clin* 2004; **54**: 8–29
3 **Huggins C, Hodges GV.** Studies on prostate cancer. I. The effect of castration, estrogen and androgen injections on serum phosphatases in Metastatic carcinoma of the prostate. *Cancer Res* 1941; **1**: 293–5
4 **Prostate Cancer Trialists' Collaborative Group.** Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. *Lancet* 2000; **355**: 1491–8
5 **Goktas S, Crawford ED.** Optimal hormonal therapy for advanced prostatic carcinoma. *Semin Oncol* 1999; **26**: 162–73
6 **Sonpavde G, Hutson TE.** New approaches in hormone refractory prostate cancer. *Am J Clin Oncol* 2006; **29**: 196–201
7 **Tannock IF, de Wit R, Berry WR *et al.*; TAX 327 Investigators.** Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; **351**: 1502–12
8 **Petrylak DP, Tangen CM, Hussain MH *et al.*** Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004; **351**: 1513–20
9 **Calabro F, Sternberg CN.** Current indications for chemotherapy in prostate cancer patients. *Eur Urol* 2007; **51**: 17–26
10 **Clarke NW.** Management of the spectrum of hormone refractory prostate cancer. *Eur Urol* 2006; **50**: 428–39
11 **Hawk ET, Viner JL, Dannenberg A, DuBois RN.** COX-2 in cancer – a player that's defining the rules. *J Natl Cancer Inst* 2002; **94**: 545–6
12 **Steinbach G, Lynch PM, Phillips RK *et al.*** The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000; **342**: 1946–52
13 **Liu CH, Chang SH, Narko K *et al.*** Overexpression of cyclooxygenase-2 is sufficient to induce tumorigenesis in transgenic mice. *J Biol Chem* 2001; **276**: 18563–9
14 **Kantoff PW, Halabi S, Conaway M *et al.*** Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. *J Clin Oncol* 1999; **17**: 2506–13
15 **Picus J, Schultz M.** Docetaxel (Taxotere) as monotherapy in the treatment of hormone-refractory prostate cancer: preliminary results. *Semin Oncol* 1999; **26** (Suppl. 17): 14–8

16 **Di Lorenzo G, Pizza C, Autorino R *et al.*** Weekly docetaxel and vinorelbine (VIN-DOX) as first line treatment in patients with hormone refractory prostate cancer. *Eur Urol* 2004; **46**: 712–6
17 **Oudard S, Banu E, Beuzeboc P *et al.*** Multicenter randomized phase II study of two schedules of docetaxel, estramustine, and prednisone versus mitoxantrone plus prednisone in patients with metastatic hormone-refractory prostate cancer. *J Clin Oncol* 2005; **23**: 3343–51
18 **Collins R, Trowman R, Norman G *et al.*** A systematic review of the effectiveness of docetaxel and mitoxantrone for the treatment of metastatic hormone-refractory prostate cancer. *Br J Cancer* 2006; **95**: 457–62
19 **Berry DL, Moinpour CM, Jiang CS *et al.*; Southwest Oncology Group.** Quality of life and pain in advanced stage prostate cancer: results of a Southwest Oncology Group randomized trial comparing docetaxel and estramustine to mitoxantrone and prednisone. *J Clin Oncol* 2006; **24**: 2828–35
20 **Tannock IF, Osoba D, Stockler MR *et al.*** Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol* 1996; **14**: 1756–64
21 **Gomez-Bernal A, Cruz JJ, Garcia-Palomo A *et al.*** Biweekly docetaxel and vinorelbine in anthracycline-resistant metastatic breast cancer: a multicenter phase II study. *Am J Clin Oncol* 2003; **26**: 127–31
22 **Karavasilis V, Briasoulis E, Siarabi O, Pavlidis N.** Biweekly administration of low-dose docetaxel in hormone-resistant prostate cancer: pilot study of an effective subtoxic therapy. *Clin Prostate Cancer* 2003; **2**: 46–9
23 **Efstathiou E, Bozas G, Kostakopoulos A *et al.*** Combination of docetaxel, estramustine phosphate, and zoledronic acid in androgen-independent metastatic prostate cancer: efficacy, safety, and clinical benefit assessment. *Urology* 2005; **65**: 126–30
24 **Storlie JA, Buckner JC, Wiseman GA, Burch PA, Hartmann LC, Richardson RL.** Prostate specific antigen levels and clinical response to low dose dexamethasone for hormone-refractory metastatic prostate carcinoma. *Cancer* 1995; **76**: 96–100
25 **Pruthi RS, Derksen JE, Moore D.** A pilot study of use of the cyclooxygenase-2 inhibitor celecoxib in recurrent prostate cancer after definitive radiation therapy or radical prostatectomy. *BJU Int* 2004; **93**: 275–8
26 **McGettigan P, Henry D.** Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006; **296**: 1633–44

Correspondence: Christian Pfister, Department of Urology, Rouen University Hospital, Charles Nicolle, 1, rue de Germont, 76031 Rouen Cedex, France.
e-mail: christian.pfister@chu-rouen.fr

Abbreviations: **HRPC**, hormone-refractory prostate cancer; **COX-2**, cyclooxygenase-2; **RECIST**, Response Evaluation Criteria in Solid Tumors; **ASCO**, American Society of Clinical Oncology; **QoL**, quality of life; **KPS**, Karnofsky performance status; **NCI**, National Cancer Institute.