

Pilot trial of adjuvant paclitaxel plus androgen deprivation for patients with high risk prostate cancer after radical prostatectomy : results on toxicity, side effects and quality-of-life

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ABSTRACT

Therapeutic strategy remains unclear with no clear consensus for men with high-risk prostate cancer after radical prostatectomy. We aimed to evaluate into a prospective randomized trial the effectiveness and the feasibility of adjuvant weekly paclitaxel combined with androgen deprivation therapy (ADT) in these patients. 47 patients with high risk prostate cancer were randomized 6 weeks after radical prostatectomy: ADT alone versus combination of ADT and weekly paclitaxel. Toxicity, quality-of-life and functional results were compared between the two arms. All 23 patients completed 8 cycles of paclitaxel. Toxicity was predominantly of grade 1-2 severity. There were no differences in EORTC QLQ-C30 scores between the two groups and between baseline and last assessment at 24 months after surgery. Urinary continence was complete at one year after surgery for all patients and no significant differences was noted at each assessment between the two groups. The interim analysis of this trial confirms the feasibility of weekly paclitaxel in combination with androgen deprivation therapy in men at high risk prostate cancer with curative intent. This adjuvant combined therapy does not alter quality-of-life and continence recovery after surgery plus ADT. A larger cohort is awaited to determine the oncological outcomes of this strategy.

INTRODUCTION

Prostate cancer (PCa) is the most common solid malignancy in men in EU and the second cause of death attributable to cancer [1]. Despite of the widespread use of prostate-specific antigen (PSA) screening some patients are still diagnosed with a locally advanced prostate cancer. Therapeutic strategy remains unclear with no clear consensus for these men. Nomograms have also been established to better characterize high risk patients and predict the probability of prostate cancer recurrence for each patient [2]. Importantly, after radical prostatectomy (RP), histoprognostic risk factors for disease recurrence and disease specific survival include extracapsular extension, high Gleason score, positive surgical margins, seminal vesicle invasion and positive lymph nodes [3].

For patients with high risk prostate cancer according to the preoperative d'Amico criteria, radical prostatectomy alone leads to cancer cure in about 50% of cases [4]. Relapse is mostly due to distant micrometastasis and combination therapy should be proposed. The goal of adjuvant therapies would be to control and/or treat distant micrometastases. However, no adjuvant standard treatment after surgery is clearly recommended for high risk tumors. Adjuvant hormone therapy significantly improves survival in patients with positive lymph nodes with clear benefit for immediate androgen deprivation therapy [5,6]. In case of negative lymph nodes, this survival advantage has not been demonstrated [7]. Neo-adjuvant hormonotherapy failed to show overall survival rate increase [8]. Thompson et al. demonstrated recently that adjuvant radiation therapy improved specific survival in men with pT3 disease [9].

Taxane-based chemotherapy has been shown to prolong overall survival in patients with hormone-refractory prostate cancer [10,11]. Recently, adjuvant weekly docetaxel or paclitaxel after RP for patients with high risk prostate cancer has been demonstrated feasible with acceptable toxicity [12,13]. The Veterans Affairs Cooperative Study 553 has been designed to prospectively evaluate the efficacy of early adjuvant chemotherapy using docetaxel and prednisone added to the standard of care [14].

We reported the first randomized clinical trial evaluating adjuvant androgen deprivation therapy (ADT) with or without weekly paclitaxel after RP. The aim of our manuscript was to determine in an interim analysis the toxicity and the adverse effects of adjuvant paclitaxel after prostatectomy in patients at high risk for occult micrometastatic disease.

METHODS

Patient population.

Patients were identified prospectively at the Department of Urology in Mondor Hospital (Créteil, France). High risk prostate cancer was defined by a PSA level ≥ 20 ng/ml and/or a Gleason score ≥ 8 and/or pT3b-T4 and/or pN1. Adenocarcinoma of the prostate must be histologically confirmed on biopsy. All patients were with a life expectancy greater than 10 years. No metastatic disease was detected during physical examination, standard radiography, bone scan and computerized tomodensitometry. Additional inclusion criteria were no prior hormone therapy, radiotherapy or systemic treatment for prostate cancer, no other malignancy (except treated non-melanomatous skin cancer). No patient had contraindication for surgery or taxane administration. Patients with contraindication for anesthesia, serious cardiac disease (NYHA class II or III heart failure or recent myocardial infarction) were excluded. Written informed consent was obtained from all patients, and the study met institutional review board guidelines. The hospital's Ethics committee approved the study and the good clinical practice criteria were respected.

Treatment and monitoring.

All patients underwent retropubic or retroperitoneal laparoscopic radical prostatectomy with lymph node dissection for high risk progression prostate cancer. Randomization was performed 6 weeks after radical prostatectomy. In this prospective randomized study of adjuvant paclitaxel and androgen deprivation therapy (ADT) versus ADT alone, the patients at high risk of progression were randomized after RP

between paclitaxel 100 mg/m² once a week for 8 weeks and ADT for 3 years (PACLI) versus ADT alone for 3 years. Premedication consisted of dexamethasone 10 mg, ranitidine 50 mg and dexchlorpheniramine 5 mg and were administered by intravenous infusion 30 minutes before paclitaxel. Antiemetic treatment was based on ondansetron. Androgen deprivation therapy associated gonadotrophin-releasing hormone agonist and non-steroidal anti-androgen for 1 month, and then gonadotrophin-releasing hormone alone for 3 years. Patients with pN1 cancer received indefinite androgen deprivation therapy.

Patients were reevaluated weekly during chemotherapy before each cycle with physical examination, PSA level, routine chemical profile and complete blood count. During ADT alone, this complete assessment was performed every 4 months for first year and every 6 months for next 4 years. Intent-to-treat analysis was performed.

Primary and secondary goals of the study.

The primary goal was to evaluate the toxicity and the feasibility of this new protocol (adjuvant paclitaxel plus ADT) among patients with high risk prostate cancer. At each visit, toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0). Dose modifications were based on toxicity. In case of hematologic toxicity, dose reductions of paclitaxel to 75 mg/m² or 50 mg/m² were performed. Chemotherapy was delayed for thrombocytopenia <50,000 or neutropenia <1,000. Paclitaxel dose was decreased to 50 mg/m² in case grade 3 or 4 non-hematologic toxicity.

Secondary goals were to determine the impact of adjuvant chemotherapy on quality-of-life and functional results after RP. All patients prospectively completed self-administered questionnaires concerning their quality-of-life (EORTC QLQ-C30) and

their voiding and sexual (IIEF-5) disorders, preoperatively and 1, 3, 6, 12 and 24 months after RP. Urinary continence was defined as the absence of pads.

Statistical analysis.

Preoperative oncologic and clinical parameters were compared in order to confirm the statistical equivalence of the two groups. The qualitative data were tested using a chi-square test or Fisher's exact test as appropriate and the quantitative data using Mann-Whitney test (two-sided tests). The limit of statistical significance was defined as $p < 0.05$ using SPSS 13.0 (Chicago, Illinois) software.

RESULTS

Patient baseline.

Between February 2005 and October 2007, 47 patients were enrolled in this study and treated at the Hospital Henri Mondor, Créteil, France. Mean and median follow-up was 30.6 and 29.8 months (range: 8.4 to 48.9). Baseline patient and tumor characteristics were shown in Table 1 and compared as appropriate. The two groups were comparable with no significant difference regarding clinical and pathological predictive factors of progression.

Drug delivery and toxicity.

All 23 patients completed 8 cycles of paclitaxel for a total of 184 cycles administered. One cycle of chemotherapy was delayed in 4 patients because of rhinopharyngitis in 2 cases and positive uroculture in 2. No dose reduction was performed.

Toxicities are listed in Table 2. Results are expressed using the National Cancer Institute patient toxicity criteria Version 3.0. Alopecia was constant but reversible. Fatigue lasted an average of 2.5 days after each cycle. There was no reported grade 4 toxicity. No transfusion was required. Anemia mainly appeared after the second cycle, thrombocytopenia after the third cycle and neutropenia after the fourth cycle. No patient developed infusion reaction to paclitaxel. The cardiac heart failure was attributed to an initial lack in the baseline treatment and was not imputed to paclitaxel. The febrile neutropenia was documented as pulmonary infection needing hospitalization after the eighth cycle. Four patients had neurological disorders in fingers (grade II toxicity) which have been resolved between two and six months after the last cycle.

Functional results (see Table 3).

There were no differences in EORTC QLQ-C30 scores between the two groups and between baseline and last assessment at 24 months after surgery ($p=0.59$).

The IPSS score was improved by surgery and no differences appeared between ADT and PACLI groups. Urinary continence was complete at one year after surgery for all patients in each group and no significant differences was noted at each assessment between the two groups. In PACLI group, 3 patients reported a moderated reappearance of urinary leaks with complete resolution after chemotherapy. There were no differences for IIEF-5 scores between ADT and PACLI groups during the therapy course.

DISCUSSION

Optimal treatment in men at high risk for disease progression following local therapy is undefined. Neo-adjuvant or adjuvant therapies such as radiotherapy, ADT or chemotherapy have been studied, combined or isolated, but no standard of care is clearly recommended [5,6,7,8,15,16,17]. Thus, the role of neo-adjuvant or adjuvant cytotoxics remains unclear for high risk prostate cancer.

Accumulating clinical and preclinical data suggest that the use of early adjuvant therapy will improve the outcome in patients with high-risk localized prostate cancer. Recently, Thompson et al. demonstrated that adjuvant radiotherapy after RP significantly reduced the risk of metastasis and increased survival in pT3N0 disease [9]. At the time of the beginning of our trial, these improvements in metastasis-free and overall survival were not statistically significant [18]. Adjuvant radiation therapy is not sufficient to control and/or treat distant micrometastases. Chemotherapy represents an interesting treatment option [19]. The hypothesis is that androgen-independent tumor cells are responsible for disease progression and patient mortality. Adjuvant weekly taxane-based chemotherapy after RP for patients with high risk prostate cancer was recently demonstrated feasible with acceptable toxicity [12,13]. Kibel et al reported a median progression-free survival (PFS) that appeared better than the Kattan nomogram predicted PFS [12]. Cetnar et al demonstrated in a non randomized trial feasibility of paclitaxel associated with estramustine but with no ADT [13]. Randomized pilot trials are warranted. In this sense, the Veterans Affairs Cooperative Study 553 has been designed to prospectively evaluate the efficacy of early adjuvant chemotherapy using docetaxel and prednisone added to the standard of care [14].

Our current study tests a sequential dose-dense of weekly administration of paclitaxel (cumulative dose: 800 mg/m²) for which the feasibility and efficacy has been assessed previously [20-21]. To our knowledge, our series is the first randomized clinical trial evaluating adjuvant ADT with or without weekly paclitaxel after RP.

All patients included in this study was men at high risk of disease progression according to PSA level and pathological assessment [2,4]. No statistically significant differences appeared between the two groups of treatment (ADT versus PACLI) for all studied predictive factors. However, seminal vesicle invasion and positive lymph nodes were more frequent in ADT group. On the contrary percent of Gleason score >8 and extracapsular extension were greater in PACLI group. Differences did not reach significance. Such differences were due to the low number of included patients and should be compensated by the randomized inclusion of new cases. However, the absence of stratification on the lymph node status was a major bias in the study design.

The combination of weekly paclitaxel and ADT demonstrated a reproducible feasibility and was well tolerated over eight cycles of chemotherapy. Dose modifications or reductions were uncommon. Only 4 patients required dose delays. In agreement with another study of adjuvant paclitaxel, few patients (4.3%) encountered serious hematologic toxicity [13]. The incidence of any grade of neuropathy was 17.4%, no grade 3 or 4 cumulative sensory toxicity occurred. No patient experienced anaphylactic reaction. The use of adjuvant paclitaxel combined with ADT in an elderly population was tolerable. Toxicity was predominantly of grade 1-2 severity with a small proportion of cases with severe side effects.

Importantly, the quality-of-life was maintained in all patients treated by ADT with or without weekly paclitaxel, reflected by the fact that there were no significant differences between total scores at baseline and any subsequent times and between the two groups for the EORTC QLQ-C30 instrument. Overall quality-of-life was well maintained throughout the course of therapy. Interestingly, quality-of-life improved 1 month after RP, a finding that has been observed in other oncologic studies for patients achieving complete or partial responses with therapy. The quality-of-life due to urinary symptoms score decreased and then increased due to continence recovery at 6-12 months after surgery. A moderated increase or reappearance of urinary leaks was observed in 3 patients of PACLI group with complete resolution after chemotherapy. This phenomenon explained the moderately delayed return in continence and the slower improvement of the quality-of-life due to urinary symptoms score in the PACLI group. However, all patients were continent at 12 months after RP that was consistent with our previous published functional results obtained after surgery alone (with no adjuvant therapy) [22,23]. Updated functional results after 1085 consecutive laparoscopic prostatectomies in our department (excluding patients studied in this series) were equivalent in terms of quality-of-life and continence recovery. The EORTC quality-of-life was scored 41, 37, 37, 34, and patients were completely continent in 35.7%, 62.4%, 81.7%, and 96.1% of cases at 1, 3, 6 and 24 months after RP, respectively (data non published).

Actually, a longer follow-up and a larger cohort are awaited to study oncologic results of this randomized trial in terms of progression-free and overall survival in order to determine whether adjuvant paclitaxel adds any survival advantages in high risk

prostate cancer. Preliminary PSA outcomes were encouraging showing that 2 recurrences occurred in the ADT arm and 1 recurrence occurred in the PACLI arm. Clinical progression with bone metastases was reported in these 3 patients with a mean follow-up of 5.7 months after the biochemical progression. All the remaining men were disease-free after a mean follow-up of 30 months.

CONCLUSION

These preliminary data confirm the feasibility and the tolerability of weekly paclitaxel in combination with androgen deprivation therapy in men at high risk of disease progression after radical prostatectomy. Adjuvant therapy does not alter significantly quality-of-life or continence after prostatectomy plus androgen deprivation, and weekly paclitaxel does not lead to worse results in terms of potency than androgen deprivation therapy alone. Oncologic results are awaited to evaluate effects of this combination therapy on progression-free and overall survival.

Abbreviations

ADT: Androgen deprivation therapy alone

PACLI: weekly paclitaxel associated with androgen deprivation therapy

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