

Effect of neoadjuvant epirubicin and total androgen blockade on complete pathological response in patients with clinical stage T3/T4 prostate cancer

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Abstract

Aims: Most patients with stage T3–T4 prostate cancer experience disease relapse despite radiation and/or hormonal therapy, and their management remains controversial. We investigated the feasibility of, and the pathological response induced by neoadjuvant chemo-hormonal treatment in men with clinical stage T3/T4.

Methods: Fifteen patients underwent neoadjuvant therapy consisting of weekly intravenous infusions of epirubicin 30 mg/m² and total androgen blockade (TAB) for three months before undergoing radical prostatectomy, after which all received locoregional conformal radiotherapy (66 Gy) and then continued with TAB and three additional months of epirubicin.

Results: After neoadjuvant therapy, PSA levels decreased in all 15 patients and became undetectable in two. None of the patients achieved a complete pathological response, but a 35–75% reduction in tumour size was observed in all cases, and all the patients were able to undergo successful prostatectomy. Pathological assessments of the surgical specimens revealed negative margins in 13 patients. After a median follow-up of 34 months (range 11–62), 14 patients (93%) are still clinically and biochemically disease free. No grade 3 or 4 complications occurred.

Conclusion: This study suggests that neoadjuvant treatment with epirubicin and TAB is feasible and well tolerated in patients with clinical stage T3–T4 prostate cancer.

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Introduction

Advanced prostate cancer is a heterogeneous disease that has stymied the medical community for decades. Patients with stage T3/T4 prostate cancer and no overt signs of metastatic disease are at high risk of disease recurrence after definitive treatment.^{1,2} Over 50% of patients experience disease relapse despite radiation therapy, hormonal therapy or their combination, and overall survival is poor even in the very few cases amenable to surgical resection, mainly because of occult metastases.³

Neoadjuvant therapy attempts to change the prognosis, and may allow the systemic treatment of undetectable micrometastases. Furthermore, it may increase the number of patients with locally advanced tumours able to undergo radical prostatectomy. As neoadjuvant treatment can lead to a complete pathological response that strongly predicts improved overall survival in solid tumours such as breast cancer,⁴ there is considerable interest in extending its use to other cancers, including high-risk localised prostate cancer. However, randomised trials of neoadjuvant hormonal ablation followed by prostatectomy have failed to demonstrate any improvement in overall survival rates.⁵ Furthermore, the results of trials of neoadjuvant chemotherapy have been somewhat lacklustre because of the lack of tumoral response to ineffective agents.⁶ Doxorubicin has

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shown some activity in the treatment of patients with hormone-refractory prostate cancer (HRPC).⁷ Epirubicin, an analogue of doxorubicin, has proved to be effective in relieving bone pain and improving performance status.⁸

We investigated the feasibility of, and the pathological response induced by neoadjuvant chemo-hormonal treatment with epirubicin and total androgen blockade (TAB) in men with clinical stage T3/T4. The secondary endpoints were toxicity and clinical response.

Patients and methods

Patient characteristics

The entry criteria included histologically confirmed prostate adenocarcinoma clinical stage T3 or T4. Despite their advanced stage, men with clinically minimal pelvic lymph adenopathy may be cured with a pelvic lymphadenectomy, but they were also included as they are still considered to be at high risk.

All the prostate biopsy specimens were reviewed at our institution to confirm the diagnosis and to assign a Gleason score. Digital rectal examination (DRE), chest X-rays, bone scans, abdominal and pelvic computed tomography (CT), and endorectal magnetic resonance images (MRI) were obtained from all patients at enrolment. The patients who had previously received hormone, radiation or chemotherapy for prostate cancer were considered ineligible; the other exclusion criteria were an ECOG performance status of ≥ 2 , active infection, congestive heart failure, or a history of myocardial infarction within the preceding year. All the patients had to have adequate hematological (leukocytes $> 3000 \mu\text{l}^{-1}$, platelets $> 100\,000 \mu\text{l}^{-1}$), renal and hepatic function.

The study was approved by our local Ethics and Scientific Committee, and all the patients gave their written informed consent.

Neoadjuvant treatment and response criteria

Within two weeks of enrolment, neoadjuvant treatment was started with intravenous (i.v.) epirubicin 30 mg/m^2 weekly for 12 cycles, oral bicalutamide 50 mg/day and, after 15 days, subcutaneous (s.c.) LH-RH (leuporelin 3.75 mg) every 28 days, for 3 months.

The men were evaluated weekly to assess response and toxicity. Specifically, they underwent a physical examination including DRE and complete blood counts, and serum PSA measurements were made monthly. Electrocardiography and echocardiography were used to assess left ventricular ejection fraction (LVEF) at baseline and after three months.

Complete and partial responses were, respectively, defined as the complete disappearance or at least a 25% reduction in tumour mass (as assessed by means of imaging techniques) without the appearance of any new lesions, and with stable or $>25\%$ decrease in PSA levels. Stable disease

was defined as a $<25\%$ decrease in tumour mass and PSA levels, without the appearance of any new lesions; disease progression was defined as evidence of new tumour masses, a $>25\%$ increase in existing masses, or a $>50\%$ increase in PSA levels on two successive occasions separated by at least two weeks.

Endorectal MRI was used for both the staging (a maximum of two weeks before the start of neoadjuvant therapy) and the response evaluations (within 10 days of the end of neoadjuvant therapy). The same team of radiologists read the examinations.

Two weeks after completing neoadjuvant therapy, the patients underwent radical prostatectomy and bilateral pelvic lymph node dissection.

After surgery, a complete pathological response was defined as complete tumour eradication, and any pathological downstaging was recorded, also with respect to the pretreatment clinical stage.

Adjuvant treatment

Within three weeks of surgery, all of the men underwent adjuvant radiation therapy to the prostatic bed and pelvis to a total dose of 66 Gy (1.8 Gy/fraction) followed by i.v. epirubicin 30 mg/m^2 weekly for 12 cycles, and androgen deprivation with bicalutamide 50 mg/day and s.c. leuporelin 3.75 mg every 28 days until the occurrence of relapse, or for a maximum of five years.

The patients with stable or progressive disease after neoadjuvant treatment could continue treatment or be given local therapy including radiotherapy.

Pathology

Whole-mount sectioning of the complete radical prostatectomy specimens was used to evaluate the pathological stage of prostate cancer and the status of the resection margins as precisely as possible. The entire surface of the removed and intact prostate was coated with Indian ink and fixed for 48 h in neutral-buffered formalin (4%), and then step-sectioned at 4-mm intervals perpendicularly to the long (apical–basal) axis of the gland. All the sections were stained with hematoxylin–eosin and examined by light microscopy to assess the pathological stage and the status of the resection margins.

Follow-up

The patients were seen one month after the end of radiotherapy, and then every three months during the first year, every four months during the second, and every six months thereafter. At each visit, they underwent DRE, and their serum PSA levels, complete blood cell counts, electrolyte levels, and liver and renal function were determined. Endorectal MRI and/or CT were performed every six months.

A biochemical relapse was defined as a serum PSA level of >0.1 ng/ml on at least three occasions separated by intervals of at least two weeks; the time to relapse was calculated from surgery to the first serum PSA measurement of >0.1 ng/ml.

Statistical considerations

The primary endpoint of the study was to define the complete pathological response (CR) rate after the chemo-hormonal neoadjuvant treatment (i.e., achievement of pT0 status). Several studies reported pathological CR rates of 0% with androgen ablation alone.⁶ Thus, a pathological CR rate of 10% or higher in this study would be a significant finding. Initially, according to a two-stage accrual design, 19 eligible patients will be entered into the study. If one or more pathological CRs are seen in this sample, an additional 16 eligible patients will be entered. If two or more responses are seen out of 35 total eligible patients, the treatment will be considered worthy of further investigation.

Results

Clinical characteristics

The trial was opened in January 2001 and closed on 30 October 2005. We enrolled 15 patients (median age 66 years; range 56–75): 12 in clinical stage T3 (three T3aN0, seven T3bN0, and two T3bN1), and three in stage T4 (two T4N0 and one T4N1); their Gleason biopsy scores were 6–9.

Response to neoadjuvant treatment

All the patients received the neoadjuvant treatment and were evaluable for response and toxicity. PSA levels decreased in all the patients, becoming undetectable (<0.1 ng/ml) in two, and a DRE-revealed reduction in tumour size was demonstrated in all cases. Despite the significant decrease in PSA levels and tumour volume, no complete pathological response was observed (Table 1). Endorectal MRI showed a 35–75% reduction in tumour size; the percentage down-stage was 60%. All the patients were able to undergo successful prostatectomy, and pathological assessments of the surgical specimens revealed negative margins in 13 cases. The Gleason score changed from 7 to 8 in two patients, and from 8 to 9 in one.

Surgical complications

No operative or post-operative mortalities occurred. A variable degree of periprostatic fibrosis increased the difficulty of dissecting the prostate in a manner similar to that observed after neoadjuvant hormonal therapy. The median operative time (skin incision to skin closure) was 175 min (range 128–342), and median blood loss during prostatectomy was 648 ml (range 420–1860 ml). The patients were

Table 1

Main characteristics of 15 prostate cancer patients undergoing neoadjuvant therapy at baseline, and before and after surgery

Criteria	Baseline	Before surgery	After surgery
Gleason score			
6	1	—	1
7	6	—	4
8	5	—	6
9	3	—	4
PSA (ng/ml)			
<0.1	0	2	15
0.1–10	3	13	0
>10	12	0	0
Clinical response by DRE	—	15	—
Clinical response by MRI remission			
35%–50%	—	5	—
50%–75%	—	10	—
Surgical margins			
Positive	—	—	2
Negative	—	—	13
Tumour stage			
T2	0	6	3
T3a	3	6	4
T3b	9	3	7
T4	3	0	1
Lymph nodes			
N0	12	15	15
N1	3	0	0

hospitalised for a median of four days (3–8 days). No post-operative rectal injury was recorded, and 94% of the patients were completely continent (no pads).

Toxicity

The toxicity data indicate that our neoadjuvant approach was well tolerated (Table 2). Neutropenia and anemia were the most frequent side effects, but were grade 1 or 2 in most cases; grade 3 neutropenia was observed in only one patient. There was no case of congestive heart failure, and all the cycles were administered on an outpatient basis.

Table 2

Number of patients experiencing the most frequent treatment-related adverse events (15 evaluable patients)

	Grade 1	Grade 2	Grade 3
Hematological			
Neutropenia	10	4	1
Anemia	5	3	—
Thrombocytopenia	3	2	—
Non-hematological			
Nausea/vomiting	8	4	—
Diarrhea	2	1	—
Constipation	1	1	—
Fatigue	4	2	—
Alopecia	4	6	—
Gynecomastia	8	5	—

Follow-up

After a median follow-up of 34 months (range 11–62), 14 of the 15 enrolled patients are still clinically and biochemically free of disease, and continue to have undetectable serum PSA levels. One patient whose initial clinical stage was T4N1 was classified as T3bN0 after neoadjuvant treatment, but experienced a biochemical relapse 26 months after radical prostatectomy without any evidence of metastatic disease. A CT scan and positron emission tomography (PET) revealed a pathological mediastinal lymph node four months after the biochemical relapse: a CT-guided biopsy confirmed the presence of a metastatic lymph node of prostate cancer origin; no other distant metastases were found. This patient is still alive with a serum PSA level of 3.8 ng/ml, and is now receiving second-line chemotherapy.

Serum testosterone levels were measured before, and every six months after surgery, and remained at castration level (<50 ng/dl) in all the patients.

Discussion

The heterogeneity of the hormone responsiveness of prostate cancer and the limited availability of active chemotherapeutic agents have stimulated research in neoadjuvant treatment of patients with locally advanced disease. However, the use of chemotherapy, hormonal therapy, or their combination before radical prostatectomy is still controversial because of the mixed results.

Our patients with clinical stage T3–T4 prostate cancer received three months' treatment with neoadjuvant epirubicin and TAB, and the high rates of biochemical and clinical responses meant that all of them were able to undergo radical prostatectomy, after which the incidence of negative margins was very high (86.6%).

Neoadjuvant treatment

As far as the chemo-hormonal protocol is concerned, epirubicin was chosen because of our encouraging experience with it in the treatment of advanced prostate cancer, and the 50 mg dose of bicalutamide was chosen because it is the dose that most studies have evaluated in combination with an LH-RH agonist in the neoadjuvant/adjuvant setting.^{7–9}

Comparison with other studies

The biochemical response rate and reduction in tumour size were slightly better than those observed with hormone therapy alone: in some reports, prostate volume and PSA significantly decreased after three months' hormonal treatment before surgery.^{10,11} Although it is difficult to compare our study with others, the inclusion criteria and results are similar to those of a phase II trial by the Southwest Oncology Group, which showed the feasibility of radical prostatectomy

in patients with clinical T3/T4 carcinoma of the prostate after neoadjuvant hormonal therapy: 55 of the 61 eligible patients underwent prostatectomy, with 70% negative surgical margins, and the estimated 5-year progression-free and overall survival rates were, respectively, 70% and 90%.¹²

The high percentage of negative surgical margins and downstaging in our study suggest that chemo-hormonal therapy may make T3/T4 tumours more resectable than hormonal therapy alone. However, it is necessary to point out that the impressive percentages of negative margins in our study and those of others might be a treatment artefact as margin status may be obscured in neoadjuvant studies with androgen deprivation therapy.⁵

No complete pathological response was observed, but it is worth noting that the rate of complete pathological responses rarely exceeds 15% even in relatively chemotherapy-sensitive tumours such as breast cancer.⁴

The reduction in tumour size was established by means of endorectal MRI, but it is known that radiological diagnostic evaluations are not specific enough to establish the presence of prostate cancer within the prostate gland.

Despite the encouraging results, our study was stopped because of excessively slow accrual, which was probably due to some surgeons' inclination to operate, in these cases, without patients having undergone previous neoadjuvant therapy.

Other studies have recently reported the feasibility of neoadjuvant chemo- or chemo-hormonal therapy in high-risk localised prostate cancer. Pettaway et al. treated 33 patients with ketoconazole and doxorubicin, alternated with vinblastine, estramustine and androgen ablation, four of whom experienced grade 3–4 hematological toxicity. No complete pathological response was observed and, after radical prostatectomy, the surgical margins were positive in 17% of the patients; furthermore, 31% experienced a biochemical relapse after a median follow-up of 13 months.¹³

Clark et al. treated 16 patients with three cycles of estramustine and etoposide, 28% of whom experienced grade 3 toxicity. After radical prostatectomy, the positive surgical margin rate was 13%, and the biochemical relapse rate after a median follow-up of 14 months was 12%.¹⁴

Konety et al. studied the feasibility and safety of neoadjuvant estramustine, paclitaxel and carboplatin in 36 patients, 22% of whom experienced deep vein thrombosis. After radical prostatectomy, the positive surgical margin rate was 22%, and the biochemical relapse rate after a median follow-up of 29 months was 55%.¹⁵

The clinical trial by Febbo et al. involved 19 patients treated with neoadjuvant docetaxel, and reported a >50% decrease in PSA levels in 58%, and a clinical response in 68%.¹⁶

Another recent study of 22 men with high-risk clinically localised prostate cancer reported a decrease in PSA levels in 95%, and negative surgical margins in 76% after neoadjuvant mitoxantrone and docetaxel.¹⁷

It is difficult to make comparisons with previous trials because of the heterogeneity of the studied populations

and treatment strategies, and the small size of our own study population. However, our results are intriguing especially because all the patients were in clinical stage T3 or T4, and their Gleason scores were 6–9 (some of the other neoadjuvant studies also included patients in clinical stage T1 or T2, and with lower Gleason scores). These encouraging data may be attributable to the efficacy of the proposed chemo-hormonal protocol. It is worth noting that epirubicin is effective in HRPC, and other authors have reported interesting results with anthracyclines, with most patients experiencing significant palliative effects.^{18,19}

In relation to the above studies, it is true that the neoadjuvant protocol of Pettaway et al. also included an anthracycline (doxorubicin, the more cardiotoxic analogue of epirubicin), but its dose intensity was 10 mg/m²/week and therefore relatively lower than the 30 mg/m²/week of epirubicin administered by us.

Toxicity

As expected, our neoadjuvant chemo-hormonal therapy was well tolerated. Epirubicin-related neutropenia was common, but reached grade 3 in only one patient. The radical prostatectomy was slightly more difficult than in untreated patients due to the desmoplastic reaction around the prostate reported in trials of neoadjuvant hormone therapy.¹¹ However, a comparison with untreated patients taken as historical controls at our institutions showed that the median operation time was only about 30 minutes longer than that usually found, and the intra- and post-operative complications were similar.

Follow-up

Although it was not the primary goal of this study, it is worth mentioning that only one patient experienced a biochemical relapse after a follow-up of 34 months. It is too early to talk about a favourable prognosis and the patients are still on TAB, but the rate of no biochemical evidence of disease is nevertheless excellent. All the patients continue to be monitored every six months by means of DRE, serum PSA measurements and endorectal MRI, and the prolongation of median follow-up will clarify their real prognosis.

Adjuvant therapy

It is difficult to say whether the addition of post-surgical radiotherapy and/or chemo-hormonal adjuvant treatment may help improve prognosis. The role of adjuvant radiotherapy and chemo-hormonal treatment after radical prostatectomy must still be defined, but some studies suggest that they increase biochemical recurrence-free survival in high-risk patients.^{20,21}

Furthermore, on the basis of recent studies of metronomic chemotherapy, it is possible that the apparently favourable prognosis of our patients may also be due to the

antiangiogenic effects of low i.v. doses of epirubicin given at frequent intervals.^{22,23} The continuous or metronomic low-dose chemotherapy allows the administration of cytostatics at low and well-tolerated concentrations without any prolonged interruptions. Furthermore, as antiangiogenic effects cause anti-tumour effects, the continuously administered low-dose chemotherapy may enhance the antiangiogenic effect and thus lead to a marked anti-tumour effect.²⁴

Conclusion

We found that neoadjuvant treatment with epirubicin and TAB was feasible and well tolerated in patients with clinical stage T3–T4 prostate cancer.

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