Weekly paclitaxel and epirubicin in the treatment of symptomatic hormone-refractory advanced prostate carcinoma: report of a phase II trial

B. Neri[a], G. Cipriani[a], C. Fulignati[a], M. Turrini[a], R. Ponchietti[b], R. Bartoletti[c], A. Della Melina[c], V. Di Cello[c], A. Dominici[c], D. Maleci[c], A. Raugei[c], D. Villari[c] and G. Nicita[c]

The efficacy of weekly paclitaxel in androgen-independent prostate cancer and its addictive cytotoxicity with anthracycline derivatives led us to determine the safety and efficacy of a weekly schedule of paclitaxel and epirubicin. Between October 2000 and November 2002, 32 patients were enrolled in this study. Patients characteristics included a median age of 72 years (range 68–77), adequate hepatic, cardiac, renal and bone marrow functions, ECOG performance status of 1–2, and no prior chemotherapy. All patients had received hormonal manipulation and seven patients (22%) had received prior palliative radiation therapy. The regimen consisted of paclitaxel 70 mg/m^2 i.v. infusion for 2 h and epirubicin 30 mg/m^2 in bolus every week. Treatment was continued for 3 months or until disease progression or unacceptable toxicity were observed. During the study, prostate-specific antigen (PSA) was monitored and response was defined as a 50% reduction in PSA levels, to be confirmed 4 weeks later. Thirty-one patients were evaluable for toxicity and 21 for objective response. Seventeen patients (57%) had a decline above 50% in PSA level that lasted more than 4 weeks with a median time to PSA progression and a median duration of PSA response of approximately 5.5 months. Ten of the 21 patients with measurable disease (47%) had a confirmed objective response (one complete response and 20 partial responses). Thirteen of 25 symptomatic patients (56 %) had improvement in pain. The median time to disease progression was 7.6 months and the median survival was 12.9. The most prominent grade 3 toxicities were reversible myelosuppression and fatigue. Nausea, vomiting, diarrhea and peripheral edema were minimal. No evidence of cardiac toxicity was recorded. Alopecia was frequent, but reversible, in all patients. We conclude that despite the small sample size, this study demonstrates that the combination of weekly paclitaxel and epirubicin is a well-tolerated regimen for androgen-independent prostate cancer. The results imply that a combination of these agents in a weekly schedule may have clinical potential in prostate cancer treatment. *Anti-Cancer Drugs* 16:63–66 © 2005 Lippincott Williams & Wilkins.

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[a]Department of Internal Medicine–Experimental and Clinical Oncology Center, University of Florence, Florence, Italy, [b]Urology Clinic, University of Siena, Siena, Italy and [c]Urology Clinic, University of Florence, Florence, Italy.

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Correspondence to B. Neri, Department of Internal Medicine, Oncological Day Hospital (CTO), Largo Palagi 1, 50139 Florence, Italy.
Tel: +39 554279748; fax: +39 554278237;
e-mail: brunoneri@unifi.it

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Introduction

Prostate carcinoma is the primary cause of mortality and morbidity in the male elderly population in Western countries [1], with a further progressive increase of about 3% yearly over the last decade [2]. Prostate carcinoma is a hormone-dependent tumor for which the primary and most effective therapeutic approach to date is androgen blockade. However, although the majority of patients respond favorably to this type of treatment, the duration of such response is often unforeseeable. Randomized trials on the efficacy of androgen blockade in patients with advanced disease have shown a mean time to disease progression of 12–18 months and a mean survival time of 24–36 months [3,4]. This is in agreement with the clonal selection model proposed by Isaac and Coffey [5], according to which the progression of prostate carcinoma primarily involves the hormone-refractory cell population. The available data concerning the chemotherapy treatment of androgen-independent prostate carcinoma (AIPC) are not entirely satisfactory. It should be noted that the evolution of AIPC has been associated with an overexpression of the *bcl-2* oncogene that protects the tumor population from the apoptotic phenomenon induced by most chemotherapeutic agents [6,7]. This is probably the reason why chemotherapy treatments of AIPC have produced only transient responses and/or marginal benefits in terms of symptom palliation [8], while recent clinical trials on the association of

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estramustine, vinblastine, etoposide, paclitaxel or docetaxel have raised new interest on the use of antiblastic chemotherapy in this disease [9–11]. Starting from such considerations, we address three specific issues. First, of the available chemotherapeutic agents, those acting on microtubules have been shown to provide the most promising results. Second, anthracycline derivatives may reduce apoptosis also in the cells of prostate carcinoma that overexpress the *bcl-2* oncogene [12]. Finally, experimental and clinical observations concerning other diseases have shown that the association of paclitaxel (TAX) and epirubicin (EPI) may determine an additive response [13,14]. Based on these premises, and considering the advanced age of most patients, we decided to evaluate the tolerability, first, and then the clinical activity of the TAX–EPI association using a weekly treatment schedule, in order to effectively monitor the co-morbidity directly related to the specific toxicity of the agents used.

Patients and methods

Patients were considered to be eligible for the trial if they had a histologically documented prostate carcinoma in the advanced and/or metastatic phase, that had progressed during standard hormone treatment. Patients were also required to meet the following criteria: informed consent; an Eastern Cooperative Oncology Group performance status of 1–2; normal renal, hepatic, cardiac and bone marrow function; no prior treatment with antiblastic chemotherapy.

The disease was considered to be progressing when any of the following events occurred: an increase in prostate-specific antigen (PSA) levels recorded during two consecutive measurements with at least a 1-week interval between measurements; an increase of more than 25% in the size of metastatic lesions or the appearance of new lesions; appearance of new skeletal lesions as documented by bone scintigraphy.

Androgen blockade, achieved by administering LHRH analogs, was maintained in all patients.

At study entry and before starting the treatment, all patients underwent a thorough medical examination; moreover, standard blood chemical values, serum testosterone levels and PSA levels were also determined. A total-body bone scintigraphy, a specific X-ray of the locations where pain symptoms were reported, and a computed axial tomography of the chest, abdomen and pelvis were also performed.

Treatment schedule

Patients included in the study were treated weekly for 3 months with: TAX 70 mg/m^2 and EPI 30 mg/m^2. TAX was diluted into 500 cm^3 of saline solution and infused within 2 h, followed by EPI diluted into 100 cm^3 of saline solution and infused in bolus. Dexamethasone 8 mg, ranitidine 50 mg and prometazine 50 mg were administered as a prophylaxis for taxol hypersensitivity reactions. Ondansetron 8 mg was administered at the beginning of each treatment course to prevent vomiting. In case of hematological toxicity above grade 2, drug doses were reduced by 25% in the following administrations or the treatment was postponed until a complete recovery was achieved.

Toxicity and response evaluation criteria

The following data were recorded weekly for each patient: vital functions, grade of side-effects and performance status. A complete blood test was also performed weekly. Every 4 weeks, patients underwent a physical examination, PSA levels were measured and target lesions were instrumentally evaluated. For the evaluation of changes in the severity of pain symptoms, the McGill–Melzac oral questionnaire was used [15]. It is a five-point scale, where 0 = no pain, 1 = mild pain, 2 = troublesome pain, 3 = distressing pain, 4 = great pain and 5 = unbearable pain.

A reduction in PSA levels of at least 50% confirmed for at least 4 weeks and a reduction of at least 2 points in the rating scale for pain symptoms were considered as the efficacy criteria. The effect of treatment on measurable lesions was also determined in accordance with the response criteria used for solid tumors (WHO criteria [16]).

Statistical methods

An optimal two-stage design was employed in the protocol [17] using standard statistical methods. If no complete responses (CR) or partial responses (PR) were noted in the first cohort of 14 patients, a response rate of more than 15% could be excluded with a 95% confidence interval, causing the accrual stop. If at least one CR or PR was observed, more than 30 patients were entered in the study to determine the response rate more accurately.

Results

Table 1 shows the characteristics of patients who entered the study. One of the patients quit the study after the third treatment week on account of refusal. Of the 31 patients who completed the treatment, only one reported a CR in lymph nodes localization. Of the other 20 patients who showed measurable lesions, nine (45%) reported a PR (liver, lung, lymph nodes, soft tissues), eight (40%) showed a stabilization of the disease and three (15%) showed a progression of the disease. The median time to disease progression was 7.6 months (range 4.1–10.2), while the median survival time was 12.9 months (range 10.5–24). At the time of this analysis, 16 patients are still alive and four have been followed-up for 24 months.

Table 1 Patient characteristics

Characteristics	No. patients	%
Age (years) [mean (range)]	72 (68–77)	32
ECOG performance status		
0	5	16
1	19	59
2	8	25
Metastatic locations		
bones	24	75
lymph nodes	5	13
lung	3	10
liver	2	7
soft tissues	1	3
pelvis	2	7
Hormone therapy[a]		
LHRH agonists ± antiandrogen agents	32	100
Base line PSA levels (ng/ml)		
range	21–1700	
median	192	
Intensity of pain at study entry (grade)		
0	7	21
1	3	9
2	12	38
3	8	25
4	1	3
5	1	3

[a]During the study, all patients continued their current hormone therapy.

Table 2 Results

Results	No. patients	%
Biological response	31	100
reduction in PSA levels of >50%	18	56
reduction in PSA levels of <50%	7	23
Response to treatment	21[a]	100
CR	1	5
PR	9	43
stabilization	8	38
progression	3	15
Pain symptoms	25	100
improvement	13	56
stabilization	4	16
worsening	8	28

[a]Patients with measurable locations of the disease.

A reduction in PSA levels of above 50% was reported in 17 patients (57%), with a mean duration of response of 5.5 months (range 2.1–7.0), while a reduction in PSA levels of below 50% was observed in seven patients (26%). With regard to pain symptoms, 13 patients out of 25 (56%) reported an improvement, 16% reported a stabilization of symptoms and 28% reported a worsening of symptoms (Table 2).

Overall, the treatment was well tolerated and a total of 254 courses of therapy were administered. In one case (3%), the dose was reduced due to grade 3 hematological toxicity, while in 6% of patients it was sufficient to postpone the following treatment by 7 days. Grade 3 anemia was observed in two patients and leukopenia without fever was reported in two different patients. Table 3 shows a list of the adverse events observed during the study; adverse events are reported by severity grade.

Table 3 Toxicity

Toxicity	WHO grade (%)			
	1	2	3	4
Anemia	19 (63)	10 (33)	2 (6)	–
Thrombopenia	24 (77)	7 (23)	–	–
Leukopenia	17 (54)	12 (40)	2 (6)	–
Nausea/vomiting	21 (67)	10 (33)	–	–
Anorexia/weight loss	21 (67)	10 (33)	–	–
Fatigue	17 (55)	14 (45)	–	–
Alopecia	20 (64)	11 (36)	–	–
Cardiac toxicity	26 (83)	5 (17)	–	–
Liver toxicity	28 (90)	3 (10)	–	–
Renal toxicity	31 (100)	–	–	–
Neurological toxicity	24 (77)	7 (23)	–	–

Discussion

AIPC remains an unsolved problem in the treatment of solid tumors. In the past, chemotherapeutic agents had shown a marginal activity in patients with advanced disease; however, new studies have shown that a promising antiblastic activity is shown by chemotherapeutic agents acting at the level of microtubules, in particular taxanes. Recently, Rosenbaum and Eisemberger reported their experience in a large series of prostate cancer patients with a weekly docetaxel schedule. They observed promising results with this regimen administered both as adjuvant therapy and in patients with advanced stage disease [18,19]. Based on these considerations, and since a weekly EPI regimen has already shown a certain degree of activity in the treatment of advanced prostate carcinoma [20] and clinical trials conducted at the same time on other neoplastic diseases have shown an addictive activity of TAX and EPI [21,22], we planned a phase II trial to verify whether the association of these two chemotherapeutic agents according to a weekly treatment schedule offered a good tolerability and an antiblastic activity sufficient to control the pain symptoms that are often reported during the advanced stage of this disease.

The study showed that the TAX–EPI association may be effective and well tolerated in patients with AIPC, and that weekly administrations of these agents significantly improve the overall tolerability of the treatment. In particular, the treatment schedule adopted was very well tolerated and 97% of patients completed the projected 3-month period of treatment. The most relevant toxicity involved the hematological system, with four patients (12%) who showed anemia and grade 3 leukopenia, respectively. None of the patients reported thromboembolic events or other events associated with cardiac toxicity or fatigue above grade 2. Fifty percent of patients showed a reduction in circulating PSA levels of above 50%; this response was higher that that observed in other studies using other chemotherapeutic agents, in particular estramustine [9–11]. During the study, only one of the 21 patients with measurable disease reported a CR,

nine patients (47%) showed a PR and eight patients (38%) showed a stabilization of the disease; these results are consistent with those observed in other trials using various associations of vinblastine, etoposide, paclitaxel and docetaxel with or without estramustine—although such trials were usually characterized by higher gastrointestinal and thromboembolic toxicities. With regard to the correlation between objective response and reduction in PSA levels, we observed a decrease in PSA levels in all responders, although only four patients reported a reduction of more than 50% compared to baseline. Moreover, none of the patients who were responders for both PSA reduction and objective response showed a progression of the disease until PSA levels remained low. This observation seems to confirm the hypothesis of certain authors, who suggest that a significant reduction in PSA levels may be associated with a better control of symptoms and a longer survival of these patients. The results of this study show that the association of TAX and EPI in a short (12 weeks) weekly treatment schedule may control the progression of AIPC, with a good control of pain symptoms in 56% of patients and with mild, fully reversible toxicities. Moreover, these preliminary results are consistent with those reported in previous studies [18,19], considering treatment tolerability, overall response and PSA reduction. Since most AICP patients are elderly people who often show a number of concomitant diseases as well as a reduced bone marrow function, we believe that symptom control and good tolerability should be the primary objectives to be pursued in the treatment of AIPC. These objectives could be further improved; in patients who were responders in terms of objective response and/or clinical benefit, by administering an intermittent treatment that should be started, as suggested by some authors [23], as soon as the disease resumes its progression.

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