Short-term versus Long-term Addition of Cyproterone Acetate to Buserelin Therapy in Comparison with Orchidectomy in the Treatment of Metastatic Prostate Cancer

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In an open, multicenter, three-armed, randomized study, we compared the effects of short-term (2 weeks) and continuous addition of the antiandrogen cyproterone acetate to the luteinizing hormone-releasing hormone agonist buserelin to those of orchidectomy in patients with advanced prostate cancer. No significant differences among the three treatment arms with respect to response rate, subjective response, time-to-progression, overall survival, and cancer deaths were observed. It was concluded that the short-term or continuous addition of cyproterone acetate to buserelin administered intranasally did not improve treatment results compared to orchidectomy only. *Cancer* 1993; 72:3858–62.

Key words: prostate cancer, complete androgen blockade, luteinizing hormone–releasing hormone agonist, buserelin, antiandrogen, cyproterone acetate, orchidectomy.

Endocrine therapy of prostatic cancer consists of a variety of both medical and surgical ablative treatment modalities.[1–2] In view of the fact that androgens form the most important group of hormones involved in the growth regulation of prostate cancer, most endocrine therapies are designed to suppress androgen secretion and/or antagonize the action of androgen on tumor cells. Although orchidectomy is considered to be the gold standard for the therapy of metastatic prostate cancer, ablative treatment modalities are being replaced increasingly by medical therapy. Several phase II studies and, more recently, some randomized studies, have indicated that medical castration by luteinizing hormone-releasing hormone (LHRH) agonists is as effective as surgical castration or treatment with high dose estrogens, but has virtually no serious side effects.[3–9] During the last years, the most interest regarding endocrine therapy for prostate cancer has been directed at "complete androgen blockade", since Labrie et al.[10–12] reported excellent results with this type of approach in nonrandomized studies. Therefore, suppression of testicular androgen secretion by medical or surgical castration in combination with antiandrogens (either pure or steroidal) to block the remaining adrenal-derived circulating androgens is being applied increasingly in randomized clinical trials.[13–24] The results of these studies are conflicting[13,15] and are now the subject of a metaanalysis.[13]

In 1984, the European Organization for the Research and Treatment of Cancer (EORTC) Genitourinary Group decided to perform two new randomized trials comparing the efficacy of an LHRH agonist in combination with an antiandrogen to standard therapy

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(i.e., surgical castration). Because we had documented in a previous pilot study[25] that biochemical and clinical flare-up of disease, caused by the initial increase of plasma testosterone levels during single LHRH agonist therapy, could be prevented adequately by adding an antiandrogen during the first 2 weeks of treatment, we added a third treatment arm. This arm was designed to compare the efficacy of chronic combination therapy with that of the short-term (2 weeks) addition of an antiandrogen to an LHRH agonist therapy, aiming only at preventing flare-up and not at inducing complete androgen blockade. The present study (EORTC 30843) is the only three-armed study on complete androgen blockade.

Materials and Methods

Only patients with metastatic prostate cancer (M1 or N4M0) were eligible for the trial. Patients were ineligible if they had a second primary malignancy, had received previous endocrine treatment, or had a World Health Organization performance status higher than 2. Skeletal metastases and/or lymph node/soft tissue metastases had to be proven by bone scan and x-rays or by cytodiagnosis. Previous radiotherapy or surgical intervention (for relief of obstruction or radical prostatectomy) was permitted. After stratification for performance status, metastatic status, and medical center, patients were randomized to: (1) undergo orchidectomy; (2) receive buserelin and cyproterone acetate (CPA; three daily doses of buserelin 0.5 mg subcutaneously for 1 week, followed by three daily doses of 400 μg spray intranasally, plus three daily doses of 50 mg CPA for only 2 weeks); or (3) receive the same dosages as group 2, but with CPA administered continuously until tumor progression was evident.

Strict criteria for response and progression were used and comparable with those reported previously.[26] In summary, objective criteria for progression were: (1) a more than 25% increase in the size of known osteolytic, soft-tissue, and/or visceral metastatic lesions; (2) an increase of more than 25% in the primary tumor when measured by ultrasound or of 50% when measured by rectal examination (if primary tumor measured was at least 30 ml or 3 × 3 cm); and (4) new lesions. The primary prostatic tumor could be measured by transrectal echography, computer tomography, or digital examination. Lymph nodes could only be measured by computer tomography, and soft tissue metastases by direct measurement or x-ray. Bone metastases were screened every 6 months by bone scan. New hot spots were accepted as an objective sign of progression only if they were still evident in a subsequent scan, their appearance change in subsequent x-rays, or they were proven by biopsy. Subjective or nonspecific criteria for response were performance status and pain, changes in serum levels of hemoglobin, prostate acid phosphatase, alkaline phosphatase, and prostate specific antigen (optional). Serum testosterone levels were measured to monitor therapy compliance. Although objective progression had to be confirmed by repeated x-rays or bone scans, which often took 1–3 months, the time of first signs of progression were always noted and used to define time to progression. All randomized patients were followed for survival.

Table 1. Eligible Patients by Institution

Inselspital, Bern	50
VU, Amsterdam	48
Erasmus University, Rotterdam	34
J. Gutenberg, Mainz	25
Ramaz, Carpi Modena	23
Chu, Toulouse	22
AMC, Amsterdam	21
Zuiderzh., Rotterdam	14
OLVG, Amsterdam	14
RRTI/DDHK, Rotterdam	11
PR, Hull	11
CS La Paz, Madrid	10
St. James Hospital, Leeds	9
AVL, Amsterdam	8
Varese	7
St. Maria, Lisbon	7
St. Franc. Roosendaal	6
WA, Den Bosch	6
AZ, Leiden	5
St. Maartens, Kortrijk	5
Sternberg, Rome	4
Refaja, Dordrecht	3
Palermo	3
AZ, Gent	1
Total	347

Results

Between November 1984 and September 1989, 368 patients were entered in this study by 24 institutions. Of the 222 patients evaluated thus far by the study coordinator, 21 patients have been deemed ineligible. Patient entry for the 347 eligible patients is given by institution in Table 1. The distribution of patients and disease characteristics (Tables 2 and 3) were well balanced among the three treatment groups.

In the 136 patients evaluated for response, an objective response (complete response and partial response) was observed in 54%, 47% and 45% of the patients in the treatment groups one, two, and three,

Table 2. Patient Characteristics at Entry on Study

Characteristic	Total no. (%)*
Age (yr)	
< 60	35 (10)
60–69	111 (33)
70–74	75 (22)
75–79	76 (22)
> 80	43 (13)
Unknown	7
WHO performance status	
0	177 (52)
1	130 (38)
2	30 (9)
3	3 (1)
Unknown	7
Pain at entry	
None	155 (46)
Mild	110 (32)
Moderate	61 (18)
Severe	8 (2)
Intractable	6 (2)
Unknown	7
Weight loss	
< 5%	234 (77)
6–10%	44 (15)
11–20%	23 (8)
> 20%	1
Unknown	45
Cardiovascular disease	
Yes	144 (42)
No	196 (58)
Unknown	7
Leg edema	
Yes	38 (11)
No	302 (89)
Unknown	7

* Percentage of total numbers of patients with known results.

respectively (Table 4). After 6 weeks of therapy, of those patients who had no pain at entry (Table 2), 90% remained free of pain while 10% reported pain. Of those patients who had mild pain at entry, after 6 weeks, 56% were free of pain, 36% still had mild pain, and 8% were worse. In those patients who had at least moderate pain at entry, 71% were better after 6 weeks, 25% had experienced no change, and 4% were worse. Among the patients still alive, the median duration of follow-up is 189 weeks. At this time, 239 patients (69%) have shown tumor progression, and 244 (70%) have died with a median duration of survival of approximately 2 years. There were no significant differences overall among the three treatment groups with respect to response rate, degree of pain relief, time to progression, or duration of survival.

Toxicity consisted mainly of hot flushes in up to 56% of the patients during treatment. The occurrence of hot flushes was reported less frequently by the pa-

Table 3. Disease Characteristics in 347 Eligible Patients

Characteristic	Total no. (%)
Stage	
M1	319 (92)
M0N4	28 (8)
T category	
0	6 (2)
1	10 (3)
2	35 (11)
3	160 (49)
4	116 (35)
Unknown	20
N category	
0	85
1	8
2	14
3	4
4	92
Unknown	144
Histopathologic grade	
1	39 (12)
2	144 (43)
3	148 (45)
Unknown	16
Bone metastases by bone scan	
Yes	301 (89)
No	31 (9)
Suspicious	8 (2)
Unknown	7
Site of metastases	
N4 only	28 (8)
Bone	301 (88)
Visceral	15 (4)
Soft tissue	1 (< 1)
Unknown	7
Alkaline phosphatase	
≤ 1.25 N	155 (46)
1.26–2.5 N	79 (24)
2.5–5 N	53 (16)
5.1–10 N	30 (9)
> 10 N	18 (5)
Unknown	12
Prostatic acid phosphatase	
≤ 1.25 N	63 (19)
1.26–2.5 N	64 (19)
2.6–5 N	52 (16)
5.1–10 N	41 (12)
> 10 N	113 (34)
Unknown	14
Hemoglobin ≤ 12.5 μ/dl	63 (19)
Creatinine ≥ 1.25 N	33 (10)

Table 4. Tumor Response in 136 Patients Evaluated for Response

	CR	PR	NC	PD	Insufficient data	Total
Orchidectomy	11 (23)	15 (31)	10 (21)	5 (10)	7 (15)	48 (100)
BUS + CPA 2 wk	10 (19)	14 (28)	9 (17)	10 (19)	9 (17)	52 (100)
BUS + CPA continuous	5 (14)	11 (31)	8 (22)	2 (5)	10 (28)	36 (100)
Total	26 (19)	40 (29)	27 (20)	17 (13)	26 (19)	136 (100)

Values in parentheses are percentages.

CR: complete response; PR: partial response; NC: no change; PD: progressive disease; BUS: buserelin; CPA: cyproterone acetate.

tients who were treated with CPA continuously (45%), however, than by the patients who underwent orchidectomy (63%) or in whom CPA was stopped after the first 2 weeks (61%). Gynecomastia was reported only by 9% of the patients. In only two patients who were treated with buserelin and CPA continuously did treatment have to be discontinued due to pain caused by nasal irritation (1 patient) and multiple episodes of severe epistaxis accompanied by the development of angina pectoris and congestive heart failure (1 patient). In five patients, side effects necessitated a change in treatment. One patient who underwent orchidectomy had severe hot flushes, and CPA was added to his treatment. In two patients in group 2, treatment was modified as follows: CPA was added to the treatment of one patient who reported severe hot flushes, and the nasal spray was temporarily stopped in the other patient due to epistaxis. Finally, in two patients in group 3, CPA was stopped due to gastrointestinal side effects.

Discussion

Our study confirmed the results of other studies, which showed that medical castration by an LHRH agonist is as effective as surgical castration. Furthermore, we demonstrated that the short-term addition of an antiandrogen for 2 weeks prevents the occurrence of biochemical and clinical flare-up of disease. Flare-up can occur in the first week of single treatment with LHRH agonists as a consequence of the initial stimulation of the pituitary-gonadal function before the effects of medical castration are reached (after about 3 weeks).[25,27] Monitoring of the plasma testosterone levels indicated that these testosterone levels remained low as long as buserelin was taken.

More important is the question whether complete androgen blockade improves clinical outcome.[13,14] Labrie et al.[11] reported a 96% response rate and long-term survival in patients with metastatic prostate cancer who were treated with medical castration in combination with a pure antiandrogen, the goal of which was to block remaining circulating androgens derived mainly from the adrenals. Although the strikingly good results of the nonrandomized studies of Labrie[10–12] were never confirmed by consecutive randomized studies, some of these randomized studies showed a minor but significant advantage of combined treatment modalities over single treatment (medical or surgical castration) with respect to response rate, subjective response, or progression-free and overall survival as parameters.[13,15,16,19,28] Our three-armed randomized study, however, did not show any beneficial effect of continuous combination treatment compared to that of medical or surgical castration alone in regard to these parameters. Previously the EORTC Genitourinary Group did not observe any additional beneficial effect by adding CPA to orchidectomy.[22] The absence of a greater antitumor effect of the combination treatment in our study might be explained by the following: (1) different dosages, types, and modes of administration of the drugs used; (2) the prevention of a possible flare-up by administration of CPA for 2 weeks in the control group continuously treated with buserelin alone; (3) lack of an extra beneficial effect of the combination treatment, per se; or (4) incomplete androgen blockade. A recent review of 765 patients in nine different series found that 10.9% had suffered disease-flare and that 15 had died in the presence of acute symptoms of exacerbation.[29] Flare may explain the difference observed between the two treatment groups in the study by Crawford et al.[16]: Disease progressed more rapidly in patients treated with the LHRH agonist leuprolin during the first 3 months, after which the survival curves became parallel. It has to be recognized, however, that some studies also found that combined treatment with an LHRH agonist plus an antiandrogen offered a better result than orchidectomy, which was used as the control arm (e.g., EORTC trial 30853)[19] or when an antiandrogen was added to treatment by surgical castration.[18,24] It is striking that those studies, which demonstrated a better effect of combination treatment (though mostly minor and occurring early), used a pure antiandrogen in their combi-

nation treatment modality. In contrast, other studies that used pure antiandrogens did not demonstrate any extra beneficial effect of these agents and sometimes even suffered a greater rate of patients drop-out because of the side effects of pure antiandrogens.[13-15,23] Therefore, it may be concluded that large randomized trials comparing the efficacy of pure and steroidal androgens, especially in combination with surgical or medical castration, are strongly warranted.

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