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A RANDOMIZED DOUBLE-BLIND STUDY EVALUATING ANANDRON® ASSOCIATED WITH ORCHIECTOMY IN STAGE D PROSTATE CANCER

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Summary—A randomized double-blind study with a 3-yr follow-up comparing the two arms "orchiectomy + Anandron® (300 mg)" vs "orchiectomy + placebo" in 125 patients with stage D prostate cancer has confirmed the beneficial effects of the combined Anandron® therapy on subjective parameters and on the best objective response (NPCP criteria), although these effects were not statistically significant, but failed to detect any improvement in time-to-disease progression or survival. Comparison with the results of other trials emphasizes the urgent need to establish suitable prognostic factors by further clinical research before evaluating the benefits of individual drugs.

INTRODUCTION

Although Huggins *et al.* [1] suggested that surgical castration might be a successful palliative treatment of advanced prostate cancer, the responses as determined in controlled trials on the basis of objective criteria (NPCP, UICC, etc.) have not been spectacular: about 30% of patients experience a positive response and 40% have stable disease. Devising a therapy directed against androgen-dependent tumor cells in the prostate or in metastases to improve upon this score is a considerable challenge.

Medical castration by LH-RH-analogs has only proven as successful as orchiectomy (for examples, see [2, 3]) and, moreover, this therapy is associated with an early rise in LH and testosterone (T) that can lead to isolated but sometimes very severe cases of disease flare (e.g Ref. [4]). Therefore, to improve upon the results of castration, a combination therapy has been proposed that associates a non-steroid anti-androgen to castration by LH-RH-analogs [5–7]. The advantage of this "total androgen blockade" lies in the elimination of all known sources of androgen influence on prostate cancer growth, i.e. it both suppresses testicular T synthesis and blocks the action of androgens on target cell receptors. Several studies have indeed indicated that the prostate tissue levels of dihydrotestosterone after castration are not negligible and these are presumed to arise partly from conversion of adrenal precursors [7–12].

If remanent tissue androgen levels can sustain or promote tumor proliferation, it is logical to block their formation by, for instance, the use of 5α-reductase inhibitors presently under development or, better still, block their action by interfering with the effective function of androgen receptors (AR) implicated in hormone-dependent cell proliferation. Several anti-androgens that compete for AR binding but with different activity profiles are available: cyproterone acetate, flutamide, Anandron® (nilutamide), Casodex (ICI 176,334) (for reviews, see Refs, [13–19]). Cyproterone acetate binds to several steroid hormone receptors (AR, progesterone and glucocorticoid receptors) and is a progestin with pituitary inhibitory activity whereas flutamide, its active metabolite hydroxyflutamide, and Anandron bind to only AR and probably exert their antiandrogenic activity *via* this mechanism. Nevertheless, high circulating levels of Anandron can also inhibit the formation of Δ_4-androstenedione and lead to accumulation of 17-hydroxy-pregnenolone presumably by inhibition of $C_{17,20}$ lyase [20, 21]. Flutamide exerts a similar action [22]. None of

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these anti-androgens is a competitive inhibitor of 5α-reductase.

Since the initial clinical pharmacology studies establishing a striking decrease in prostatic acid phosphatase on initiation of combination therapy with Anandron [5], later confirmed in double-blind trials [23], and since the spectacular claims of F. Labrie regarding the clinical efficacy of combined therapy [24], a number of trials have been initiated with the above anti-androgens in combination with castration (surgical or medical) in order to refute or substantiate these claims. Although little doubt seems to persist on the rationale of short-term administration of an anti-androgen to prevent any undue disease flare on inception of LH-RH-analog treatment [5, 23, 25–28], controversy still prevails over the need to pursue the combination to block the action of adrenal androgen metabolites.

Published clinical data on combination treatments using nonsteroid anti-androgens have highlighted a gain in survival and/or increase in time-to-progression with buserelin + Anandron [29], leuprolide + flutamide [30] and, to a lesser extent, in the first short-term analysis of a trial with leuprolide + Anandron [31, 32]. Greater efficacy of the combination treatment has not been confirmed in a study on Zoladex® + flutamide [33]. Non-comparative trials have been performed vs orchiectomy (ORX) (e.g. Zoladex + flutamide vs ORX) [34], but only the anti-androgen Anandron has been used in trials comparing ORX + anti-androgen to ORX + placebo [29, 35–38]. The overall pooled results of several trials show a trend in favor of the combination treatment [38, 39] which has been recently confirmed by the results of a large multicentric study [40].

In April 1983 we also initiated a randomized double-blind multicenter trial comparing ORX + Anandron to ORX + placebo. The preliminary analysis with a median follow up of 23.4 ± 8.9 months has been published [38, 39] and we now report the results of the final analysis.

PROTOCOL DESIGN

Nine centers in France participated in the study. The consulting physicians were A. Caty (Centre Oscar Lambret, Lille), J. Couette (Centre François Baclèse, Caen), J. Douchez (Centre Claudius Regaud), J. P. Droz (Institut Gustave Roussy, Villejuif), P. Fargeot (Centre François Leclerc, Dijon), P. Kerbrat (Centre Eugène Marquis, Rennes), P. Mangin (Centre Hospitalier Régional Morvan, Brest), A. Petiot (Clinique Générale de Bourgogne, Chalon sur Saône) and J. Toubol (Hôpital Pasteur, Nice). Treatment was allocated according to a separate balanced randomization for each center.

Patients with histologically proven stage C or D prostate cancer were eligible for admission unless they had already received some form of hormonal treatment. Previous radiotherapy to the prostate region was an exclusion criterion for stage C patients, but not for stage D patients if the metastases were outside the radiation field. All patients were recruited between April 1983 and December 1986.

The following data were recorded at admission, at 1 and 3 months, and then every 3 months: physical status, clinical symptoms, rectal, abdominal or perineal ultrasound, and levels of prostatic acid phosphatase and of plasma hormones. An intravenous pyelogram, a bone scan, and lung, pelvis and spine radiographs were performed at admission, and then every 6 months; CAT scans and lymphography were performed when necessary.

Efficacy of treatment was evaluated on the basis of symptoms: bone pain (analgesics could be prescribed as needed to alleviate pain), lower urinary tract obstruction and performance status; prostatic acid phosphatase levels, reponse according to the National Prostate Cancer Project (NPCP) criteria [41] (successive bone scans of almost all patients at each center were reviewed "blind" by one and the same person): time to progression of cancer; interval between initiation of treatment and disease relapse as given by the dates on the case report form (patients with progressive disease on placebo were treated at the discretion of the investigator but most often received Anandron); and time to death from cancer or another cause.

The eligibility criteria, the follow-up visit schedule and the case reports forms were the same as in several other studies on Anandron. The data of all these trials were analyzed by the same statisticians.

PATIENTS AND DEMOGRAPHIC CHARACTERISTICS

At the time of analysis in March 1990 all patients had more than 3 yr of follow-up. 151 patients had been recruited: 125 were stage D, 26 were stage B or C. Only the results for stage

Table 1. Comparability of pretreatment characteristics in stage D evaluable patients

	Orchiectomy + placebo	Orchiectomy + Anandron	*P*-value
Age (yr)			
Mean	72.4	71.6	0.55[a]
Range	52–87	56–88	
Weight (kg)			
Mean	67.2	70.2	0.14[a]
Range	39–95	49–93	
Local spread of cancer			
Intracapsular	49%	52%	0.77[b]
Extracapsular	51%	48%	
Distant spread of cancer			
D1		4%	
D2 (lymph nodes)	2%	—	
Bone only	86%	88%	0.67[b]
Soft tissue (± bone)	12%	9%	
Hemoglobin			
< 12 g/dl	33%	27%	0.49[b]
> 12 g/dl	67%	73%	

[a] Wilcoxon rank sum test.
[b] χ-square test.

Table 2. Comparability of efficacy variables in stage D evaluable patients

	Orchiectomy + placebo (%)	Orchiectomy + Anandron (%)	*P*-value[a]
Metastasis related pain			
None	55	61	
Moderate	32	21	0.33
Severe	12	18	
Urinary obstruction			
None	35	37	
Moderate	43	37	0.73
Severe	22	26	
Performance status			
Normal	27	23	
Symptomatic	43	36	0.44
Impaired	30	42	
Prostatic acid phosphatase			
≤ N	24	27	
N–5 N	29	33	0.70
> 5 N	48	40	
Alkaline phosphatase			
≤ N[b]	47	66	
N–2 N	19	13	0.11
> 2 N	34	21	

[a] χ-square test.
[b] N = normal value.

Table 4. Best objective responses (NPCP criteria)

	O + P[a]	O + A[a]	*P*-value[b]
n[c]	59	45	
CR	2 (3%)	1 (2%)	
PR	29 (49%)	30 (67%)	
CR + PR	31 (52%)	31 (69%)	0.09
Stable	19 (32%)	10 (22%)	
Progression	9 (16%)	4 (9%)	

[a] O = orchiectomy, P = placebo, A = Anandron.
[b] χ-square test.
[c] *n* = number of patients who met NPCP assessment criteria and have been in the study for at least 6 months.

D patients will be analyzed here. Of these, 65 had been orchiectomized and had received 300 mg Anandron daily kindly supplied by Roussel–Uclaf, France. Twelve patients were excluded from the efficacy analysis (4 in the placebo group and 8 in the Anandron group): 9 for incorrect staging, 2 for previous hormone therapy and 1 with a life expectancy of less than 3 months. The two arms were well balanced with respect to inclusion criteria (Tables 1 and 2).

RESULTS

There were consistent, although not statistically significant, subjective improvements in bone pain, obstructive symptoms and performance status on administration of Anandron (Table 3). The best objective response (NPCP criteria) recorded at any time in patients who had been in the study for at least 6 months (Table 4) was complete or partial response (CR + PR) for 52% of the patients in the orchiectomized + placebo group vs 69% in the orchiectomy + Anandron treatment group. The number of patients with progressive disease fell from 16 to 9% on association of Anandron. These differences between the two groups in favor of Anandron were on the borderline of statistical significance ($P = 0.09$).

Table 3. Subjective and biochemical improvements

		Improvement (%)				
		Pts (*n*)	Mo 1	Mo 3	Mo 6	*P*-value[a]
Bone pain	O + P[b]	27	78	85	81	NS
	O + A[b]	21	81	95	94	
Obstructive symptoms	O + A	42	57	63	69	NS
	O + A	35	51	83	81	
Performance status	O + P	40	47	58	57	NS
	O + A	39	62	71	77	
Prostatic acid phosphatase	O + P	42	36	51	50	NS
	O + A	33[c]	45	66	69	

[a] Wilcoxon rank sum test on differences with baseline score. NS = not significant.
[b] O = orchiectomy, P = placebo, A = Anandron, Pts (*n*) = number of patients, Mo = month.
[c] Number of patients with abnormal baseline.

Table 5. Overall incidence of adverse experiences

	Orchiectomy + placebo ($n = 78$)	Orchiectomy + Anandron ($n = 72$)	P-value[a]
Body as a whole	14 (18%)	15 (21%)	0.65
Cardiovascular	9 (12%)	11 (15%)	0.50
Digestive	7 (9%)	22 (31%)	0.001
Endocrine	13 (17%)	13 (18%)	0.82
Metabolic and nutritional	6 (8%)	4 (6%)	0.59
Musculoskeletal	3 (4%)	2 (3%)	1.00
Nervous system	7 (9%)	7 (10%)	0.87
Respiratory	4 (5%)	7 (10%)	0.27
Skin and appendages	4 (5%)	7 (10%)	0.27
Ocular	2 (4%)	13 (18%)	0.004
Total number of patients with one or more adverse experiences	45 (58%)	56 (78%)	0.008

[a] χ-square test.

Table 6. Detailed incidence of adverse experiences

	Orchiectomy + placebo ($n = 78$)	Orchiectomy + Anandron ($n = 72$)
Digestive system		
Cholelithiasis	—	1 (1%)
Constipation	—	1 (1%)
Diarrhea	—	2 (3%)
Dysphagia	1 (1%)	—
Gingivitis	—	1 (1%)
Rectal bleeding	—	1 (1%)
Hepatitis	—	2 (3%)
Cirrhosis of liver	1 (1%)	—
Melena	—	1 (1%)
Nausea	2 (3%)	6 (8%)
Intestinal obstruction	—	1 (1%)
Gastrointestinal pain	1 (1%)	3 (4%)
Anorexia	—	3 (4%)
Pancreatitis	—	1 (1%)
Vomiting	—	3 (4%)
Gastrointestinal carcinoma	2 (3%)	2 (3%)
Total	7 (9%)	23 (31%)
Ocular side effects		
Imparied adaptation to darkness	1 (1%)	9 (12%)
Chromatopsia	—	2 (3%)
Diplopia	—	1 (1%)
Eye disorder	2 (3%)	2 (3%)
Abnormality of accommodation	—	1 (1%)
Cataract	1 (1%)	—
Total	3 (4%)	13 (18%)

The actuarial progression-free rate was not statistically different between the two arms ($P = 0.96$) nor was any difference observed in time to death from prostate cancer or from any other causes.

Placebo and drug were generally well tolerated. 45/78 patients of the placebo group experienced some side-effects while these occurred in 50/72 (78%) of the Anandron group (Table 5). The difference in tolerance mainly concerned the digestive and ocular [42] systems (Table 6). The initial dosage was modified because of adverse reactions in 12 patients (5 in the placebo group and 7 in the Anandron group). Eight patients (1 in the placebo group and 7 in the Anandron group) definitively discontinued treatment and one patient temporarily.

DISCUSSION

In the present study, administration of the nonsteroid anti-androgen Anandron increased the objective response rate by 17% over orchiectomy, even though this increase was not statistically significant ($P = 0.09$). This value can be compared with the 22 and 28% improvements recorded in two other trials based on the same protocol [29, 35, 36] and with the 8 and 13% improvements obtained with Anandron or flutamide in two trials where surgical castration was replaced by LH-RH analog administration [30–32] (Table 7). So far, a gain in time-to-progression or in survival has been observed in two trials [29, 30, 36] but, in our study on a total of 113 evaluable stage D patients, no such difference was noted. However, the results of a recent multicenter study [40] on over 400 evaluable patients have established a significantly longer progression-free survival in the orchiectomy plus Anandron group that confirms the above trends always in favor of the addition of an anti-androgen.

Although association of anti-androgen therapy to castration can and does benefit certain patients, we are not yet able to distinguish the reasons for success or failure. Discrepancies in trial results could be due to differences in

Table 7. Best objective responses recorded in castration ± anti-androgen trials

	Orchiectomy + placebo (%)	Orchiectomy + anti-androgen (%)	P-value	Statistical improvement in time to prog. and survival
Béland	16	38[a]	0.004	Yes
Brisset	33	61[a]	<0.02	No
Namer	52	69[a]	0.09	No
	Leuprolide + placebo (%)	Leuprolide + anti-androgen (%)		
Crawford	35.3	43.6[b]	NS	Yes
Crawford	38	51[a]	0.01	Too early

[a] Anandron.
[b] Flutamide.

the protocols (e.g. possibility of treatment of patients in relapse with the study drug), differences in the drugs (e.g. Anandron vs flutamide), differences in the size and characteristics of the patient population in spite of similar selection criteria. Tumors that have evolved in the hypogonadic aging male may well respond differently from tumors in the younger patient and not until suitable prognostic factors have been established [43–47] can we hope to differentiate clearly between treatments. Furthermore, tumors evolve towards hormone independence [48]. If it is possible to halt or delay this evolution by appropriate hormone manipulation [7, 49], antihormone treatment will only have a significant inhibitory effect on disease progression either if it is initiated much earlier than stage D and/or if it comprises an additional element of site-directed cytotoxicity. A cytotoxic action of high Anandron concentrations on rat prostate cell-lines has been reported [50] and may contribute towards the efficacy of this drug known to have molecular targets other than the steroid hormone receptor [51, 52]. An ingested single massive dose equivalent to 43 times the therapeutic dose has proven to be inoffensive [53].

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