Eur J Cancer, Vol. 27, No. 9, pp. 1100–1104, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Phase II Study of the Pure Non-steroidal Antiandrogen Nilutamide in Prostatic Cancer

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The activity of the pure non-steroidal antiandrogen nilutamide as a single agent was evaluated in 44 patients with metastatic carcinoma of the prostate. Objective (partial) response rates (95% confidence limits) were 38.5 (18.7)% in 26 previously untreated patients and 5.5 (11%) in 18 patients progressing on primary androgen suppressive procedures. The most frequent side-effects were decreased adaptation to darkness (29.5%), slight nausea (31.8%) and alcohol intolerance (18.2%). In addition, treatment was discontinued in 3 patients because of gastrointestinal symptoms. A non-significant increase in testosterone levels was shown in the untreated group during the first month of treatment, after which the levels remained stable. About half of the sexually active men claimed the maintenance of libido and sexual potency during treatment. Although our study confirms a significant incidence of visual disturbances, the activity data coupled with the ability of maintaining sexual interest suggest that single therapy with non-steroidal antiandrogens may deserve comparison to conventional endocrine treatment in controlled trials.
Eur J Cancer, Vol. 27, No. 9, pp. 1100–1104, 1991.

INTRODUCTION

THE CONTRIBUTION of extragonadal androgens (mainly of adrenal source) in the growth promotion of human prostate cancer has recently received increased consideration [1, 2], to the extent that the use of antiandrogens (i.e. androgen receptor antagonists) in addition to androgen-suppressive procedures has gained widespread acceptance in the management of advanced prostatic cancer [3]. Among antiandrogens, pure non-steroidal compounds have received much attention in that, unlike steroidal molecules such as cyproterone acetate, they are devoid of any androgenic activity [4, 5], do not interfere with other steroid hormone receptors [4, 5] and do not have antigonadotropic activity due to the progestational component, which, in turn, may be responsible for serious complications [6]. Studies in humans have shown that this pure and specific antagonistic action interferes with the negative feedback of androgens at hypothalamic level, resulting in an increase in luteinising hormone (LH) and consequently in a rise of testosterone levels [7, 8]. Based on extrapolations in animals, such hypergonadotropic hypergonadism has been claimed in humans as a progressively increasing phenomenon, which may ultimately neutralise the effect of the antiandrogen [7]. For this reason, modalities that lower circulating testosterone levels were sought as adjuvants to non-steroidal antiandrogens, and therefore the experience with these agents as sole therapy is scanty. Conversely, a theoretical advantage of the non-steroidal compound in maintaining serum testosterone levels is preservation of libido and potency, which is desirable in the palliative management of younger patients.

A pure non-steroidal antiandrogen that has become recently available is nilutamide (Anandron) [7]. Its mode of action is comparable to that of flutamide [9], the first non-steroidal compound available in clinical practice [10]. Conversely, nilutamide has a longer half-life than flutamide [11] and does not need to be converted into an active metabolite to exert its action [5]. However, while flutamide as single agent has been tested in some pilot studies [10, 12, 13], nilutamide alone has never undergone any investigation and the current data regarding its activity and toxicity derive from studies combining the drug with orchiectomy or LH releasing hormone (LHRH) agonists to achieve a total androgen blockade [14–17].

We have therefore investigated the clinical activity, toxicity and endocrine and haematological effects of nilutamide as monotherapy of metastatic prostate cancer in a phase II study.

PATIENTS AND METHODS

The trial was designed as a cooperative multi-institutional study performed by the investigators of the Italian Prostatic Cancer Project. Patients were considered eligible if they had untreated, histologically confirmed stage D prostatic cancer, with evaluable lymph-node or bone metastases; a performance status (according to the WHO score system) between 0 and 3; and life expectancy greater than 3 months. Exclusion criteria were the following: age above 75, unless performance status was between 0 and 1; presence of heart, renal or liver failure; or any previous other neoplasm except non-melanomatous skin cancer. Since most investigators were interested in testing the activity of the drug not only in untreated disease, an additional subset of patients who had progressed on a first-line androgen suppressive procedure was also included. Written consent was obtained from each patient after the study had been approved by the ethics committee of the National Institute for Cancer Research of Genoa. Patients were then registered by phone at the clinical trials office of the same institute. Nilutamide, supplied by Roussel Pharma, Milan, in 50 mg tablets, was administered at the daily oral dose of 300 mg (2 tablets every 8 h), according to pharmacokinetic data available at the time [5, 7, 9]. The drug

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Revised 5 June 1991; accepted 19 June 1991.

Table 1. Patients' characteristics

Entered	44
Median age (range)	71 (54–82)
Median performance status (range)	1 (0–3)
Stage of disease (AUS)	
D1	5
D2	39
Primary tumour (UICC)	
T2	4
T3	27
T4	13
Grading (Gaeta system)	
G1	3
G2	18
G3	16
G4	7
Previous treatment	
None	26
LHRH agonist	8
Cyproterone acetate	6
Orchiectomy	2
Estramustine phosphate	2
Median duration of primary treatment (range)	15 months (3–72)

Table 2. Overall objective response

	Untreated		Pretreated	
	n	%	*n*	%
PR	10/26	38.5 (18.7)	1/18	5.5 (11)
SD	11/26	42.3 (18.9)	12/18	66.7 (22)
PD	2/26	7.7 (11.8)	3/18	16.7 (17)
NE	3/26	11.5 —	2/18	11.1 —

PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.
95% confidence limits are given in parentheses.

was started in pretreated patients provided that previous hormonal administration had been suspended for at least 4 weeks (or 5 weeks if depot LHRH agonists had been employed) but not longer than 6 weeks. The main characteristics of patients are summarised in Table 1. Pretreatment evaluation included complete blood haematology and biochemistry, including prostatic acid phosphatase; chest X-ray; bone scan with skeletal films of pathological areas; transrectal ultrasounds and computed tomography (CT) of the pelvis; and hepatic ultrasounds if liver enzymes were altered. The patients were clinically evaluated at monthly intervals for the first 3 months and every 3 months thereafter, with laboratory studies performed at each visit. Complete imaging investigations were performed at 3-month intervals. All patients' records were centrally reviewed by two independent clinicians. The NPCP criteria were used to evaluate response [18]. Since objective regressions in the hormone-relapsing disease are uncommon and difficult to assess, the behaviour of serum prostate-specific antigen (PSA) was also included as a reliable indicator of minimal antitumour activity in pretreated patients.

In a subgroup of 12 untreated patients followed at the coordinating centre of Genoa, blood samples were taken to simultaneously measure the following hormones: LH, testosterone and oestradiol. In 11 pretreated patients serial concentrations of PSA were also centrally measured. All determinations were performed in duplicate by RIA using commercially available kits purchased from Diagnostic Product Corporation (Los Angeles). The intra-assay and interassay coefficients of variation were below 7% and 12%, respectively. Normal levels were as follows: LH, 5–20 U/L; testosterone, 3.6–9.6 ng/ml; oestradiol 6–44 pg/ml; and PSA, below 2.5 ng/ml. Finally, since prolonged antiandrogen therapy might also affect erythropoiesis [19], haemoglobin levels of the untreated cases were studied in comparison with a similar group of 56 stage D2 patients treated with a LHRH agonist [20], who served as controls. 6 patients complaining of visual disturbances (decreased adaptation to darkness) were submitted to complete ophthalmological check, which included psychophysical tests, darkness adaptation (measured with a modified Goldman–Weekers adaptometer) and electroretinogram (ERG), performed using stimulation with full-field flashes under photopic and scotopic adaptation (Amplaid MK 15).

Actuarial survival and progression-free survival were estimated from the study entry using the Kaplan–Meier curves. Results of serum studies are given as the mean (S.E.). Differences in LH, testosterone and oestradiol concentrations at different times were tested by analysis of variance and the Scheffe method to account for multiple comparisons. The paired *t* test was applied to the PSA variations in the pretreated cases. The effect of the treatments on haemoglobin levels were tested using multiple linear regression. All data were analysed using BMDP statistical software [21].

RESULTS

Response to therapy

44 patients were included between March and December 1986. 5 patients were unevaluable for response: 3 patients refused the follow-up procedures before the first 3 month evaluation and 2 patients were prematurely withdrawn because of a rash and vomiting, respectively. Overall best objective response (95% confidence limits) stratified by previous treatment is summarised in Table 2. In more detail, in the untreated group there were 6 (25%) partial responses (PR) in bone, 6 PR (23%) in prostate and 5 (50%) responses in lymph-nodes (2 complete). Another PR in bone was also recorded in the pretreated group. Comparison of serum PSA concentrations in 11 pretreated cases before and after 3 months of nilutamide administration revealed a significant mean decrease [from 113.1 (S.E. 33.1) to 61.7 (22.5) ng/ml, $P < 0.05$], even though the normal level was achieved in only 1 case. Following progression on nilutamide, 13 patients of the untreated group received a second-line anticancer therapy, which consisted of LHRH agonists (9 cases) or chemotherapy (4 cases). 5 patients [38.5 (26.5)%], all treated with the agonist, obtained a partial response lasting 4, 5, 6, 10 and 11 months, respectively. Progression-free survival (PFS) and survival curves of both groups are shown in Fig. 1. In the

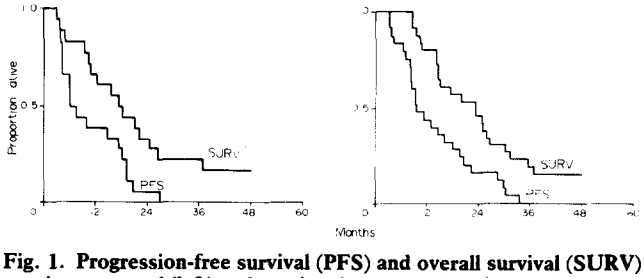

Fig. 1. Progression-free survival (PFS) and overall survival (SURV) in pretreated (left) and previously untreated patients (right).

Table 3. Main toxicity

Nausea (grade 1)	14 (31.8)
Decreased adaptation to darkness	13 (29.5)
Alcohol intolerance	8 (19.2)
Vomiting (grade 2)	2 (4.5)
Diarrhea (grade 1)	1 (2.3)
Abdominal cramps	2 (6.8)
Altered transaminases (grade 1)	1 (2.3)

No. (%).
Grades by WHO classification.

untreated group, the median PFS was 9 months and the median survival was 23 months. In the pretreated patients, the median PFS and the median survival were 6 and 17 months, respectively.

Side-effects

The main toxic effects are listed in Table 3. Treatment was discontinued in 3 patients because of moderate nausea and vomiting in 2 and abdominal cramps in the third. A higher incidence of visual complaints was reported among the patients seen at the coordinating centre (8 out of 17, 47.1%) with respect to the collaborating centres (5 out of 27, 18.5%). 6 of the 13 patients complaining of decreased adaptation to darkness were submitted to ophthalmological check, which revealed an altered darkness adaptation curve in 5, consisting mainly of elevated final threshold with abnormal ERG at periphery. Visual complaints reversed in all patients on cessation of therapy. Intolerance to alcohol intake consisted mainly of hot flushes and rash. Androgen-related effects were evaluated in untreated cases. Gynecomastia developed in 44.1%, including 2 patients who had been treated with LHRH analogues, while 53.8% complained of hot flushes. Sexual potency was assessed by interview. Of the 15 patients who had declared themselves to be sexually active before treatment, 7 (46.7%) claimed maintenance of potency during nilutamide administration and those who subsequently received LHRH agonists for disease progression, claimed loss of libido and erectile function.

Serum studies

The behaviour of hormones is illustated in Fig. 2. LH levels increased substantially from 17.5 (1.6) to a maximum of 56.5 (6.7) U/l after 6 months ($P < 0.01$). Testosterone levels showed a non-significant rise after 1 months of treatment [from basal 3.72 (0.5) to 5.12 (0.9) ng/ml] and plateaued thereafter. Serum oestradiol levels had a similar behaviour [from 29.8 (4.0) to a maximum of 47.8 (7.6) pg/ml after 2 months, not significant.]. Haemoglobin variations in the course of nilutamide treatment and in the control group treated with D-tryptophan-6-LHRH are illustrated in Fig. 3. Multiple regression analysis showed that in the group treated with the antiandrogen there was a significant increase in haemoglobin levels ($r = 0.307$, $P = 0.008$) with an elevation from basal 12.5 (0.3) to a maximum of 13.7 (0.3) g/dl. Conversely, a non-significant decline was noted in the LHRH agonist group ($r = -0.106$, $P = 0.15$). Comparison between groups revealed that the slopes of the regression lines differed significantly ($P = 0.014$).

DISCUSSION

Pure non-steroidal antiandrogens are widely employed in association with medical or surgical orchiectomy to achieve a

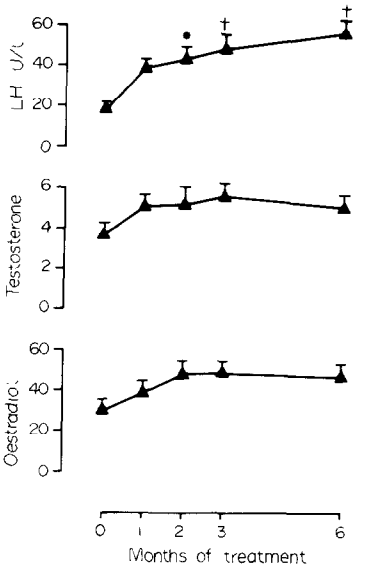

Fig. 2. Serum levels [mean (SE)] of LH, testosterone and oestradiol during treatment with nilutamide. *$P < 0.05$, †$P < 0.01$ vs. initial levels corrected for multiple comparisons. n at 0, 1, 2, 3 and 6 months were 12, 11, 11, 11 and 11.

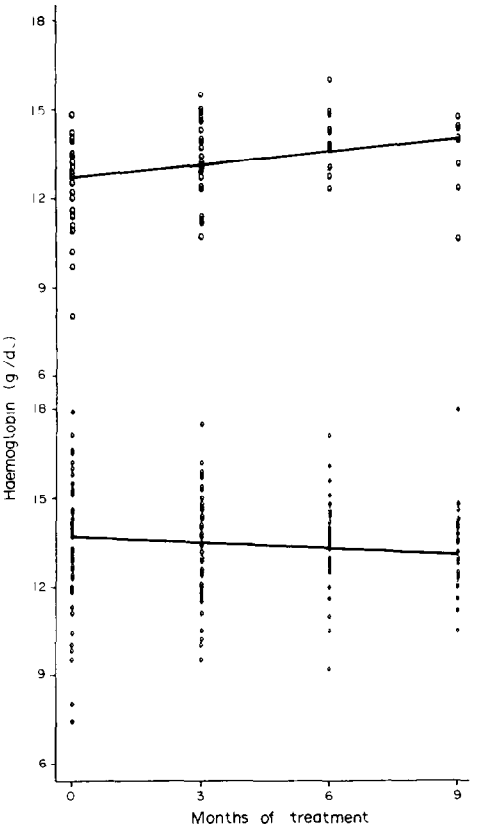

Fig. 3. Haemoglobin variations (linear regression) during treatment with the antiandrogen nilutamide (upper, $r = 0.307$, $P = 0.008$) and the LH-RH agonist D-Trp-6-LH-RH (lower, $r = -0.106$, $P = 0.14$). n at 0, 3, 6, and 9 months were: 24, 24, 14 and 12 (antiandrogen) and 56, 55, 44 and 32 (LHRH agonist).

more complete androgen blockade. Conversely, their use as single agents has so far been limited [10, 12, 13]; as a consequence, neither the activity nor the toxicity of these compounds (particularly nilutamide) have been deeply investigated prior to their vast utilisation in combination regimens. A reason for the limited experience is related to the speculated endocrine effects on the intact human gonadal axis, which may ultimately lead to inadequate control of circulating androgens [7]. In contrast to previous observations, however, there was no progressive rise of testosterone levels during chronic antiandrogen therapy in spite of significant elevations in LH levels. One possible explanation for plateauing is related to the increase in oestradiol levels, inasmuch as sustained oestrogen elevation may reduce LH bioactivity and affect Leydig cell steroidogenesis [22]. In addition, studies in elderly men have shown an increase in the immunoactivity/bioactivity ratio of LH in response to enhanced hypothalamic activity, together with a limited Leydig cell response to hyperstimulation [23]. Therefore, at least in endocrinological terms, the moderate, non-progressive testosterone rise causes less concern about possible escapes to androgenic control of prostate cancer. Additionally, since the half-life of nilutamide is extremely long (23–87 h), a prolonged antagonistic effect may still be guaranteed in spite of patient's possible decreased compliance [11].

In terms of drug activity, the 38.5 (18.7)% response rate that we have observed in untreated cases appears to be moderately important and might be compared with our previous results obtained in a similar trial of a LHRH agonist [19]. In the largest pilot study with flutamide as first-line monotreatment [10], response criteria were not really comparable to those used by the NPCP. On the basis of a not very clearly defined overall "favourable response", 87.5% of patients achieved some benefit. In other trials, all with different or unspecified response criteria, response rate ranged from 46 to 72% [11, 12]. Median progression-free (9 months) and overall survival (23 months) in the untreated subset were moderately shorter than those observed by us in a previous comparable series treated with a long-acting LHRH agonist, in which the median time was 13.5 and 27.5 months, respectively [19]. In two small trials, the effectiveness of flutamide was compared to diethylstilbestrol [11] and estramustine phosphate [12], respectively. Results were similar in the former and negative for flutamide in the latter study.

With regard to the activity of nilutamide in pretreated patients, the observed response rate seems to confirm that there should be no scientific rationale for iterative endocrine treatment, at least with antiandrogens, once castrate levels of testosterone have been achieved by the first-line regimen (24); this simple logical view is not completely supported by the minimal activity shown in the decline of PSA levels, however. Conversely, the encouraging results [38.5 (26.5)%] provided by LHRH agonist treatment following progression on nilutamide suggest that maintainance of physiological serum testosterone levels by primary therapy with non-steroidal antiandrogens may profitably preserve libido and may not preclude the benefit of a subsequent androgen-suppressive procedure.

Side-effects were relatively frequent but generally mild. As in the vast majority of the nilutamide studies [14], we used a three times daily 100 mg dose. However, according to subsequent pharmacokinetic studies [11], a reduction to a single 150 mg daily dose, which may reduce toxicity, seems the appropriate schedule. Despite the high dose and the frequent intake, nilutamide appears less toxic than flutamide at hepatic and gastrointestinal levels [25]. Conversely, it gives, with a certain frequency, unique side-effects such as decreased darkness adaptation (30%) and alcohol intolerance (19%), the explanations for which are unknown. In trials employing nilutamide as a combination agent (most of which were double-blinded) visual complaints ranged widely (from 21 to 68%) and even up to 18% in the placebo group [15–17]. The extreme variability seen also in our trial seems to confirm a certain difficulty in defining precisely the phenomenon, which resembles vitamin A deficiency [26]. The request of further evaluation of this side-effect by the drug relatory authorities has so far precluded the approval of the compound in some countries. In our limited experience, however, visual complaints were never so severe to affect quality of life. With regard to alcohol intolerance, it may seem like a slight disulfiram-like reaction. Libido and potency, as referred by patients, were preserved in approximately half of the sexually active men. This confirms previous data with flutamide, although to a lesser extent (10, 13). Why pure antiandrogens should not affect sexual behaviour remains an intriguing finding, also in light of the moderate oestrogen increase [22]. Finally, since it is known that androgens stimulate erythropoiesis [19], the observed slight increase of haemoglobin in the course of treatment with nilutamide was notable. The opposite behaviour in the control group treated with medical orchiectomy suggests that the trophic effect was not entirely due to tumour reduction in bone marrow with consequent recovery of erythropoiesis. In biological terms, this observation and that of a certain activity of secondary hormonal manipulation raise the conjecture as to whether the drug's antagonistic action upon androgen receptors was really complete or indeed potent enough. In clinical terms though, the benefit of pursuing *ab initio* a total androgen neutralisation to control disease outcome appears limited at best [3], although it may be humanly worthy. Preclinical data indicate more need for counteracting the heterogeneous androgen sensitivity of the tumour rather than treating peripheral androgens [27, 28].

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Acknowledgement—Other contributing clinicians were C.P. Baccarani, E. Bezzi, U. Fontanella, O. Gazzarini, F. Oneto, M. Pavone Macaluso, D. Pescatore, N. Positano and G.C.Zanetti. Prof. P. Periti, Dr A. Rubagotti, Dr M. Costantini, Dr P. Marroni, Miss V. Ballestrazze and Mr T. Wiley are thanked for scientific and technical support and Roussel Pharma (Italy) for financial support.

Eur J Cancer, Vol. 27, No. 9, pp. 1104–1106, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Cisplatin and Teniposide Chemotherapy for Advanced Non-small Cell Lung Cancer

Valter Iberti, Michela Donadio and Giuseppe Giaccone

30 patients with advanced non-small cell lung cancer were treated with cisplatin 80 mg/m², day 1, and teniposide 100 or 120 mg/m², days 1, 3 and 5, every 3 weeks. Myelotoxicity, nausea and vomiting and alopecia were the main side-effects. 8 patients of 26 evaluable had partial responses (31%): 6 had received 120 mg/m² teniposide and 2 had received 100 mg/m² teniposide. Overall median survival time was 251 days. Myelotoxicity was significantly lower in patients who received 100 mg/m² teniposide. Although the number of patients is small and they were not randomly assigned to the two different teniposide doses, it appears that higher dose of teniposide determined a greater degree of myelotoxicity, and also a higher response rate.
Eur J Cancer, Vol. 27, No. 9, pp. 1104–1106, 1991.

INTRODUCTION

ADVANCED non-small cell lung cancer (NSCLC) is relatively resistant to chemotherapy [1]. Cisplatin is believed to be an important ingredient of combination regimens, and syngergistic effects between cisplatin and other drugs, such as etoposide, have been suggested [2]. Teniposide (VM26), an epipodophyllotoxin like etoposide, has shown some activity in NSCLC [3]. In this study we investigated the combination of teniposide with cisplatin in a group of NSCLC patients not previously treated with chemotherapy.

PATIENTS AND METHODS

30 consecutive patients were entered in the study. Locally advanced (confined within one hemithorax and regional lym-