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Original Paper

Early Clinical Experience with Liarozole (Liazal™) in Patients with Progressive Prostate Cancer

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Liarozole (Liazal™) is the first retinoic acid (RA) metabolism blocking agent (RAMBA) in clinical practice. RAMBA therapy promotes differentiation and inhibits proliferation by increasing endogenous RA in tumours. Liarozole was investigated in two open-label pilot studies of 100 patients with progressive prostate cancer in relapse despite previous androgen ablation. Liarozole (150–300 mg twice daily, for $\geq$ 1 month) produced $\geq$ 50% reduction in prostate specific antigen (PSA) serum levels in 15 of 30 evaluable patients in study 1 (50%) and 10 of 55 patients in study 2 (18%). PSA responders had more marked reductions in prostatic acid phosphatase, alkaline phosphatase and symptom scores for bone pain and urological symptoms, and improved general well being. Plasma levels of adrenal androgens did not alter during chronic treatment with liarozole nor at adrenocorticotrophic hormone (ACTH) stimulation test. Liarozole did not alter plasma levels of adrenal androgens or cortisol. Cortisol response to ACTH stimulation was slightly blunted. Liarozole was generally well tolerated. Dermatological adverse events were probably related to increased intracellular RA. Liarozole appears to be a promising treatment option in prostate cancer. **© 1998 Elsevier Science Ltd. All rights reserved.**

Key words: prostate cancer, metastasis, retinoic acid metabolism, differentiation therapy, liarozole
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INTRODUCTION

THERE ARE an estimated 200 000 newly diagnosed cases of prostate cancer in Europe annually. Currently less than 30% of patients have disseminated disease at diagnosis; at the time the described trials were run, approximately 50% of all patients had metastatic prostate cancer at primary presentation. Androgen suppression by surgical (orchiectomy) or chemical (luteinising hormone releasing hormone (LHRH) agonists) castration, without anti-androgens is the most widely used first-line treatment of advanced metastatic prostate cancer [1], but the response is variable and 20% of patients do not respond, i.e. they have hormone-refractory prostate cancer. Furthermore, approximately 50% of patients relapse, i.e. they become resistant during the first 2 years of this hormonal therapy [2]. The outlook is invariably poor once the tumour escapes first-line hormonal treatment, as additional treatment is rarely beneficial. Chemotherapy is often considered, but is without major benefit and carries a high risk of unacceptable toxicity [3].

Based on the discovery that the imidazole derivative, liarozole (Liazal™) blocks the metabolic breakdown of retinoic acid (RA), thereby increasing levels of RA in prostate cancer cells [4], a new alternative for the treatment of prostate cancer may be suggested.

RA plays a key role in cellular proliferation and differentiation [5]. It binds to a specific nuclear receptor family and this complex interacts with the genomic apparatus to facilitate genetic expression of specific proteins involved in cell differentiation [6]. Activation of RA receptors directs the tumour cells to differentiate towards normal phenotypic behaviour.

Liarozole is the first of a new generation of RA metabolism blocking agents (RAMBA). It acts by blocking cytochrome P450-mediated 4-hydroxylation of RA. Thus, by increasing intracellular endogenous RA, liarozole exerts indirect antiproliferative, differentiating, and potentiating antitumour effects [4].

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Liarozole reduces the growth of androgen-dependent Dunning R3327G prostate carcinoma in nude mice and rats, having a similar efficacy to castration, but without lowering plasma testosterone levels [7]. Liarozole also has proven antitumour activity in steroid-insensitive TA-3 mouse mammary carcinoma and NMU-induced mammary carcinoma in rats [8]. The anticarcinogenic and antitumour activity of liarozole has been demonstrated in early clinical studies [9]. This paper describes clinical results from two pilot studies in patients with hormone-resistant metastatic prostate cancer.

Table 1. *Pain assessment scales*

Pain score	0	No pain
	1	Mild pain; analgesics not or rarely required
	2	Moderate pain; only non-narcotic analgesics required
	3	Severe pain; narcotic analgesics required occasionally
	4	Very severe pain; administration of narcotic analgesics regularly required
	5	Intolerable pain; insufficient pain relief in spite of narcotic analgesics

PATIENTS AND METHODS

Patient selection

Patients participating in study 1 were recruited from a single centre in Belgium and those in study 2 from 11 centres in Belgium and two in the Netherlands. All patients gave written informed consent. Both studies included patients with histologically proven carcinoma of the prostate, most of whom had distant metastases and had undergone bilateral orchiectomy at least 2 weeks prior to entry. Most patients had prostate specific antigen (PSA) levels ≥ 10 ng/ml (3 patients baseline PSA level < 10 ng/ml and 5 patients baseline PSA level not available) and/or elevated prostatic acid phosphatase (PAP) with clinical symptoms of progressive disease. The study was confined to patients with a life expectancy of ≥ 3 months. Patients also had to have castrate levels of testosterone. Patients with secondary malignancy other than basal cell skin cancer were excluded, as were those with serum potassium ≤ 4 mEq/l, serum creatinine > 50 Tmol/l or bilirubin > 20 Tmol/l.

Treatment

According to protocol, liarozole was administered orally on an open-label basis, twice-daily, at least 30 min before breakfast and at least 2 h after the evening meal. Patients in study 1 received liarozole at 300 mg twice daily throughout the 6-month treatment period. In study 2, liarozole was started at 150 mg twice daily and increased to 300 mg twice daily in patients whose pain scores or urological symptom scores were ≥ 2 at week 4 and in those who had failed to achieve a 50% reduction in PSA level at week 12.

Concomitant treatment with retinoids, endocrine agents, other investigational drugs, or imidazole derivatives (e.g. ketoconazole) was prohibited in both studies. Cimetidine, anticholinergics or digitalis preparations were also prohibited in study 1.

Clinical assessments

A clinical evaluation was made at the start, at weeks 2 and 4 and then monthly until the end of treatment in study 1, and at the start and every 2 weeks until the end of treatment in study 2. A subjective response was defined as a decrease of at least one point in pain with reference to the scoring system shown in Table 1, performance as assessed by the ECOG/Zubrod scale (Eastern Cooperative Oncology Group), or urological complaints based on micturition frequency, dysuria and urge.

Biochemical assessments

PSA level was determined at the start of treatment and at regular intervals throughout both studies, before intake of the medication. PAP and alkaline phosphatase (ALP, study 1 only) levels were evaluated at the same visits. ALP is considered to be a parameter for the evaluation of bone disease and is, therefore, of prognostic importance.

Biochemical responses were defined as: complete response (CR): normalisation of PSA levels; partial response (PR): $\geq 50\%$ decrease in PSA level relative to baseline level; stable disease: $< 50\%$ decrease in PSA level relative to baseline level or $< 50\%$ increase relative to the lowest prior moving average; progression: $\geq 50\%$ increase in PSA level relative to the lowest prior moving average.

Additional endocrine function tests (adrenocorticotrophic hormone (ACTH) challenge and co-administration of steroids) were undertaken in study 1. ACTH challenge tests were performed in 8 patients on days 14 and 28 after treatment. From days 15–28, dexamethasone 0.75 mg twice daily was added to liarozole so that a comparison was possible between a 2-week liarozole-only treatment and a 2-week liarozole plus dexamethasone treatment. 17I-hydroxyprogesterone, progesterone, androstenedione, dehydroepiandrosterone (DHEA), testosterone, 11-deoxycortisol, cortisol, corticosterone, 11-deoxycorticosterone and aldosterone were assessed at baseline and on days 14 and 28. In 16 other patients, trough levels of adrenal steroids were assessed during the first 5 months of treatment and compared with baseline levels. Plasma concentrations of DHEA, androstenedione, cortisol and 11-deoxycorticosterone were determined immediately before drug intake on days 1, 7, 14, 21 and 28 and then monthly until month 5. Pretreatment samples were taken at the same time of day prior to treatment to establish baseline concentrations.

Trough levels of DHEA, androstenedione, luteinising hormone (LH), 11-deoxycorticosterone, 1,25-dihydroxy vitamin D, and 1-hydroxy vitamin D were assayed on samples monitored in study 2 in 33 patients for whom sufficient plasma samples were available.

RA levels were monitored in 4 patients immediately before drug intake and at 2, 4, 6 and 8 h post-dose on days 1, 7 and 21. Pretreatment levels were monitored with samples at the corresponding times on the day before treatment was started.

Pharmacokinetic assessments

Trough plasma levels of liarozole were evaluated from blood samples taken in study 1. 6 patients received liarozole only during weeks 1 and 2 and then concomitant treatment with dexamethasone (0.75 mg twice daily) during weeks 3 and 4. The other 8 patients received liarozole alone. Plasma concentrations of liarozole were determined by high-performance liquid chromatography using fluorometric detection. The limit of detection was 0.010 Tg/ml.

Tolerability assessments

All adverse events reported by patients were documented irrespective of whether or not they were considered related to liarozole. Sitting systolic and diastolic blood pressure, heart rate and weight were recorded on entry and measurements repeated after 2 and 4 weeks and then monthly until the end of treatment in study 1, and every 2 weeks until the end of treatment in study 2. A 12-lead electrocardiogram (ECG) was recorded before treatment and at least once during treatment in study 1 and at months 2, 4 and 6 in study 2. Blood samples for routine haematology/biochemistry were taken before intake of the morning dose at the start, at weeks 2 and 4 and then monthly until the end of treatment in study 1, and at the start and every month until the end of treatment in study 2.

Statistical methods

Analysis was undertaken using an intent-to-treat approach. Differences from baseline were analysed using the Wilcoxon matched-pairs signed-ranks test for censored data. Two-tailed probabilities were used throughout and changes were considered to be significant at the 5% level. Product-limit survival estimates were performed for PSA responders and PSA non-responders. Differences in survival in the two response groups were analysed using the Wilcoxon matched-pairs signed-ranks test. The trapezoidal rule was used to determine areas under the concentration time curves for hormone assays. Differences in trough levels of liarozole in samples obtained with and without co-administration of dexamethasone were analysed using the unpaired Student's *t*-test and the Mann–Whitney *U*-test.

RESULTS

Patient outcome

Demographic and baseline characteristics are summarised in Table 2. All 31 patients in study 1 received 300 mg liarozole twice daily. In study 2, 27 patients received 150 mg liarozole twice daily and 39 patients increased to 300 mg twice daily. For 3 patients, insufficient data on the dose regimen were available. Most patients had already received systemic therapy for a first or even second or third relapse. Upon entry into the trial, they had symptomatic disease with high tumour marker values (PSA, PAP, ALP).

Table 2. Demographic data and disease characteristics

	Study 1 ($n = 31$)	Study 2 ($n = 69$)
Age, median (range) years	68.5 (55–85)	73 (55–86)
Weight, median (range) kg	72 (47–90)	71 (48.5–100)
Mean duration of disease (years)	3.4	3.0
Previous treatment		
Orchiectomy	31	50
Anti-androgens	7	31
LHRH agonists	10	29
Chemotherapy	11	14
TURP	12	0
Radiotherapy	9	0
Prostatectomy	2	0
Oestrogens	2	5
Progestins	2	0
Biochemical markers, median (range)		
PSA ng/ml ($n = 30,55$)	124 (12.7–6275)	244 (24.6–2800)
PAP ng/ml ($n = 30,61$)	31 (0.4–1905)	16.1 (0.3–1126)
ALP U/l	352 (74–1607)	—

LHRH, luteinising hormone releasing hormone; TURP, transurethral resection of prostatic; PSA, prostate specific antigen; PAP, prostatic acid phosphatase; ALP, alkaline phosphatase.

18 of 100 patients continued on liarozole beyond the expected 6-month duration (6 from study 1 and 12 from study 2). The median duration of treatment was 75 days in study 1 (range: 28–996 days) and 83 days in study 2 (range: 1–1090 days). 36 patients withdrew because of progression, 28 due to adverse events only, 3 due to progression and adverse events. At the data census date for analysis, 2 patients were still alive and 21 had died, of whom 9 also had an adverse event, 8 were lost to follow-up and 2 were non-compliant (Table 3).

Survival

Median survival after the start of liarozole was 192 days in study 1 and 180 days in study 2. 46 patients survived for > 6 months (16 in study 1, 30 in study 2). The product-limit survival estimate showed 75% of patients in both studies remained alive after 3 months and 25% after > 1 year. 81 patients died due to prostate cancer (Table 3).

Tumour response

2 cases of bi-dimensional lesion response were observed in study 1. 1 patient had > 25% reduction in pelvic lymph node volume after 12 weeks and another had > 50% reduction in supra-clavicular lymph node volume after 8 weeks. Measurable disease was not assessed in study 2.

Prostate size

In study 1, 6 of 13 evaluable patients had > 35% reduction in prostate volume (range: 39–66%), while another 4 patients had a minor decrease in volume. In study 2, 9 patients had prostate size evaluations for > 2 months; 4 showed a decrease in prostate size at some time point, with a maximal reduction of 40%.

PSA levels

30 of 31 patients in study 1 and 55 of 69 patients in study 2 were evaluable for PSA. 15 were not evaluable because PSA levels were not available ($n = 6$), < 20 ng/ml ($n = 3$) or because there were no follow-up values ($n = 6$). Of 85 patients, evaluable for PSA, there were 2 CRs and 13 PRs in study 1 and 1 CR and 9 PRs in study 2 (Table 4). Hence, the overall PSA response rate was 29% (CR 4%, PR 26%).

As the anti-androgen withdrawal effect was only described after the start of these trials, this was not taken into account in the trial design. Of 7 patients in study 1 who received an anti-androgen, 1 PSA response (PR) was observed. Of 27 patients in study 2 treated with an anti-androgen as part of the last treatment before trial entry, 1 PSA CR and 2 PSA PRs were observed. In total, for 21 of 25 responders, a possible involvement of the withdrawal effect could be ruled out completely.

A statistically significant reduction in median PSA levels was observed from the first week of treatment in study 1 ($P = 0.03$). The largest response was noted after 3 months ($P = 0.013$) and after 4 months there was still a significant response ($P = 0.027$). The median maximal reduction in PSA

Table 3. Patient outcome

	Study 1 ($n=31$)	Study 2 ($n=69$)
Duration of treatment, median (range), days	75 (28–996)	83 (1–1090)
Summary of withdrawal		
Adverse events	7	21
Progression	13	23
Adverse events + progression	0	3
Death	6	15*
Non-compliance	2	0
Lost to follow up	2	6
Ongoing	1	1
Patient outcome		
Death		
Prostate cancer	26	55
Pneumonia	0	3
Sepsis	0	1
Lung oedema	1	0
Acute abdominal syndrome	1	0
Cerebrovascular disease	0	1
Lost to follow-up	2	8
Alive	1	1

*9 patients died on the day they withdrew from the study with adverse events.

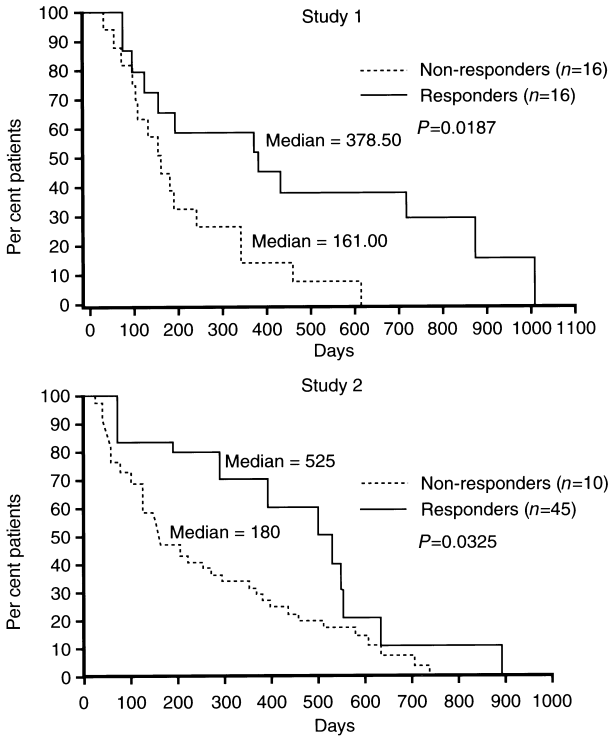

Figure 1. Relationship between prostate specific antigen (PSA) response and survival.

level for the entire patient group was 47.5%, indicating that, generally, there was a good total response, with only 4 of 30 evaluated patients failing to show a decrease or stabilisation in PSA levels. 5 patients in study 1 who had $\geq 50\%$ reduction in PSA levels also had an objective response on prostate size ($>35\%$ reduction). The 2 patients with a reduction of measurable lesions ($>25\%$ reduction relative to baseline for lymph nodes) also had $\geq 50\%$ reduction in PSA levels.

Reductions in median PSA levels were also observed in study 2, but did not reach statistical significance. The 10 responders were equally divided between 150 mg and 300 mg doses. A further 27 patients had stable disease of whom 14 had decreasing PSA levels, although by less than 50%. 18 patients had PSA values that increased by 50% or more.

In terms of prognostic factors, PSA responders in study 1 had lower baseline PSA levels (80.4 ng/ml versus 150 ng/ml) and longer time to pretrial progression (40 months versus 26 months) than non-responders. There were no prognostic differences between responders and non-responders in study 2.

In both studies, patients with $\geq 50\%$ reduction in PSA levels also had significantly longer survival times than non-responders (Figure 1): median survival was 12.2 months versus 5.3 months in study 1 ($P=0.019$) and 17.2 months versus 5.9 months in study 2 ($P=0.033$).

Table 4. Prostate specific antigen response

	Number of patients		
	Study 1	Study 2	Total $n=85$ (%)
Complete response	2	1	3 (4)
Partial response	13	9	22 (25)
No change	11	27	38 (45)
Progression	4	18	22 (26)
Not evaluable	1	14	

PAP and ALP

PAP was elevated at baseline in 25 patients in study 1 and in 58 patients in study 2. Reductions in PAP level were observed during the first month in study 1, but not thereafter. Median PAP levels tended to increase during study 2 (data not shown). ALP was monitored in study 1 only; 22 patients had elevated levels at baseline. Significant reductions in ALP level were observed after 1 month ($P=0.032$) and at the end of treatment ($P=0.008$; data not shown). PAP and ALP responses corroborated those obtained for PSA, in that PSA responders showed more marked reductions in PAP and ALP than the PSA non-responders.

Symptoms

Patients who were PSA responders tended to have better symptom scores than PSA non-responders. Statistically significant reductions in pain score were observed at week 2 in study 1 and between week 2 and week 12 (month 3) in study 2 (Figure 2).

There was a tendency for all urinary symptoms to improve, mostly within the first 3 months. Improvements in dysuria and urge incontinence reached statistical significance after 2 months in studies 1 and 2 for dysuria, and after 2 weeks, 3 months and 4 months for urge incontinence in study 2 only. Assessment of patients' overall condition showed trends towards improvement, although changes were not statistically significant.

Endocrine function

Short-term treatment with 300 mg liarozole twice daily for 2 weeks had little effect on baseline basal plasma concentrations of testosterone, androstenedione and DHEA (data not shown). Liarozole did not prevent the physiological rise in androstenedione and DHEA induced by ACTH stimulation.

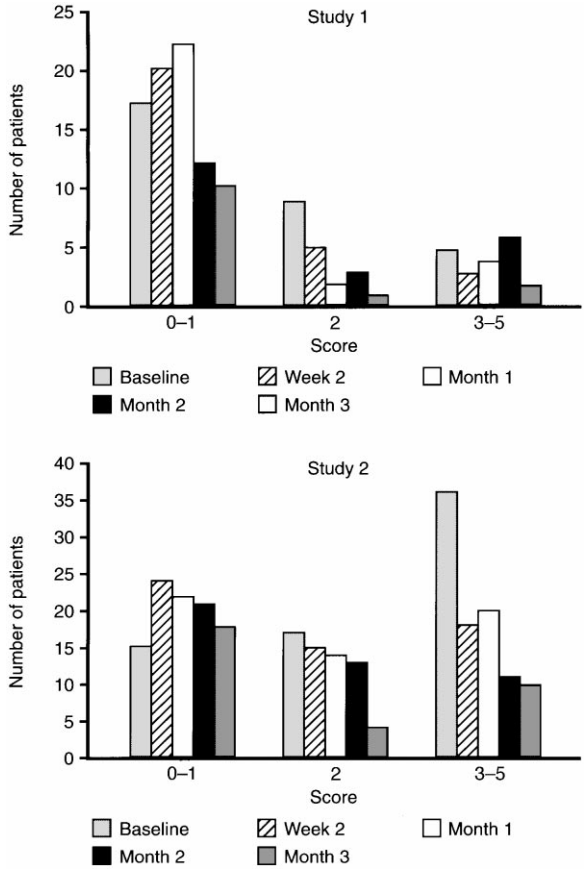

Figure 2. Summary of pain scores.

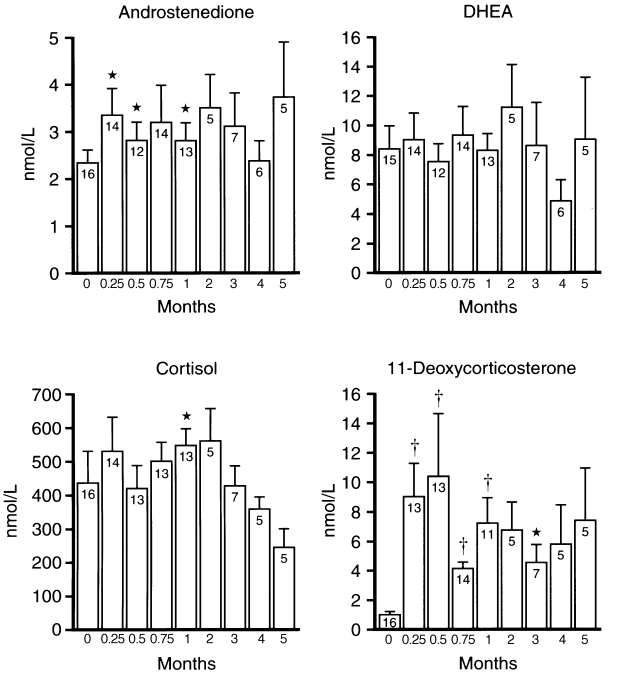

Figure 3. Effect of chronic treatment with liarozole on plasma levels of androstenedione, dehyroepiandrosterone (DHEA), cortisol and 11-deoxycorticosterone. *Significantly different from baseline levels, $P < 0.05$. †Highly significantly different from baseline levels, $P < 0.01$.

However, combination therapy with liarozole and dexamethasone for 2 weeks significantly reduced the 0–4 h AUC for all three hormones. Testosterone AUC was reduced from 2899 ± 455 to 1757 ± 450 nmol.h/l ($P = 0.03$); androstenedione AUC was reduced from 20.0 ± 3.6 to 8.4 ± 1.6 nmol.h/l ($P = 0.015$) and DHEA from 40 ± 13 to 16.7 ± 3.18 nmol.h/l ($P = 0.03$).

The ACTH-induced rise in plasma cortisol was only slightly blunted after 2 weeks of liarozole, but was significantly reduced after 2 weeks of liarozole and dexamethasone. Liarozole significantly increased levels of the precursor 11-deoxycortisol, and progesterone and 17I-hydroxy-progesterone. Liarozole plus dexamethasone had no additive effect.

Liarozole alone and in combination with dexamethasone partially blunted the ACTH-induced rise in aldosterone. The precursor corticosterone showed a normal ACTH-induced increase with liarozole alone.

Liarozole caused a 10-fold rise in 11-deoxycorticosterone but only a modest increase was seen after liarozole plus dexamethasone.

Prolonged treatment with liarozole for up to 5 months in orchiectomised patients had no effect on plasma DHEA levels, but significantly increased androstenedione (Figure 3). No significant change in cortisol was detected, but 11-deoxycorticosterone levels rose by 5- to 15-fold.

Liarozole 300 mg twice daily for 21 days had no consistent effect on circadian variations in DHEA, androstenedione or cortisol levels in the 4 patients in whom this was tested. Endocrine parameters in study 2 were not markedly altered by liarozole. The only obvious change was an increase in 11-deoxycorticosterone with respect to baseline.

RA

During chronic dosing, RA was determined at days 0, 1, 7 and 21 (Table 5). Maximal levels were seen 4 h after dosing; by 8 h RA levels had returned to pretreatment values.

Pharmacokinetic assessments

In patients receiving 300 mg liarozole twice daily (study 1), the mean (± S.D.) trough concentration was 0.71 ± 0.40 Tg/ml (range: 0.093–1.59 Tg/ml). Near peak plasma concentrations were in the range of 1.67–10.6 Tg/ml and averaged 4.67 ± 1.79 Tg/ml. Trough and near peak plasma concentrations of liarozole remained constant throughout long-term treatment in patients treated for 200–250 days and were not influenced by co-administration of corticosteroids (Figure 4).

Tolerability

29 of 31 patients in study 1, and 66 of 69 patients in study 2 reported adverse events. The most common were skin disorders, dry mouth, nausea and vomiting, fatigue and oedema (Table 6).

Table 5. Plasma retinoic acid levels

	Mean ± SEM ($n = 4$) (ng/ml)			
	Day 0	First dose	Day 7	Day 21
Predose	1.85 ± 0.28	1.75 ± 0.23	1.50 ± 0.13	1.45 ± 0.31
4 h postdose	1.70 ± 0.17	3.35 ± 0.21	3.00 ± 0.58	2.77 ± 0.33
8 h postdose	1.02 ± 0.46	0.97 ± 0.53	—	—

SEM, standard error of the mean.

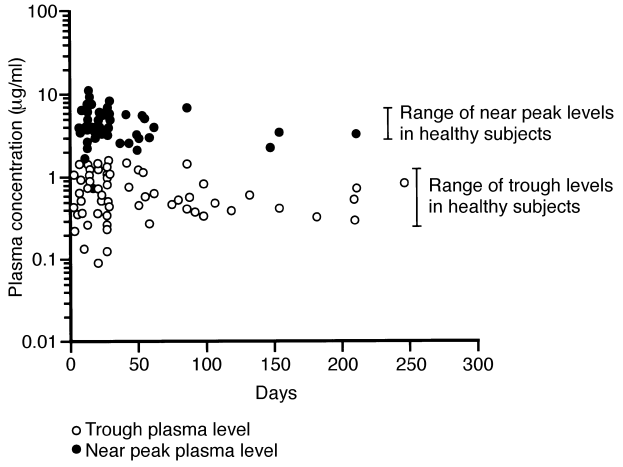

Figure 4. Plasma concentration time curve for liarozole alone.

In total, 40 patients withdrew because of an adverse event (of whom 3 also had progression and 9 died); of these, 11 withdrew because of an adverse event considered at least possibly related to liarozole. Adverse events necessitating withdrawal were most commonly skin disorders, nausea or vomiting.

There were no treatment-related or clinically important changes in heart rate, systolic or diastolic blood pressure or ECG parameters. In study 2, there was a small but statistically significant decrease in weight at week 20 (−5.9 kg; $P = 0.019$) and at endpoint (−3.6 kg; $P < 0.001$).

There were no clinically relevant changes in laboratory parameters except for those related to disease progression. It is known that some laboratory values can be directly associated with prostate cancer, such as an increase in urea levels, white blood cells, platelet level, potassium level, and a decrease in haemoglobin, red blood cells and haematocrit.

DISCUSSION

The aim of these two pilot trials was to evaluate the efficacy and tolerability of liarozole, a new cytochrome P-450 inhibitor, in a population of relapsed prostate cancer patients who had undergone complete or partial androgen blockade. In general, the outcome for these patients is poor. There is no standard therapy available and treatment is limited to palliation. The median time from first progression to death is usually in the range of 1 year, whereas the time from symptomatic relapse to death is approximately 6 months, ranging from a few days to 1.5 years [10]. The patients in our studies constitute a high-risk group: high age, high tumour markers, symptomatic relapse, and in most cases a second or third relapse. This explains the short median survival of only 6 months in these studies.

Table 6. *Summary of adverse events*

	Number of events	
Most frequent adverse events	Study 1 ($n = 31$)	Study 2 ($n = 69$)
Dry mouth	18	33
Asthenia/fatigue	18	15
Oedema	11	15
Pruritus	15	16
Desquamation	14	3
Dry skin	7	20
Nail disorder	6	11
Rash	6	11
Nausea and vomiting	7	26
Constipation	0	10

Since, in prostate cancer, measurable disease is rare (< 10%), PSA was used as a surrogate parameter at all visits during follow-up. The ability of liarozole to reduce PSA levels suggests that this new form of RAMBA therapy has a direct effect on prostate tumour tissue. The response rate was unexpectedly high in study 1 where 15 of 30 patients showed a decrease in PSA level of $\geq 50\%$ during treatment. In study 2, the PSA response rate was lower (18%), principally because this group represented a population with worse baseline parameters, e.g. higher PSA level, higher tumour grade, more extensive pretreatment, worse performance scores and worse pain scores with more use of non-narcotic and narcotic analgesics. Anti-androgen withdrawal did not influence these findings.

Our results confirm that PSA responders generally have a much better prognosis than non-responders. In both studies, median survival was longer for responders than non-responders. The difference in survival appeared to be independent of baseline differences in prognostic variables such as performance status, haemoglobin or ALP. Interestingly, PAP and ALP levels also decreased most markedly in PSA responders. The observation in study 1 that the majority of responders also had a clinical response indicates a possible relationship between PSA response and tumour response. This observation is in keeping with recent reports on the value of PSA as a surrogate marker in hormone-resistant prostate cancer [11–13].

The majority of patients in both studies presented with pain due to skeletal metastasis. This disabling phenomenon presents a major therapeutic challenge. Liarozole significantly reduced pain scores after 2 weeks of treatment, with half the patients in study 1 becoming pain-free after 1 month of treatment. There were accompanying improvements in the patients' general condition, and in urological symptoms such as dysuria and urge incontinence.

The endocrinological results confirm that in orchiectomised patients, liarozole partially inhibits 11-hydroxylase, which converts 11-deoxycortisol and 11-deoxycorticosterone into cortisol and corticosterone, respectively. The accumulation of progesterone and the slight increase in 17 I-hydroxyprogesterone levels suggest that liarozole also inhibits 17-hydroxylase.

Liarozole did not alter the plasma levels of adrenal androgens after ACTH stimulation or after chronic treatment. This is in marked contrast to the results obtained with high-dose ketoconazole, another imidazole used in the treatment of advanced prostate cancer, which causes $\geq 50\%$ decrease of androstenedione and DHEA [14–16]. Ketoconazole treatment also resulted in a more marked accumulation of 11-deoxycortisol and 11-deoxycorticosterone after ACTH stimulation.

Plasma cortisol levels were not affected by long-term liarozole treatment. However, the cortisol response to exogenous ACTH was slightly, but not significantly, blunted. Increased plasma 11-deoxycorticosterone levels during long-term treatment were comparable with those reported previously with ketoconazole [15].

Trough and near peak plasma concentrations of liarozole were similar to those reported in a previous 1-week multiple-dose study in healthy volunteers (unpublished results).

We were also able to demonstrate that liarozole increases RA levels in patients with advanced prostate cancer. It is proposed that the peak RA levels observed 4 h after administration of liarozole to patients with advanced prostate cancer and the response to the continuously raised RA levels, are directly related to the antitumour effect, but this hypothesis requires further investigation.

Liarozole was generally well tolerated. The majority of patients experienced adverse events, mostly of a dermatological nature. However, these were seldom serious enough to warrant discontinuation. Dermatological events were predictable side-effects resulting from increased RA levels which mimic hypervitaminosis A. There was no evidence that liarozole was associated with clinically significant abnormalities in vital signs, body weight, ECG parameters or clinical laboratory tests. Liarozole was well tolerated in comparison with alternative forms of therapy with cytotoxic agents.

In summary, these findings provide evidence for the antitumour activity of liarozole in patients with relapsed, disseminated prostate cancer. It thereby offers a possible alternative approach for the treatment of metastatic prostate cancer.

1. Oosterlinck W, Casselman J, Mattelaer J, Van Velthoven R, Kurjatkin O, Schulman C. Tolerability and safety of flutamide in monotherapy, with orchiectomy or with LHRH-a in advanced prostate cancer patients. *Eur Urol* 1996, **30**(4), 458–463.
2. Dawson NA. Treatment of progressive metastatic prostate cancer. *Oncology* 1993, **7**(5), 17–29.
3. Small EJ, Srinivas S, Egan B, McMillan A, Rearden TP. Doxorubicin and dose-escalated cyclophosphamide with granulocyte colony-stimulating factor for the treatment of hormone-resistant prostate cancer. *J Clin Oncol* 1996, **14**(5), 1617–1625.
4. Wouters W. Retinoid metabolism and its inhibition by liarozole-fumarate. *Ann Oncol* 1994, **5**(Suppl. 9), S45–S47.
5. De Luca LM, Darwiche N, Jones CS, Scita G. Retinoids in differentiation and neoplasia. *Scientific American* 1995, **2**(4), 28–37.
6. Ong DE, Chytil F. Retinoic acid-binding protein in rat tissue. *J Biol Chem* 1975, **250**(15), 6113–6117.
7. Van Ginckel R, De Coster R, Wouters W, *et al.* Antitumoral effects of R75251 on the growth of transplantable R3327 prostatic adenocarcinoma in rats. *Prostate* 1990, **16**(4), 313–323.
8. Wouters W, De Coster R, Van Ginckel R, *et al.* Antitumoral activity of R075251 in experimental models. *Proc Am Assoc Cancer Res* 1990, **414** (abstract 31).
9. Denis L. Liarozole-fumarate, a novel anti-tumoral drug: clinical update. International Symposium on Recent Advances in Diagnosis and Treatment of Prostate Cancer, Quebec City (Canada), 21–23 September 1995.
10. Beynon LL, Chisholm GD. The stable state is not an objective response in hormone-escaped carcinoma of prostate. *Br J Urol* 1984, **56**(6), 702–705.
11. Iversen P, Rasmussen F, Asmussen C, *et al.* Estramustine phosphate versus placebo as second line treatment after orchiectomy in patients with metastatic prostate cancer. DAPROCA study 9002. Danish Prostatic Cancer Group. *J Urol* 1997, **157**(3), 929–934.
12. Kelly WK, Scher HI, Mazumdar M, Vlamis V, Schwartz M, Fossa SD. Prostate-specific antigen as a measure of disease outcome in metastatic hormone-refractory prostate cancer. *J Clin Oncol* 1993, **11**(4), 607–615.
13. Pienta KJ, Redman B, Hussain M, *et al.* Phase II evaluation of oral estramustine and oral etoposide in hormone-refractory adenocarcinoma of the prostate. *J Clin Oncol* 1994, **12**(10), 2005–2012.
14. De Coster R, Caers I, Coene MC, Amery W, Beerens D, Haelterman C. Effects of high-dose ketoconazole therapy on the main plasma testicular and adrenal steroids in previously untreated prostatic cancer patients. *Clin Endocrinol* 1986, **24**(6), 657–664.
15. De Coster R, Mahler C, Denis L, *et al.* Effects of high-dose ketoconazole and dexamethasone on ACTH-stimulated adrenal steroidogenesis in orchiectomized prostatic cancer patients. *Acta Endocrinol* 1987, **115**(2), 265–271.
16. Trachtenberg J. Ketoconazole therapy in advanced prostatic cancer. *J Urol* 1984, **132**(1), 61–63.

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