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Finasteride in Association With Either Flutamide or Goserelin as Combination Hormonal Therapy in Patients With Stage M1 Carcinoma of the Prostate Gland

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BACKGROUND. It was very reasonable to consider that the combination of the 5α-reductase, finasteride, and a pure antiandrogen such as flutamide should provide an effective form of maximal androgen blockade (MAB). Finasteride decreases intraprostatic levels of 5α-dihydrotestosterone (DHT), and the antiandrogen would restrain the biological action of the residual DHT by interfering with its association with androgen receptor. This form of MAB should sustain the concentration of testosterone in plasma, thereby maintaining sexual function and reasonable quality of life. In order to investigate this, a randomized multicenter phase II clinical trial of patients with untreated M1 cancer of the prostate was developed and undertaken.

METHODS. Patients were randomly allocated to one of three treatment schedules: 1) goserelin, 3.6 mg, s.c., monthly in combination with flutamide, 250 mg., t.i.d. and a placebo, daily, in the image of 2 × 5 mg finasteride; 2) goserelin, 3.6 mg., s.c., monthly in combination with finasteride, 10 mg (2 × 5 mg, daily) and a placebo (t.i.d.) in the image of flutamide; and 3) finasteride, 10 mg (2 × 5 mg, daily) in combination with flutamide (250 mg, t.i.d.). The reduction in concentration of serum PSA at 24 weeks was the endpoint of interest.

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RESULTS. Baseline prostate-specific antigen (PSA) levels of the patients in the three groups were very similar. There was a substantial decrease in levels of PSA in the three groups prior to the end of the study, the percent decrease in the groups being: 1) goserelin and flutamide combination, 99.1% (95% Confidence interval (CI), 97.7, 99.6); 2) goserelin and finasteride combination, 98.75% (95% CI, 97.1, 99.5); and 3) finasteride and flutamide combination, 97.6%, 95% CI, 94.5, 98.9). In the Generalized linear model (GLM) analysis, there was no center by treatment group interaction ($P = 20$), and there were no significant differences between centers ($P = 0.059$) nor among the three treatment groups ($P = 0.16$).

CONCLUSIONS. The decrease in levels of PSA in such a group of patients with M1 cancer of the prostate over a 24-week period was surprisingly large, and the differences in these decreased levels between the three treatment arms were remarkably small. There were no apparent differences in bone scan scores, World Health Organization (WHO) performance status, and pain scores between the arms. With regard to sexual function associated with quality of life, there were the understandable difficulties of data collection from patients treated with goserelin. *Prostate 40:105–114, 1999.*

KEY WORDS: **clinical trial; prostate cancer; treatment; maximal androgen blockade; finasteride; PSA; flutamide**

INTRODUCTION

Carcinoma of the prostate gland is one of the most common forms of cancer in men worldwide, and the incidence is increasing [1]. Despite the current interest in screening initiatives and the detection of early confined cancer [2,3], a large proportion of patients still presents with disseminated disease. Treatment for advanced prostatic cancer through the past six decades has been centered on various forms of androgen ablative therapy on the basis of the classical studies of Huggins and Hodges [4] and Huggins et al. [5], which established that the growth, not only of the gland but also of the tumor, was regulated by androgens.

Undoubtedly, an adequate level of circulating testosterone is essential to sustain the growth, development, differentiation, and function of the normal prostate gland [6]. Indeed, a source of circulating testosterone would appear to be a prerequisite to the pathogenesis, not only of cancer of the prostate, but also of benign prostatic hyperplasia (BPH), since neither condition develops after early castration or hypopituitarism. It is generally accepted that the clinical behavior of prostatic cancer reflects its androgen responsiveness [7]. Consequently, in the short term, medical or surgical castration provides effective therapy for the disseminated disease, with the concentration of plasma testosterone falling to approximately 5% of pretreatment levels [8]. The substantial proportion of patients who experience symptomatic relief [7] is consistent with the fact that 90–95% of the circulating testosterone originates in the testis, the remainder being of adrenal origin [9].

It is now well-recognized that cancer of the prostate at this stage is effectively incurable and that medical or surgical castration can only provide palliation [7]. The disease soon progresses and because of this, considerable attention is directed to offering an effective, safe, least-toxic form of therapy to sustain the patient's quality of life. In relation to this, there has also been considerable controversy [7] as to whether "maximal androgen blockade" (MAB) provides real clinical benefit over monotherapy.

The concept of MAB centers on the possible clinical need to maximally counteract the biological effects of androgens on the prostate cancer. There is no doubt that the "residual testosterone" in plasma after castration is of adrenal origin, either secreted directly, or synthesized by peripheral tissues from various adrenal androgens. Moreover, the prostate has been shown to metabolize these adrenal androgens to 5α-dihydrotestosterone (DHT), the active intraprostatic androgen. For MAB, therefore, therapy involves castration, together with the administration of an antiandrogen such as flutamide or bicalutamide, to counter the intraprostatic biological effects of the DHT. The ''pure'' antiandrogen interferes with the binding of DHT to the androgen receptor (AR) within the prostate, thereby interfering with the process by which the DHT-AR complex can regulate the genome by its association with the androgen response elements of the DNA.

Over the past decade, surgery, or the use of luteinizing hormone-releasing hormone (LH-RH) analogues such as goserelin, has been the principal means of providing castration, goserelin eliciting its antigonadal effect by inhibiting pituitary function and thereby decreasing the concentration of plasma testosterone to the level found after surgical castration [10]. There is still controversy as to whether, overall, MAB in the form of a combination of surgical castration and administration of an LH-RH analogue, together with an antiandrogen, provides clinical benefit [11]. It may well do so, but only for a subgroup of patients with good performance status and minimal disease [12].

Nevertheless, accepting the logic of MAB in the management of newly diagnosed, metastatic prostate cancer and mindful of the patient's quality of life [7], it is clearly important to identify the best-tolerated form of MAB. Since treatment with an LH-RH analogue results in impotence and loss of libido, the associated reaction of patients is the perceived, if not actual, depreciation in the quality of their lives. This, together with the dose-limiting side effects associated with flutamide therapy, i.e., nausea, diarrhea, vomiting, and gynecomastia, can provoke an understandable reaction against certain current forms of therapy for advanced prostatic cancer.

On the basis of such considerations, it is very reasonable to consider the clinical potential of using finasteride, a 5α-reductase enzyme inhibitor, in combination with flutamide as a form of MAB. It would be assumed that such a form of therapy should provide adequate MAB, yet maintain sexual interest and potency. It is well-established that finasteride inhibits the capacity of the prostate to synthesize DHT from testosterone [13], a reduction in the intraprostatic concentration of DHT of up to 80% being reported. The associated flutamide would again counter the biological influence of the "residual DHT" on tumor growth, but what is most important, the concentration of DHT would fall as a result of finasteride administration, the levels of testosterone are sustained, thereby providing a reasonable chance of maintaining libido and potency [13,14]. One of the trial investigators, Dr. J. Trachtenberg, reported in a preliminary investigation [15] that patients with advanced disease, treated with the combination of finasteride and flutamide, sustained erectile function.

In order to test this hypothesis, an appropriate randomized, multicenter phase II clinical trial was established and conducted.

MATERIALS AND METHODS

The primary hypothesis of this study was that 10 mg of finasteride, in combination with goserelin acetate or flutamide, in stage M1 prostate cancer patients, would have clinical efficacy similar to the "gold standard" goserelin and flutamide combination, as determined by the decrease in plasma prostate-specific antigen (PSA) levels compared to baseline. A secondary hypothesis was that 10 mg of finasteride, in combination with goserelin acetate or flutamide in these patients, would have clinical efficacy similar to the combination of goserelin and flutamide, as determined by number of metastatic lesions on bone scan and change in WHO performance status.

Patients eligible for inclusion into the study had to be between ages 40–75 years, with histologically confirmed adenocarcinoma of the prostate; evidence of skeletal metastases from bone scan investigations at the screening visit with a bone scan score of 2 or 3 (1–5, or 6–20 metastatic lesions, respectively, as defined on bone scan); a WHO performance status rating of 0–2, based on previous reports; and a concentration of PSA in serum, removed at the screening visit, of 10 ng/ml or greater. Life expectancy of more that 1 year was anticipated, and patients were required to give fully informed written consent.

Men were excluded from the trial who had previously received hormonal therapy, including orchidectomy, or any chemotherapeutic treatment or medication directed to the management of prostate disease. Also excluded were patients who previously had received radiation therapy outside the pelvis, or pelvic radiation, within the previous 12 months; who had evidence of metastasis to the central nervous system, or evidence of spinal cord compression; who had values for tests of liver function that were more than twofold greater than the upper limit of normal; a creatinine level greater that 2.5 mg/dl; severe cardiovascular disease; history of illness that in the opinion of the investigator might confound the results of the study, or possibly pose additional risk to the administration of goserelin, flutamide, or finasteride to the patient; history of drug or alcohol abuse; and evidence of malignancy other than prostate or skin cancer, but excluding melanoma. Finally, patients were excluded if they failed to sign informed consent.

This was a randomized, multicenter, phase II study of patients with stage M1 adenocarcinoma of the prostate, who had previously been untreated for the condition. Men were randomly allocated to one of three treatment schedules:

Group 1: Goserelin, 3.6 mg s.c., monthly, together with flutamide, 250 mg t.i.d. and a placebo, (daily) in the image of 2 × 5 mg finasteride;

Group 2: Goserelin, 3.6 mg s.c., monthly, together with finasteride, 10 mg (2 × 5 mg daily) and a placebo (t.i.d.) in the image of flutamide; and

Group 3: Finasteride, 10.0 mg (2 × 5 mg daily), together with flutamide, 250 mg, t.i.d.

Treatment was given for a period of 24 weeks, with patients entering the study, at most, 2 weeks after the screening visit and then being randomly assigned to their treatment group at week 0. Responsibility for randomization was taken by the Division of Epidemiology and Biostatistics, European Institute of Oncology (Milan, Italy). Patients were evaluated for clinical response at the end of 12 and 24 weeks and could be discontinued from the study at any time if they dem-

TABLE I. WHO Performance Status

Performance scale	Activity	Grade status
Able to carry out all normal activity without restriction	Normal	0
Restricted in physically strenuous activity but ambulatory and able to carry out light work	Restricted activity	1
Ambulatory and capable of all self-care, but unable to carry out any work: up and about 50% of waking hours	Self-care	2
Capable of only limited self-care: confined to bed or chair more than 50% of waking hours	Incapacitated	3
Completely disabled: cannot carry on any self-care, totally confined to bed or chair	Disabled	4

onstrated any objective evidence of disease progression requiring an immediate change in therapy.

Flutamide (or its matching placebo) was to be taken three times daily, before meals. Finasteride (or matching placebo) was to be taken once per day, before breakfast. Goserelin was to be administered monthly, s.c., by a qualified person at the visit to the clinic; there was no sham injection.

A fine-needle biopsy was made of the prostate at the screening visit if the diagnosis of cancer had not already been established. The patients were then randomized (week 0) and further examined at weeks 2, 4, 8, 12, 16, 20, and 24. A bone scan was performed at the screening visit and also at week 24 (or whenever the clinician believed that a bone scan was indicated).

A WHO performance rating (Table I) was administered at weeks 0, 12, and 24. Apart from the determination of serum PSA level at the screening visit, all subsequent PSA and hormone measurements were undertaken by a central specialized analytical laboratory (BioClinical Services International, St. Mellons, Cardiff, UK) under the direction of Professor K. Griffiths.

PSA was measured using the Hybritech Tandem-R immunometric assay (Hybritech, Liege, Belgium). Testosterone and DHT were determined by highly specific and sensitive gas chromatography-mass spectrometric analysis. Wallac immunofluorometric Delfia assays (EG & G Wallac, Milton Keynes, Bedfordshire, U.K.) were used for the measurement of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Quality control of the analysis was undertaken in association using the British National Health Service Supraregional Assay Service assay monitoring programs, those relating to the steroid analysis being the national responsibility of the Tenovus Cancer Research Centre SAS Steroid Reference Laboratory (Cardiff, UK).

The statistical analysis was undertaken by the Division of Epidemiology and Biostatistics, European Institute of Oncology (Milan, Italy) under the direction of Professor P. Boyle, using the SAS package. The analysis, based on the change in serum PSA levels from baseline to the end of the study at 24 weeks, could only be used for those patients who completed the study and is open to a possible bias. Analysis of variance was conducted using Generalized Linear Model Procedures of Statistical Analysis System (proc GLM of SAS), containing explanatory effects for treatment, treatment center, and interaction between treatment and treatment center. A repeated measures analysis of variance was also conducted using 1) only cases with complete information; 2) all available data on all patients (this assumes that dropout can be ignored as regards the differences between the treatments); and 3) imputation procedures to carry out the intent-to-treat analysis [16].

RESULTS

Patients (106) from 20 international centers were randomized to the three treatment groups, goserelin and flutamide (35 patients), goserelin and finasteride (36 patients), and finasteride and flutamide (35 patients). Of the patients entered, 5 were subsequently shown to be ineligible, 4 had less than the minimum number of bone lesions, and 1 had no confirmational evidence of the presence of a tumor. This latter case was randomized on the basis of a previous histological report confirming cancer with a G3 differentiation. This patient was included in the analysis, since the balance of evidence strongly favored eligibility. Moreover, 2 other patients were subsequently shown to have had previous hormonal therapy. In total, 6 patients were ineligible and were retained for the intention-to-treat analysis, but were not included in any analysis of evaluable or eligible patients.

No record of treatment could be found for 2 patients, one randomized to goserelin and flutamide, and the other to goserelin and finasteride. Another patient dropped out of the trial at visit 7 and there was no record of an injection site in the previous records. In the records of the 67 patients who should have

TABLE II. Degree of Differentiation of Prostate Cancer by Treatment Group

Group assessment	High degree (%)	Medium degree (%)	Low degree (%)	None (%)
Goserelin and flutamide	5.7	34.3	57.1	2.9
Goserelin and finasteride	13.9	50.0	33.2	2.8
Finasteride and flutamide	17.1	48.6	31.4	2.9

received six goserelin injections, there were eight discrepancies, five associated with dropout, and evidence of treatment continuing in the other three. Within the protocol of the trial, the data analysis procedures were established in relation to intention to treat and consequently, no provision was made for the analysis of data from patients who did not adhere to the protocol.

As a result, of the 106 patients who were randomized, only 82 completed the study as required by the protocol. This 23% dropout is close to the 25% envisioned in the early calculations on sample size, established when the trial was being planned. There is, however, no evidence that the dropout rate was greater in any one arm of the study compared to the others ($P = 0.35$). The majority of the patients who were withdrawn, did so at the investigation of the investigator (11 patients). Nine withdrew for adverse events and four at their own request.

The concentration of PSA in plasma was determined by one central laboratory. The number of samples available for analysis at each visit peaked at visit 3 (96 samples). This was the second visit after randomization. This number subsequently declined as withdrawals took place.

The mean age of the patients in the study was 71 years, with a range of 51–85 years. In the three arms of the trial, 1) goserelin and flutamide, 2) goserelin and finasteride, and 3) finasteride and flutamide, the mean ages were 70, 71, and 73, respectively. With regard to cancer grade, there was a tendency for the patients in arms 2 and 3, those men receiving finasteride, to have tumors with a higher degree of differentiation (Table II) compared to the other arm (chi-square = 6.1, four degrees of freedom: $P = 0.47$).

The baseline PSA values in the three treatment arms were very similar (Table III), with marked falls in these values as the patients were treated and the trial proceeded. The percent reduction in PSA concentrations of patients who received goserelin and flutamide was 99.1% (95% CI, 97.7, 99.6), 98.75% for those patients who received goserelin and finasteride (95% CI, 97.1, 99.5), and 97.6% for those who received finasteride and flutamide (95% CI, 94.5, 98.9). In the GLM analysis, there was no treatment center by treatment group interaction ($P = 0.20$), and there were no significant differences between the centers ($P = 0.059$), nor among the three treatment groups ($P = 0.16$). Residual analyses confirmed that the assumption of homogeneity of variance was valid and that the normal assumption was also valid. The relationship between the change in log PSA and the randomization value of log PSA was investigated. None was found, thereby implying a constant percent reduction in PSA concentration, irrespective of the baseline PSA value. Imputation and then exclusion of ineligible cases had no effect on the conclusions.

The protocol analysis was based on data from all patients except three on whom no follow-up information was available, with "baseline PSA" concentration imputed from the "screening visit PSA" level, wherever the former was not recorded. Wherever necessary, the "end of study PSA" concentration was imputed by the last-value-carried-forward method. This procedure is equivalent to taking the patient's last visit as the "end of study" visit. There was no evidence of a significant treatment center effect ($P = 0.48$), although there was a treatment effect present ($P = 0.02$). Comparison of the means, using the Bonferroni adjustment, revealed that the reduction in log PSA from the baseline value was greater in the goserelin and flutamide arm compared to the finasteride and flutamide arm ($P = 0.03$). There were no significant differences between the goserelin and flutamide and goserelin and finasteride arms ($P = 0.11$).

There were no significant differences in the change in bone scores between the three arms of the study ($P = 0.60$), and there was no evidence to suggest any differential effect of the three treatment groups on the WHO performance score ($P = 0.51$) over the 24 weeks of the trial.

The hormone measurements were also undertaken by the central laboratory. The data presented (Figs. 1–3 and Table IV) are based on the mean concentrations determined on plasma taken from those patients eligible for analysis.

The mean values for LH quickly decreased after treatment commenced in the two groups of patients receiving goserelin (Figs. 1, 2), whereas the LH concentration rose in the plasma of those given the combination of finasteride and flutamide (Fig. 3). The standard deviation of the mean values was also found to increase in relation to time as the trial progressed, for patients in the finasteride and flutamide arm, indicat-

TABLE III. PSA Information as Baseline and the Change to the End of the Study, Using All Data Imputation, Intent-to-Treat

Group	Baseline mean log (PSA) (s.d.)	Change in log (PSA) mean (s.d.)
Goserelin and flutamide	5.19 (1.70)	−4.68 (2.16)
Goserelin and finasteride	5.11 (1.40)	−4.34 (1.83)
Finasteride and flutamide	5.00 (1.66)	−3.86 (1.82)

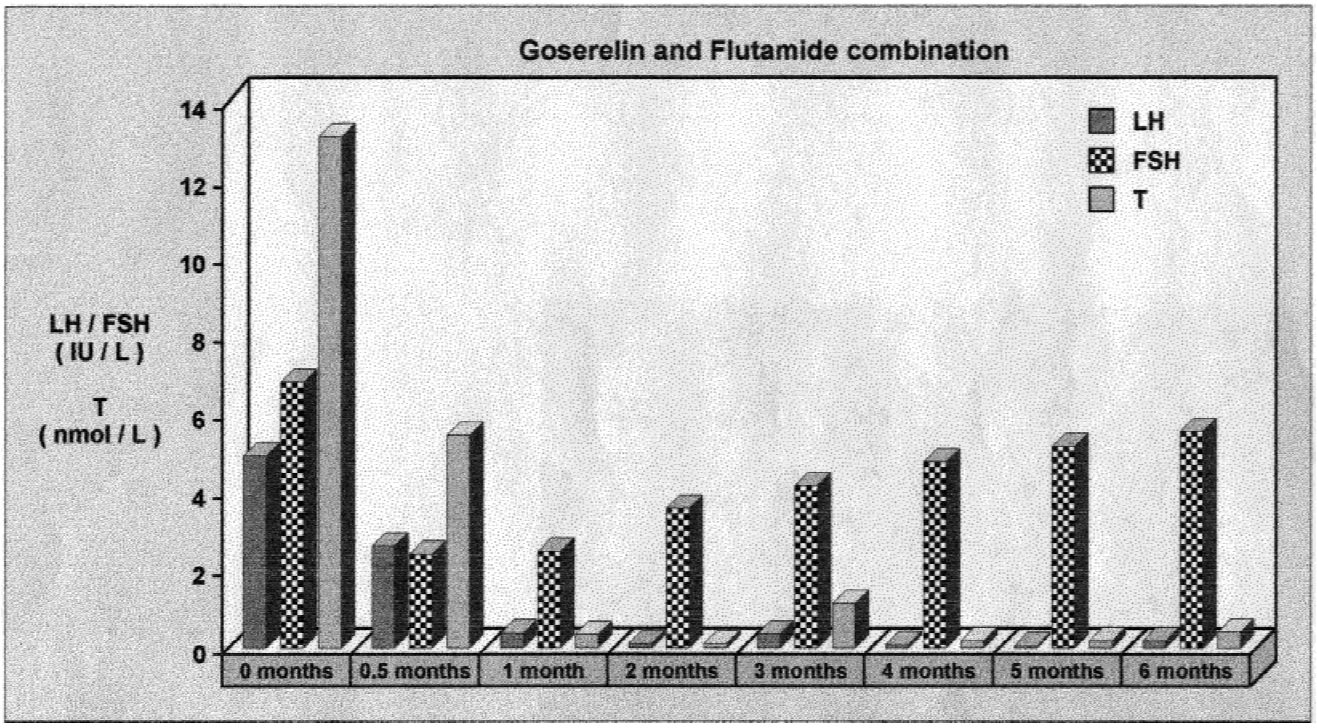

Fig. 1. Mean LH, FSH, and testosterone concentrations in serum of patients with M1 carcinoma of the prostate, randomized to receive the goserelin and flutamide combination.

ing a greater dispersion of LH measurements towards the end of the study, compared to the beginning.

The mean serum FSH levels were fairly constant over time in the samples from patients in the finasteride and flutamide arm (Fig. 3). In patients treated with goserelin (Figs. 1, 2), the mean value decreased abruptly and then increased steadily throughout the period of the trial. It did not, however, increase to the original baseline level.

The pattern with testosterone was similar to that of LH. Shortly after commencement of the study, the mean testosterone value decreased in patients treated with goserelin (Figs. 1, 2). In patients treated with the finasteride and flutamide combination, the mean value rose sharply during the first 4 weeks (visit 3) and remained at this level throughout the period of the trial (Fig. 3). Variability in mean testosterone levels was found to be greater in samples from patients in the finasteride and flutamide arm, but only from visit 3 onwards. This indicates that the spread of values was greater. The concentration of DHT in serum was reduced in patients on all treatment schedules (Table IV).

DISCUSSION

Essentially, this relatively simple trial was established and conducted to evaluate the clinical potential of using the 5α-reductase inhibitor, finasteride, in combination with the "pure" antiandrogen flutamide as a form of maximal androgen blockade (MAB) therapy for patients with M1 disseminated cancer of the prostate. This combination was compared to the "gold standard" MAB of goserelin combined with flutamide, as well as to a third arm of goserelin and finasteride in combination. Since the early preparatory work on establishing the study commenced in late 1994, it was not possible to consider using bicalutamide as it was not registered at the time.

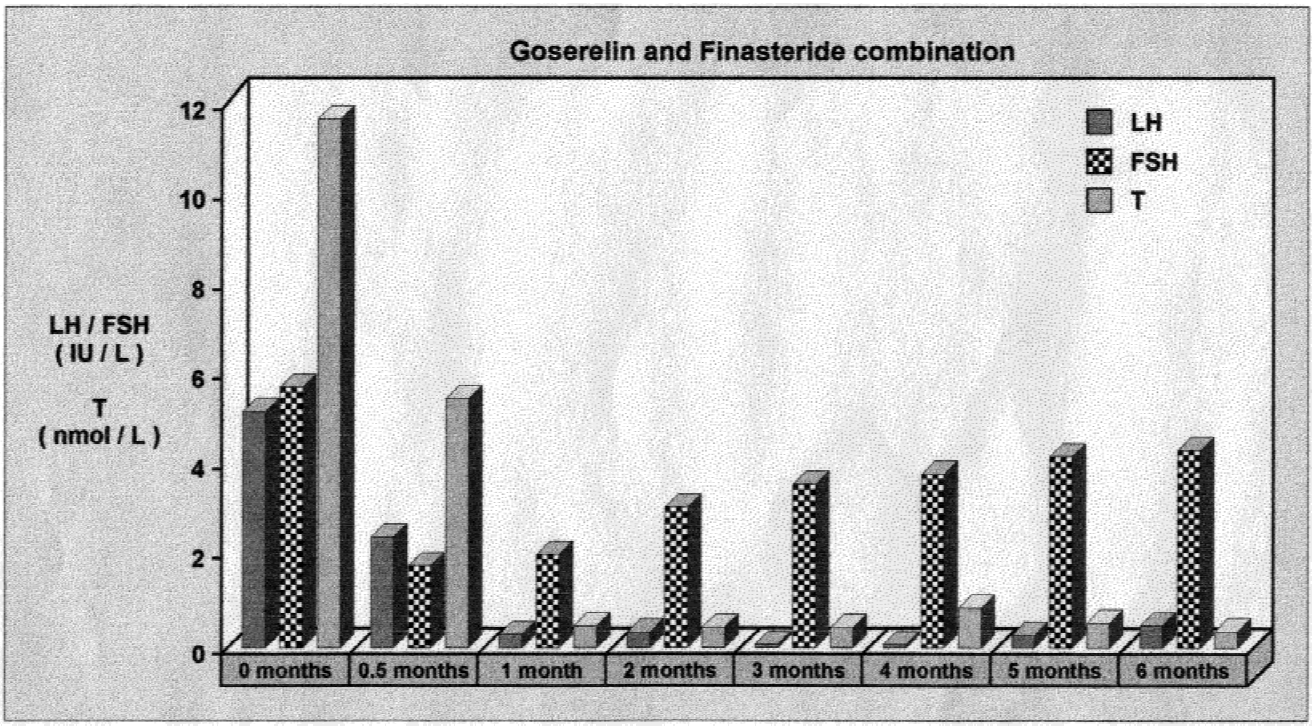

Fig. 2. Mean LH, FSH, and testosterone concentrations in serum of patients with M1 carcinoma of the prostate, randomized to receive the goserelin and finasteride combination.

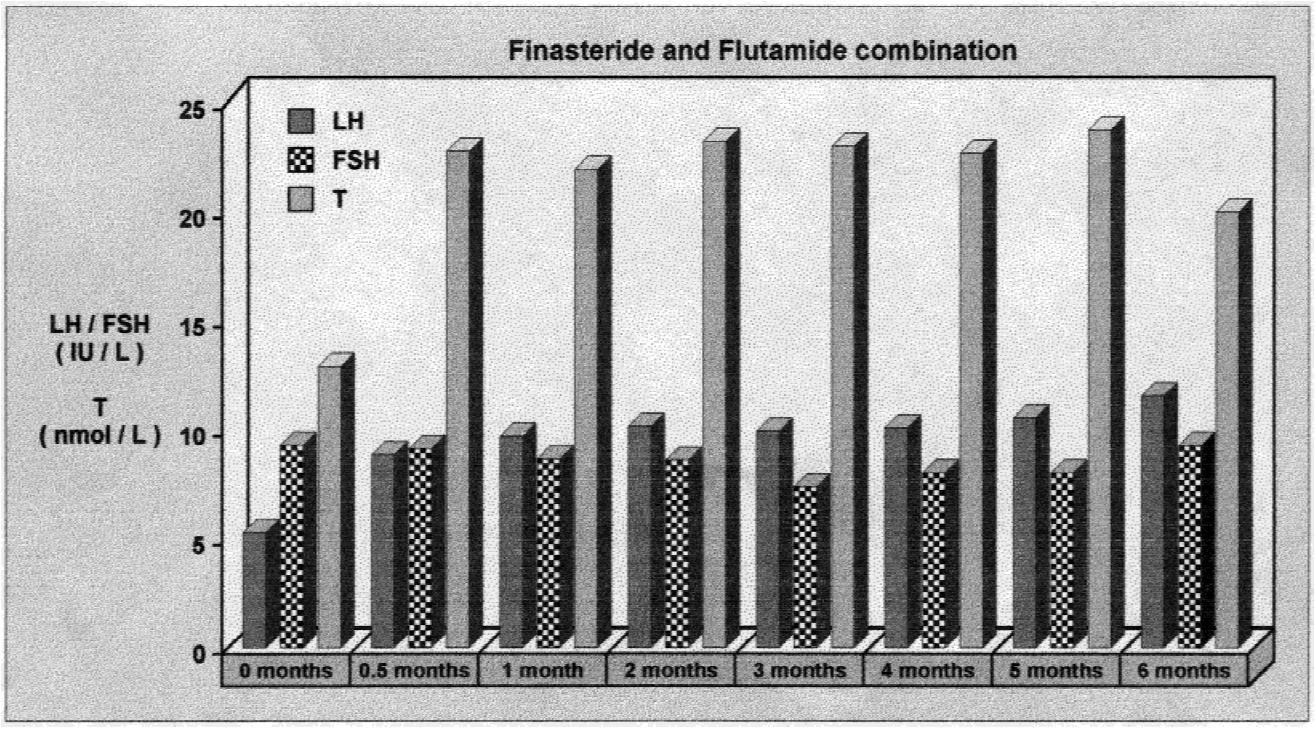

Fig. 3. Mean LH, FSH, and testosterone concentrations in serum of patients with M1 carcinoma of the prostate, randomized to receive the finasteride and flutamide combination.

TABLE IV. 5α-Dihydrotestosterone Concentrations (pg/ml) in Serum of Patients

Treatment	Week 0	Week 2	Week 4	Week 8	Week 16	Week 24
Goserelin + flutamide	950 ± 1,050	240 ± 360	60 ± 220	30 ± 160	50 ± 180	50 ± 170
Goserelin + finasteride	750 ± 740	210 ± 810	30 ± 130	40 ± 140	30 ± 110	10 ± 70
Finasteride + flutamide	1,110 ± 890	170 ± 320	140 ± 310	100 ± 250	180 ± 340	130 ± 280

There was a marked decrease in the concentration of PSA in the plasma of all patients who completed this study, i.e., men in all three arms of the trial, with no significant difference, overall, between treatment groups ($P = 0.22$). In the data analysis performed as required in the protocol, using all patients in the trial and with imputation and last result carried forward, it would appear, however, that the combination of goserelin and flutamide, the "gold standard" treatment, reduced the levels of PSA significantly more than the combination of finasteride and flutamide ($P = 0.03$). The repeated measures analysis of variance of eligible patients revealed significant differences in the changes in log PSA values from baseline levels through the period of the trial. The principal difference related to the greater reduction in the PSA values ($P = 0.001$). At all time points of the study, there was no evidence that the reduction in log PSA was greater with goserelin and flutamide than with the other two arms of the study. The intent-to-treat analysis yielded findings which were both qualitatively and quantitatively similar to those with no imputation, from the analysis of data from eligible patients.

There was no evidence of any significant differences between the three treatment arms in the bone scan scores, the WHO performance scores, and the pain scores. Real analysis of data relating to quality of life assessment was not possible due to the well-known difficulties of collecting information from patients with reduced sexual activity and potency after treatment with goserelin. Information on libido, sexuality, and potency was, however, collected from patients treated with the finasteride and flutamide combination.

During evaluation of the findings from this study, it is important to remember that the availability of the principal "study endpoint" as stated in and required by the prepared protocol, essentially the 24-week concentration of PSA in plasma relative to the baseline (week 0) value, is not as good as was hoped. Within the study, there were 14 patients (13%) who did not have a baseline PSA value, and 7 patients completed the study to the 24-week endpoint, but a final sample of serum was not made available for PSA determination. However, imputation of baseline PSA concentration from the value determined at the "screening visit" would not appear unreasonable, although there may be doubts as to whether it is reasonable, for the analysis, for those patients without the last PSA level to carry the "last determined" PSA level concentration forward as the "end of study" 24-week value. There are good arguments, however, put forward by many, that in the assessment of "response" to treatment by consideration of the change in PSA levels from pretreatment values, the really important period is after 12 weeks of therapy. Many clinicians would argue that the change in PSA values after 12 weeks of treatment is the critical time for patient evaluation. Therefore, the proportion of patients is important whose PSA concentration "normalized" to less than 4 ng/ml at 12 weeks [17] and the percentage who reached 0.57 ng/ml.

Also important in this study was that, overall, the patients with the goserelin and flutamide combination had less differentiated tumors than those in the other arms of the trial (Table I).

A total of 937 adverse events was recorded. Among the group of patients who completed the study, 75% of those treated with goserelin and flutamide reported an adverse event at week 24. Of those on goserelin and finasteride, 96% reported adverse events at this time, as did 85% of men on finasteride and flutamide. The most common events were hot flushes, breast pain, gynecomastia, diarrhea, and pain, general but often localized to joints, legs, and neck. There were 80 adverse events relating to the endocrine system, 91% from the patients treated with the finasteride and flutamide combination.

With regard to the adverse events which, in the case report forms, were recorded as "definitely related to treatment," there were no differences in the proportions of patients in each arm, reporting such events at each visit.

With regard to differences in the "adverse event rate" per person that were associated with those recorded as being "unlikely to be related to treatment," 21% of patients in the goserelin and flutamide arm had reported such events by the end of the study, compared to 15% of those patients treated with finasteride and flutamide and 9% of those in the goserelin and finasteride arm.

The endocrine profiles, i.e., changes in serum hormone concentrations throughout the study period, followed a pattern that was expected from previous studies [10,15]. Most important were the data indicat-

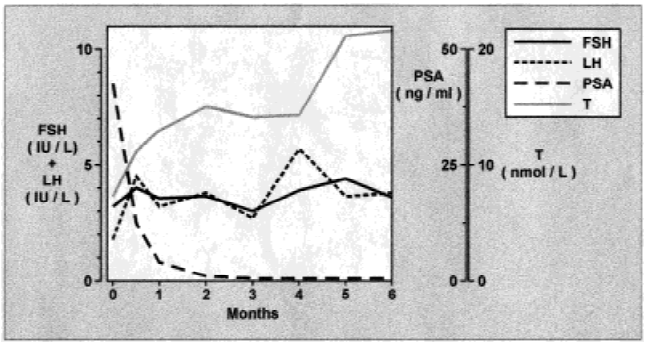

Fig. 4. Typical profile of changes in the concentration of hormones and PSA in the serum of a patient with M1 carcinoma of the prostate, treated with the finasteride and flutamide combination.

ing that the level of testosterone in the serum of patients treated with the finasteride and flutamide combination was maintained, if not increased, by the therapy. A typical profile from such a patient is shown in Figure 4. PSA levels decreased, there were minimal changes in the FSH and LH concentrations, and the level of testosterone was markedly elevated. A typical profile for a patient treated with the goserelin and flutamide combination is shown for comparison in Figure 5, showing the dramatic fall in the concentrations of LH, FSH, and testosterone as, well as PSA.

Despite the obvious difficulties encountered with this study and the problems associated with the occasional "tardiness" with which data were recorded and samples collected, it does not seem unreasonable to state, after a careful evaluation of the information that accumulated, that there was little difference between the primary and secondary outcomes of this trial relative to the three treatment arms.

Essentially, the decline of plasma PSA, from baseline through 24 weeks, was remarkably large in such a group of patients with M1 metastatic carcinoma of the prostate. The differences between the fall in plasma PSA values between the three treatment groups were surprisingly small.

Furthermore, there were no apparent differences in the bone scan score, the WHO performance score, or in the pain score, between the three arms of the study. The problems of data collection on sexual issues of libido, sexual performance, and potency were expected in those patients who were treated with goserelin. Unfortunately, within the clinic, real consideration is rarely given to the type of person who should collect such information from these fragile and easily embarrassed patients who see themselves failing in their sexual relations. This is clearly understandable, but if such data are to be collected, then more precise, pragmatic advice may be necessary from those experts who better appreciate such problems and who can instruct the "prostate clinics." Those patients treated with the finasteride and flutamide combination were undoubtedly more sexually active than men in the "goserelin arms," such that it may possibly be concluded, although from a somewhat subjective viewpoint, that at least one aspect of their quality of life was not influenced unduly, by their disease and its treatment. This was of course expected from the data on the analysis of hormones, which clearly showed that in patients on finasteride and flutamide, the concentration of testosterone in plasma was sustained throughout the 24 weeks of treatment.

The efficacy with which the finasteride and antiandrogen combination therapy sustained the concentration of testosterone in serum is also important with regard to other aspects of the patient's endocrine status. Although not apparently seen as a particularly serious issue, the decline in serum testosterone levels in patients treated with LH-RH analogues will undoubtedly lead to changes in bone mineral density and, in the long term, to osteoporosis. Although it may be that such changes will not place patients with disseminated disease in any further significant risk relating to bone fractures, the fact that treatment with finasteride and flutamide maintains serum testosterone levels and is probably not associated with bone loss, would appear to offer an additional benefit. It would be assumed that the decline in testosterone levels in serum induced by LH-RH treatment is associated with a concomitant fall in serum estradiol concentrations which is the endocrine change related to bone loss. It would be interesting, in future phase III studies of therapeutic regimens involving comparison between the use of LH-RH analogues and finasteride and antiandrogen combinations, if prospective longitudinal studies were undertaken to monitor the capacity of the combination treatment to prevent bone mineral loss.

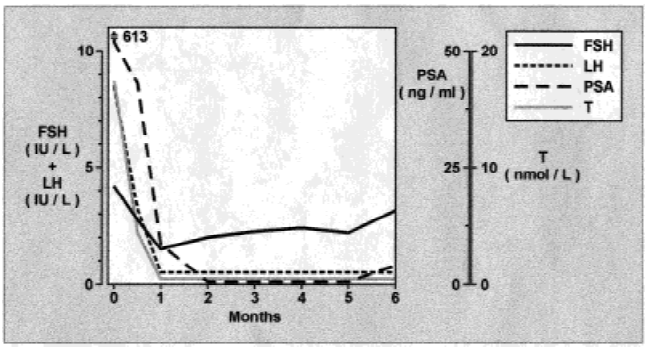

Fig. 5. Typical profile of changes in the concentrations of hormones and PSA in the serum of a patient with M1 carcinoma of the prostate, treated with the finasteride and flutamide combination.

It seems reasonable to suggest, therefore, that the trial did provide the necessary information to direct more attention to the clinical potential as a form of MAB therapy, of the combination of finasteride, a 5α-reductase inhibitor, with an antiandrogen, either flutamide, as used in this study, or bicalutamide, which would now be the preference of many urologists. The results suggest that a further randomized phase III trial would be justified, possibly for M1 disease, but also for patients with M0 disease with regionally advanced cancer. The duration of that study should be longer. It also seems not unreasonable to consider the combination of finasteride and an antiandrogen in long-term adjuvant therapy studies, using serum PSA levels as the monitoring "marker" of disease control, or progression and survival as the principal endpoint.

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