

BILATERAL ORCHIECTOMY WITH OR WITHOUT FLUTAMIDE FOR METASTATIC PROSTATE CANCER

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ABSTRACT

Background Combined androgen blockade for the treatment of metastatic prostate cancer consists of an antiandrogen drug plus castration. In a previous trial, we found that adding the antiandrogen flutamide to leuprolide acetate (a synthetic gonadotropin-releasing hormone that results in medical ablation of testicular function) significantly improved survival as compared with that achieved with placebo plus leuprolide acetate. In the current trial, we compared flutamide plus bilateral orchiectomy with placebo plus orchiectomy.

Methods We randomly assigned patients who had never received antiandrogen therapy and who had distant metastases from adenocarcinoma of the prostate to treatment with bilateral orchiectomy and either flutamide or placebo. Patients were stratified according to the extent of disease and according to performance status.

Results Of the 1387 patients who were enrolled in the trial, 700 were randomly assigned to the flutamide group and 687 to the placebo group. Overall, the incidence of toxic effects was minimal; the only notable differences between the groups were the greater rates of diarrhea and anemia with flutamide. There was no significant difference between the two groups in overall survival ($P=0.14$). The estimated risk of death (hazard ratio) for flutamide as compared with placebo was 0.91 (90 percent confidence interval, 0.81 to 1.01). Flutamide was not associated with enhanced benefit in patients with minimal disease.

Conclusions The addition of flutamide to bilateral orchiectomy does not result in a clinically meaningful improvement in survival among patients with metastatic prostate cancer. (N Engl J Med 1998;339:1036-42.)

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ADENOCARCINOMA of the prostate is the most commonly diagnosed malignant neoplasm in the United States.¹ Presently, there is no curative treatment for patients with metastatic prostate cancer, who have a progressive and eventually fatal clinical course. The median survival of cohorts of patients with metastatic disease who have entered large-scale, prospective, randomized trials during the past three decades has been relatively stable (range, 24 to 36 months).²⁻⁶

Initially, the growth of prostate cancer requires androgens. This is the rationale for endocrine ma-

nipulations that rely on the suppression of testosterone production to control androgen-dependent tumor growth.²⁻⁶ Androgen deprivation has substantial palliative effects, but in virtually all patients the tumor eventually progresses to an androgen-insensitive state in which no treatment can prolong survival.⁷

Suppression of androgens of testicular origin is the focus of androgen-deprivation treatment. This can be accomplished by surgical castration or by medical suppression of testicular function with synthetic analogues of gonadotropin-releasing hormone.²⁻⁶ However, after ablation of the testes by either means, the incorporation of androgens into the cell nucleus continues, as a result of undiminished production of androgens by the adrenal glands.⁸⁻¹⁰ The effects of these androgens can be counteracted by adding an antiandrogen drug such as flutamide to testicular ablation. This form of combined androgen blockade enhances antitumor effects and reduces the size of normal prostate glands and seminal vesicles in animal models.⁸⁻¹⁰

Since the early 1980s, numerous randomized clinical trials have evaluated the efficacy of combined androgen blockade.¹¹ Three large trials, including our previous trial,¹² suggested that combined androgen blockade conferred an important survival advantage.¹²⁻¹⁴ An overview of the literature, published in 1995,² and a 1997 meta-analysis of studies of combined androgen blockade¹⁵ did little to resolve the controversy over the advantages of combined androgen blockade.^{16,17} In our previous trial, conducted in patients who had prostate cancer with distant metastases and who had not previously received antiandrogen agents, we compared leuprolide acetate plus flutamide with leuprolide acetate plus placebo. Patients in the group receiving combined androgen blockade had superior progression-free and overall survival. We began the present study in 1989 to evaluate combined androgen blockade further. The primary differ-

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ence from the previous trial was the method of castration: bilateral surgical orchiectomy replaced daily administration of subcutaneous leuprolide acetate.

METHODS

Eligibility

All eligible patients had histologically confirmed adenocarcinoma of the prostate, with bone or distant soft-tissue metastases, and a Southwest Oncology Group performance status score from 0 to 3 on a scale of 0 to 4 (0 denotes fully active; 1, restricted in strenuous activity but ambulatory; 2, ambulatory and capable of self-care but unable to work; 3, capable of only limited self-care and confined to a bed or chair >50 percent of the time; and 4, completely disabled, unable to manage self-care, and totally confined to a bed or chair). Patients with a performance status of 3 were eligible only if pain was the primary cause of their functional impairment. Patients were required to have adequate renal function (indicated by a serum creatinine concentration not greater than two times the upper limit of normal); a white-cell count of at least 3000 per cubic millimeter; no previous or concomitant hormonal treatment, chemotherapy, or treatment with biologic-response modifiers; no other malignant tumors within the previous five years, with the exception of skin cancer other than melanoma; no history of serious infections; and a signed informed-consent form. Previous or concomitant palliative radiation to metastatic sites at the time of study entry was allowed.

Study Design

This study was conducted as a double-blind, randomized trial with flutamide and placebo groups. Patients in both groups underwent immediate bilateral orchiectomy. The dosage of flutamide consisted of two 125-mg capsules taken orally three times daily until a progression of disease was noted, at which time the assigned treatment was revealed; patients in the flutamide group were treated at the discretion of their physicians, whereas those in the placebo group could be given open-label flutamide. Because the survival of patients with androgen-insensitive prostate cancer has not been shown to be prolonged by any treatment, and because consistency with our previous trial was necessary, the design of this trial did not include guidelines for treatment after progression, and crossover from placebo to flutamide was optional. The treatments used after disease progression were not recorded.

Registration was performed at a coordinating center by telephone. Patients were prospectively stratified according to their performance status (0 to 2 vs. 3) and extent of disease (minimal vs. extensive). Minimal disease was defined as nodal metastases, pelvic and axial skeletal involvement detectable on bone scans, or both. Extensive disease included appendicular skeletal involvement (with or without axial skeletal involvement), visceral (lung or liver) metastasis, or both. Randomization was dynamically balanced with respect to these stratification factors, according to the method of Pocock and Simon.¹⁸

Eligibility was assessed after registration only with reference to the data gathered before randomization. Only the patients who clearly did not have distant metastases at the time of randomization were regarded as ineligible for inclusion in the analyses.

Assessments

All eligible patients underwent a base-line history taking and physical examination, a complete blood count, and measurements of serum creatinine, liver enzymes, alkaline phosphatase, acid phosphatase, serum testosterone, and prostate-specific antigen (PSA). These studies were repeated one and three months later and every three months thereafter. All laboratory assessments were performed at the local participating institution. Pathological specimens obtained before randomization were submitted for review at the study center. Patients underwent chest radiography, bone scanning, bone radiography, and computed tomography of

the abdomen and pelvis at base line, at six-month intervals for the first two years, and then at the discretion of the investigators. Radiologic studies (at a minimum, a bone scan) were obtained if the PSA level rose by more than 25 ng per milliliter during any three-month period after the initial two-year period.

End Points

The primary end point was death from any cause. The chief secondary end point was progression-free survival. Disease progression was defined as an increase of 50 percent or more or of 10 cm² (whichever was smaller) in the sum of the products of the largest perpendicular diameters of measurable lesions, as compared with the smallest sum observed; reappearance of any lesion or overt worsening of any lesion that could be evaluated; a patient's inability to return for evaluation because of a deterioration in his condition (unless the deterioration was clearly not due to a progression of disease); and any worsening visible on a bone scan. Patients with a rising PSA level as the only evidence of worsening of disease were not considered to have objective progression.

Another secondary end point was a PSA response, defined as a PSA level of less than 4.0 ng per milliliter at any time after randomization. Patients were included in the analysis of this secondary end point only if their base-line PSA level had been measured with an assay calibrated to 4 ng per milliliter as the upper limit of normal. This method of patient selection is independent of group assignment and follow-up events. Follow-up PSA values included all values obtained through the date of progression. We assumed that patients for whom data were insufficient did not have a PSA response.

Statistical Analysis

The accrual goal for this trial was 1248 eligible patients, all of whom would have an equal probability of being assigned to either study group. The size of the study population was computed¹⁹ according to the following assumptions: one-sided testing, a power of 90 percent, an overall probability of a type I statistical error of 0.05, a mean survival in the placebo group of 28.3 months (on the basis of the results of our previous trial¹²), a risk of death (hazard ratio) of 0.80 (for the flutamide group as compared with the placebo group), an estimated accrual rate of 40 patients per month, and two years of follow-up after accrual had ended. We chose a hazard ratio of 0.80 for death, corresponding to a 25 percent improvement in survival among the patients given flutamide, on the basis of the results of our previous trial.¹² The trial was planned with a one-sided hypothesis because treatment would be modified only if the flutamide group had a significantly better outcome. Two formal analyses to precede the final analysis were planned with P values of 0.008 and 0.009 as the criteria for significance, and the planned criterion for significance in the final analysis was a P value of 0.043, with an overall probability of a type I statistical error of 0.05.²⁰ The trial was overseen by the Southwest Oncology Group data and safety monitoring committee.

Patients' characteristics were compared by Fisher's exact test, as were the rates of toxic effects. Intention-to-treat analyses of survival time and progression-free survival time for each group included all patients who were regarded as eligible, with any length of follow-up. The stratified log-rank test was used for primary analysis of survival and progression-free survival in the two groups. The PSA response was analyzed by Fisher's exact test in an intention-to-treat analysis, since all patients included in the PSA-response data set were selected independently of group assignment and follow-up events, and all had a defined PSA response. Two-sided P values are reported for preplanned one-sided tests.

RESULTS

Patients

From December 1989 to September 1994, 1387 patients were randomly assigned to receive flutamide

or placebo: 700 to the flutamide group and 687 to the placebo group. An accrual overrun was allowed in order to increase statistical power in the analysis of the subgroup of black patients and the subgroup of patients with minimal disease. Two patients, both in the flutamide group, were found to be ineligible after randomization: one had no evidence of prostate cancer, and the other had transitional-cell carcinoma of the bladder. The remaining analyses dealt only with eligible patients: 687 in the placebo group and 698 in the flutamide group. There were no significant differences between the two groups with respect to the base-line characteristics used in stratification (Table 1). The stratification according to performance status was ignored in subsequent computations because fewer than 5 percent of patients in each group had a performance status of 3 (Table 1), and the results of statistical modeling with and without stratification for performance status were equivalent.

Table 1 shows the demographic characteristics, features of the disease, and laboratory values for eligible patients. The only significant difference between the two groups was in the incidence of bone pain; there were significantly more patients with bone pain in the placebo group ($P=0.03$ by statistical testing without correction for multiplicity or correlation with other attributes).

Initiation of Treatment and Follow-up

Twenty-six patients, 10 in the placebo group and 16 in the flutamide group, did not receive combined treatment, for various reasons. All the eligible patients were included in the primary, intention-to-treat analyses, with the exception that patients without follow-up data (two patients in the placebo group and one in the flutamide group) could not be included in the analyses of time to treatment failure.

Toxicity

Table 2 lists the most commonly reported toxic effects with a severity grade of 2 or greater. A total of 43 patients (33 in the flutamide group and 10 in the placebo group, $P=0.003$) were removed from the study because of drug toxicity. Overall, treatment was well tolerated, and no treatment-related deaths were reported. The only significant differences in the incidence of toxic effects between the two groups were related to diarrhea rated grade 2 or worse (6.3 percent in the flutamide group vs. 2.7 percent in the placebo group, $P=0.002$) and anemia rated grade 2 or worse (8.5 percent in the flutamide group and 5.4 percent in the placebo group, $P=0.024$).

Survival and Progression-free Survival

The primary data on overall survival and progression-free survival for 1382 eligible patients are presented in Table 3 and Figures 1, 2, and 3. Although

TABLE 1. BASE-LINE CHARACTERISTICS OF ELIGIBLE PATIENTS.*

CHARACTERISTIC	PLACEBO GROUP (N=687)	FLUTAMIDE GROUP (N=698)
Performance-status score and extent of disease — no. of patients (%)		
0–2, minimal disease	143 (20.8)	140 (20.1)
0–2, extensive disease	516 (75.1)	532 (76.2)
3, minimal disease	3 (0.4)	1 (0.1)
3, extensive disease	25 (3.6)	25 (3.6)
Age — yr		
Mean	70.3	70.2
Median	71	71
Interquartile range	65–76	65–76
Range	43–90	30–93
Black race — no. of patients (%)	154 (22.4)	155 (22.2)
Body-mass index		
Mean	26.4	26.4
Median	25.5	25.8
Interquartile range	23.0–28.1	23.3–28.5
Days from initial diagnosis to study entry		
Mean	502	683
Median	45	49
Interquartile range	12–649	11–657
Range	0–7621	0–6086
Median Gleason score†	8	8
Site of soft-tissue disease — no. of patients		
Abdominal nodes	99	93
Distant nodes	56	56
Lung or pleura	52	54
Liver	13	9
Central nervous system or brain	4	1
Other	47	38
None	488	500
Site of bone disease — no. of patients		
Extremity	285	298
Pelvis	422	435
Ribs	383	404
Spine	500	524
Skull	173	207
Other	142	151
None	65	52
Bone pain — no. of patients (%)‡	338 (57.0)	303 (51.0)
Serum testosterone — ng/dl§		
Mean	363	359
Median	340	340
Interquartile range	241–468	237–476
Serum PSA — ng/ml¶		
Mean	647	706
Median	130	193
Interquartile range	47–601	61–647

*Because of rounding, not all percentages total 100. The body-mass index is calculated as the weight in kilograms divided by the square of the height in meters.

†The values for the Gleason score are those determined in the central pathological review.

‡ $P=0.03$ for the comparison between the two groups. Information on bone pain was available for 593 patients in the placebo group and 597 in the flutamide group.

§Data were available for 485 patients in the placebo group and 487 in the flutamide group.

¶The prostate-specific antigen (PSA) values are those of patients whose base-line PSA had been measured with an assay calibrated to 4 ng per milliliter as the upper limit of normal. This analysis included 382 patients in the placebo group and 407 in the flutamide group.

TABLE 2. MOST COMMON TOXIC EFFECTS RATED GRADE 2 OR HIGHER.

TOXIC EFFECT	PLACEBO GROUP (N=669)	FLUTAMIDE GROUP (N=667)	P VALUE
	no. of patients (%)		
Diarrhea	18 (2.7)	42 (6.3)	0.002
Hepatic dysfunction	13 (1.9)	16 (2.4)	0.708
Nausea	17 (2.5)	15 (2.2)	0.859
Vomiting	13 (1.9)	12 (1.8)	0.846
Hot flashes	65 (9.7)	69 (10.3)	0.784
Anemia	36 (5.4)	57 (8.5)	0.024

flutamide appears to have a slight advantage ($P=0.14$ by two-sided stratified log-rank analysis), the difference was not statistically significant in the light of the planned one-sided P value of 0.043 for significance. The estimated hazard ratio for death in the flutamide group as compared with the placebo group was 0.91 (90 percent confidence interval, 0.81 to 1.01). (The trial was planned to have sensitivity for a hazard ratio of 0.8 or less for death, corresponding to a prolongation in survival of approximately 25 percent for the flutamide group.)

Changes in Serum PSA Levels

The PSA analysis included 789 patients, 382 and 407 from the placebo and flutamide groups, respec-

tively. These subgroups had base-line characteristics similar to those of the entire sample (data not shown). The proportion of patients in the flutamide group with at least one PSA measurement of 4.0 ng per milliliter or lower was 74 percent (95 percent confidence interval, 69.4 to 78.2 percent), as compared with 61.5 percent (95 percent confidence interval, 56.4 to 66.4 percent) for patients in the placebo group ($P<0.001$ by Fisher's exact test). Thus, the percentage of PSA responses was significantly higher among patients receiving flutamide than among patients receiving placebo, but patients in the flutamide group did not have significantly better survival.

DISCUSSION

In this trial we were unable to confirm the results of our previous trial,¹² in which we found a 25 percent or greater improvement in median survival among patients with metastatic prostate cancer who received leuprolide acetate with flutamide, as compared with those who received leuprolide alone. It is possible, however, that the results of that trial were overly influenced by a lack of compliance with the regimen of daily leuprolide acetate injections; if so, testicular suppression may have been inadequate, thereby magnifying the benefit of flutamide as compared with placebo. This possibility cannot be ruled out because that study included no provisions for systematic evaluation of serum testosterone levels.

Another explanation for the different findings of the two studies may be the transient stimulation of pituitary gonadotropins and testosterone during the

TABLE 3. OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL.*

VARIABLE	PLACEBO GROUP	FLUTAMIDE GROUP	RISK RATIO (90% CI)	P VALUE
Eligible patients with follow-up — total no. (no. who died)	685 (480)	697 (468)		
Minimal disease	146 (71)	141 (76)		
Extensive disease	539 (409)	556 (392)		
Median follow-up — mo	49.2	50.1		
Survival — median no. of months (95% CI)				
Overall, not stratified	29.9 (28.5–32.1)	33.5 (28.9–38.1)		0.16
Stratified			0.91 (0.81–1.01)†	0.14‡
Minimal disease	51.0 (40.0–?)	52.1 (48.1–63.8)		
Extensive disease	27.5 (24.6–29.9)	28.5 (25.7–31.4)		
Progression-free survival — median no. of months (95% CI)				
Overall, not stratified	18.6 (17.2–21.0)	20.4 (18.2–22.7)		0.26
Stratified				0.21
Minimal disease	46.2 (29.1–?)	48.1 (37.8–56.5)		
Extensive disease	16.0 (14.7–17.7)	17.5 (15.6–19.0)		

*The planned primary statistical test was the stratified log-rank test for survival. A question mark indicates cases in which the upper limit of the 95 percent confidence interval (CI) could not be estimated.

†The risk ratio in this analysis was the hazard ratio for death in the flutamide group as compared with the placebo group.

‡The planned primary statistical test was a one-sided, stratified log-rank test for survival with a criterion for significance of 0.043.

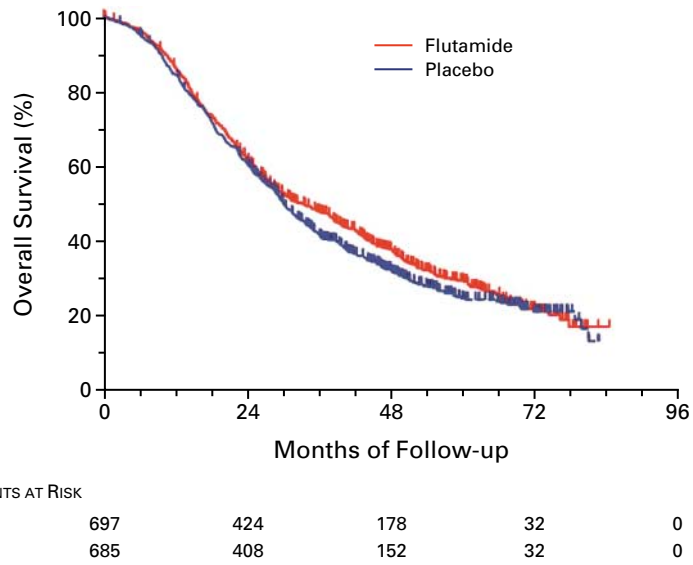


Figure 1. Overall Survival among Eligible Patients with Follow-up, According to Treatment Assignment.

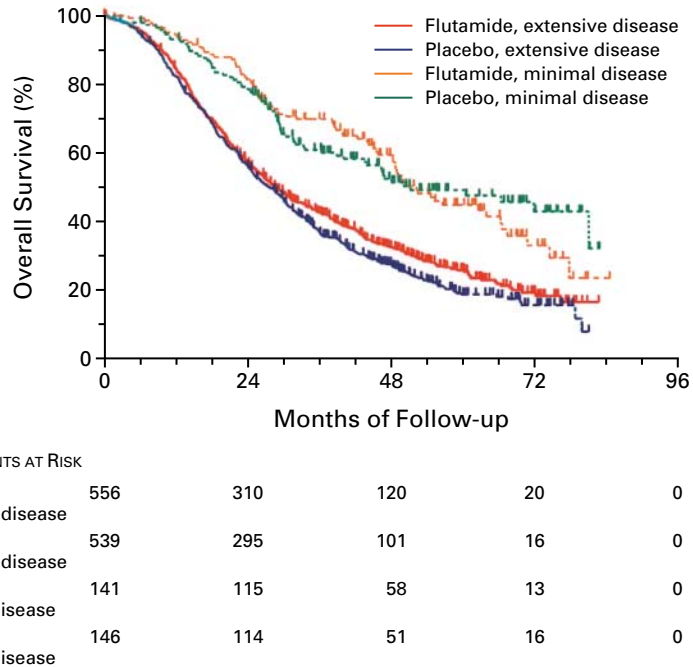
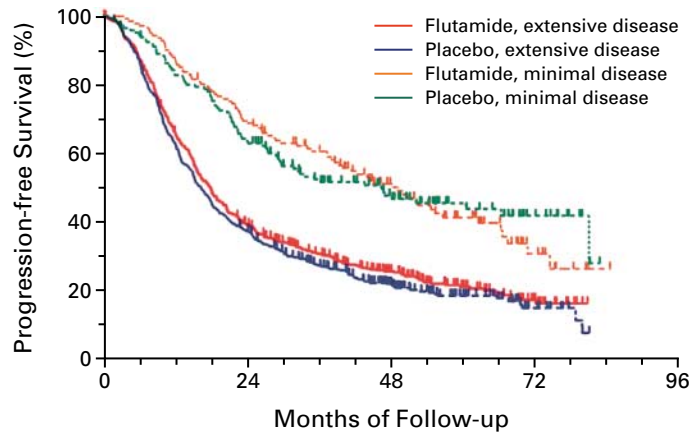


Figure 2. Overall Survival among Eligible Patients with Follow-up, According to Treatment Assignment and Extent of Disease.



NO. OF PATIENTS AT RISK		0	24	48	72	96
Flutamide, extensive disease	556	213	86	16	0	0
Placebo, extensive disease	539	196	74	12	0	0
Flutamide, minimal disease	141	97	48	11	0	0
Placebo, minimal disease	146	92	46	13	0	0

Figure 3. Progression-free Survival among Eligible Patients with Follow-up, According to Treatment Assignment and Extent of Disease.

initial two weeks of treatment with a gonadotropin-releasing hormone agonist such as leuprolide acetate.²¹ This initial stimulatory phase can be associated with a worsening of symptoms and signs of disease. However, it can be effectively counteracted by concomitant administration of nonsteroidal antiandrogens, which may have a long-term effect.²² Evidence from the earlier trial suggests that during the first 12 weeks of treatment, there are favorable trends in performance status, pain, and serum acid phosphatase concentrations in patients receiving flutamide.¹² We took these considerations into account in the design of the present trial by using bilateral orchiectomy for castration instead of leuprolide acetate.

The two trials had similar eligibility requirements and were conducted for the most part in the same participating institutions. The only distinct differences were the greater proportion of patients with minimal disease and the younger age of patients in the earlier trial ($P < 0.001$, data not shown). Yet the two trials have different implications with respect to the benefit of flutamide, and the previously observed advantage for patients with minimal metastatic disease²³ was not seen in the present trial.

In this trial, a significantly larger proportion of patients in the flutamide group had a PSA response, as compared with the placebo group (74.0 percent vs. 61.5 percent, $P < 0.001$). Two aspects of this finding are worth noting. First, the comparison of the rates of PSA response was an intention-to-treat

analysis and therefore is not subject to the dropout biases that plague most analyses of changes in biochemical markers, including those using a landmark analysis. Second, the large difference between the groups in the rates of PSA response is not reflected in a large difference in survival. The latter point suggests that PSA has no role as a surrogate marker for survival in patients with metastatic prostate cancer.²⁴

In view of the differences in the results of these two trials, it may be worthwhile to reassess the relative merits of medical and surgical methods of castration, either alone or in combination with flutamide or other antiandrogen agents. Meanwhile, a critical assessment of the present results suggests that the benefit of combined androgen blockade in patients with metastatic prostate cancer is negligible.

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