

Experience With Flutamide in Patients With Advanced Prostatic Cancer Without Prior Endocrine Therapy

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Seventy-two patients with advanced prostatic carcinoma without previous endocrine therapy were treated with an oral nonsteroidal antiandrogen, flutamide. Sixty-three patients (87.5%) had a favorable response, and 9 patients showed no response. Flutamide appears to be a safe antiandrogen, usually effective in the management of patients with advanced prostatic cancer who have had no prior endocrine therapy.

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FLUTAMIDE (Sch-13521) is a substituted anilide, 4' nitro-3' trifluoromethylisobutyranilide. In a variety of laboratory animals, it has been found to be a potent antiandrogen without estrogenic, antiestrogenic, progestational, antiprogestational, androgenic, adrenocortical, or antagonodotropic activities.^{1,2}

Two clinical trials with flutamide in the treatment of advanced prostatic carcinoma have been previously reported from Memorial Sloan-Kettering Cancer Center (MSKCC)^{3,4}: a 23% favorable response of short duration with its use in patients with advanced prostatic carcinoma refractory to conventional endocrine therapy,³ and a 90% favorable response in patients with advanced disease who had not received prior endocrine treatment.⁴ This is an update on the 21 patients in the second clinical trial, and includes 53 additional flutamide-treated patients with metastatic prostate cancer who had no prior endocrine therapy.

Materials and Methods

From July 1973 to October 1981, 74 patients with previously untreated prostatic carcinoma were treated with flutamide at Memorial Sloan-Kettering Cancer Center. Two patients discontinued the drug within 3 months, leaving 72 evaluable patients. Ages ranged from 40 to 81 years with an average of 65 years. Sixty-seven were white, and 5 were black. All had histologically proven adenocarcinoma of the prostate. Seventy had Stage D disease with bone or soft tissue metastases or both, and two had locally advanced disease (Stage C). None had received

prior endocrine treatment, although 38 had received other treatment. Twenty-two had undergone transurethral resection of the prostate for obstructive symptoms; 6 had external irradiation to the primary tumor; 7 had received palliative irradiation to bone metastases; 11 had had ¹²⁵iodine implantation with pelvic lymphadenectomy; 1 had undergone radical cystoprostatectomy and ileal conduit urinary diversion; and 3 had received combination chemotherapy with 5-fluorouracil/cyclophosphamide, and/or with cyclophosphamide/Adriamycin (doxorubicin) without response.

Initial evaluation included history, physical examination, excretory urogram (IVP), chest roentgenogram, skeletal survey and bone scan, and sometimes, liver scan, lymphangiogram, and computerized axial tomography (CAT) of the abdomen and pelvis. Laboratory studies included hemogram, urine analysis, biochemical determinations of serum acid phosphatase, alkaline phosphatase, met-hemoglobin, serum glutamic oxaloacetic and pyruvic transaminases, bilirubin, blood urea nitrogen, creatinine, glucose, uric acid, total protein, albumin, calcium, cholesterol and lactic dehydrogenase. Cystoscopy was done when indicated.

Flutamide was supplied in 125 mg gelatin coated capsules and was administered orally at a dose of 250 mg 3 times a day for a total daily dose of 750 mg. Two patients initially received a daily dose of 1500 mg for a short duration. Treatment was continued until relapse, and ranged from 2 months to 56 months, with an average of 12.5 months. Patients generally were given a trial of at least 3 months before being considered nonresponders, unless there was interval evidence of progressive deterioration. Furthermore, any favorable response lasting less than 3 months was classified as a nonresponse. Follow-up was initially at monthly intervals but, depending on the response, this interval was increased subsequently.

Patients were evaluated for evidence of tumor response and drug toxicity. The following criteria were used for

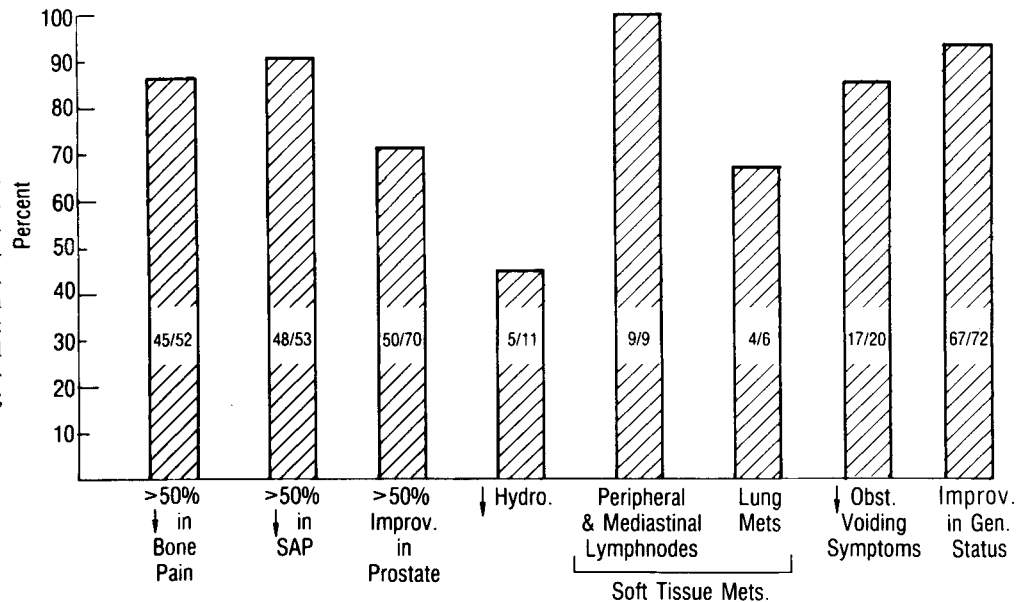
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FIG. 1. Incidence of favorable tumor response seen in various parameters after treatment with flutamide in previously untreated patients with prostatic cancer. Numerator: number of patients with positive response; denominator: number of patients with abnormal parameter; SAP: serum acid phosphatase; hydro: hydronephrosis; mets: metastases.



evaluation of response: (1) improvement in bone pain for at least 3 months (This subjective parameter was based on the patients evaluation of pain status, and on comparison of pretreatment and posttreatment requirements for analgesics); (2) decrease in an elevated serum acid phosphatase level to normal levels, or to <50% of pretreatment level if associated with relief of bone pain as defined previously; (3) decrease in size, nodularity and/or induration of the prostate gland as determined by serial digital rectal examinations; (4) decrease in size and/or number of bone metastases seen on bone scan and/or reduction of a soft tissue mass by >50%; (5) improvement in hydronephrosis secondary to ureteral obstruction as determined by serial IVPs; (6) improvement in symptoms of urinary outlet obstruction; and (7) improvement in general physiological status, with weight gain of >3% not owing to edema. Duration of response was measured from the onset of flutamide therapy until evidence of disease progression. Disease progression was evidenced by a deterioration in any one or more of the response parameters defined above.

Results

The results of this investigation are demonstrated in Figure 1. Five of the 72 patients were considered to have shown no response, and 4 progressed within 3 months; these 9 patients were considered nonresponders. The remaining 63 patients (87.5%) showed a remission with flutamide.

Bone Pain

Fifty-two patients (72.2%) had bone pain from metastatic disease. The pain was graded as 3+ severe, 2+

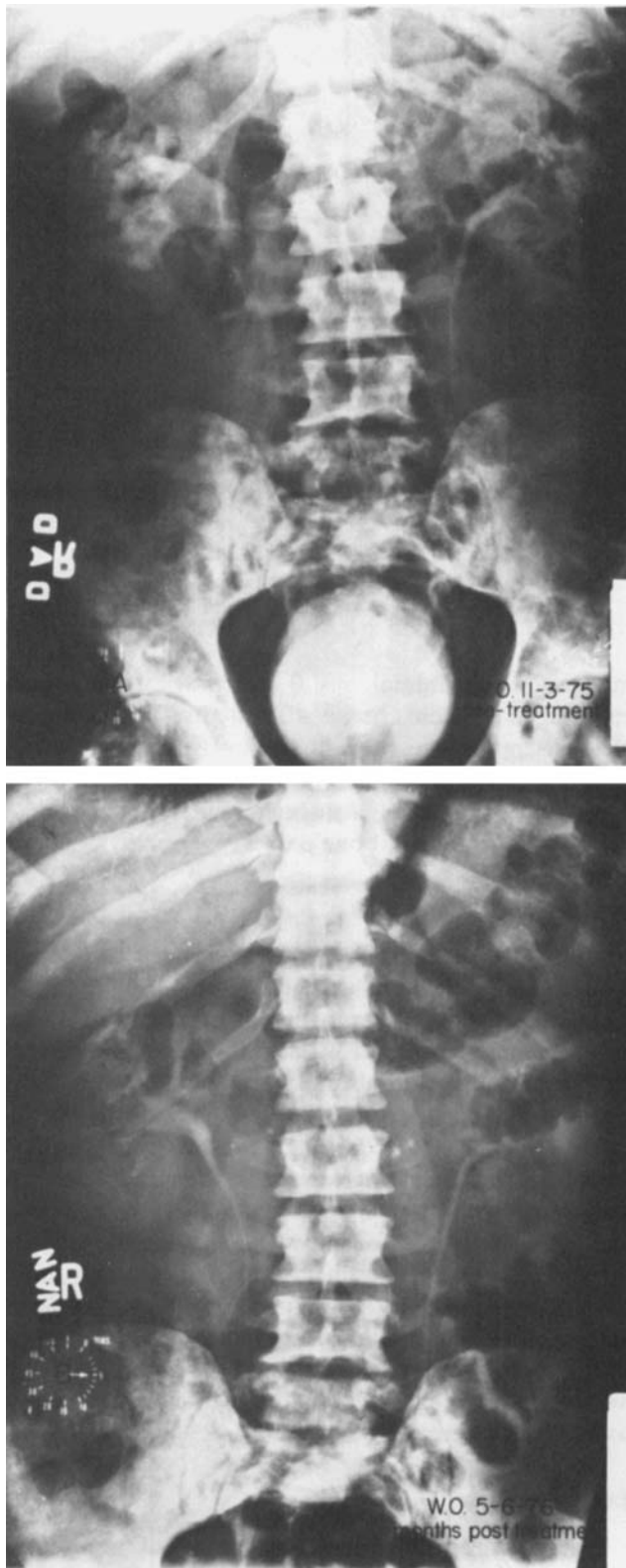
moderate, 1+ minimal, and 0 absent at each follow-up visit. Based on these criteria, 40 patients (77%) had complete disappearance of pain during treatment, usually within 4 to 6 weeks after starting flutamide; 5 patients experienced partial relief in bone pain; while 7 had no appreciable change in bone pain.

Serum Acid Phosphatase

Fifty-three patients (73.6%) had elevated serum acid phosphatase (SAP) levels ranging from 1.0 to 191.0 Bodansky units with an average of 9.96 units (normal range, 0–0.8 Bodansky units). In 39 patients (73.5%), the elevated SAP level returned to normal, usually within 2 months. Eight patients had more than 75% reduction in the enzyme levels, one a 50% to 75% reduction, three less than 50% reduction, and two an increase during therapy. The serum acid phosphatase levels correlated well with bone pain and other parameters. Usually, with a favorable response, the serum alkaline phosphatase level showed an initial rise associated with a decline in acid phosphatase levels and then fell to normal or near normal levels along with SAP. Serum testosterone levels during flutamide therapy were noted to be elevated or in a high-normal range in six patients where this was studied.

Local Response

Notations regarding prostatic size, induration, nodularity and infiltration of adjoining tissues were carefully recorded in special protocol diagrams at each evaluation. These were graded as 0 (normal), 1+ (minimal abnormality), 2+ (moderate abnormality), and 3+ (pronounced abnormality). Seventy of the 72 patients (97%) were noted to have abnormal prostatic findings on rectal examination



FIGS. 2A AND 2B. (A, top) IVP shows right hydronephrosis. (B, bottom) Six months after treatment with flutamide hydronephrosis is resolved.

at the initiation of therapy. In 14 patients (20%), the prostatic abnormality regressed to a completely normal gland during therapy; in 11 there was 75% improvement;

in 25, 50% to 75% improvement; in 14, less than 50% improvement; and in 6 no improvement.

Hydronephrosis

Seventeen patients (23.6%) had unilateral or bilateral hydronephrosis secondary to ureteral obstruction (not on the basis of bladder outlet obstruction). Follow-up studies were not done in 6, but in the remaining 11, 4 (36.3%) showed complete resolution of the hydronephrosis, 1 showed more than 50% improvement in the hydronephrosis, and there was no change in the other 6 patients (Figs. 2A and 2B).

Bone and Soft Tissue Metastases

It proved impossible by the parameters utilized to evaluate precisely bone metastases. Of the 55 patients (76.4%) with bone metastases, follow-up studies were considered to show stable disease in 38 (70%), a definite progression in 7 (12%), and equivocal improvement in the degree and/or number of areas of increased uptake seen on bone scan in 10 (18%). One patient with a pathologic fracture showed definite healing during therapy.

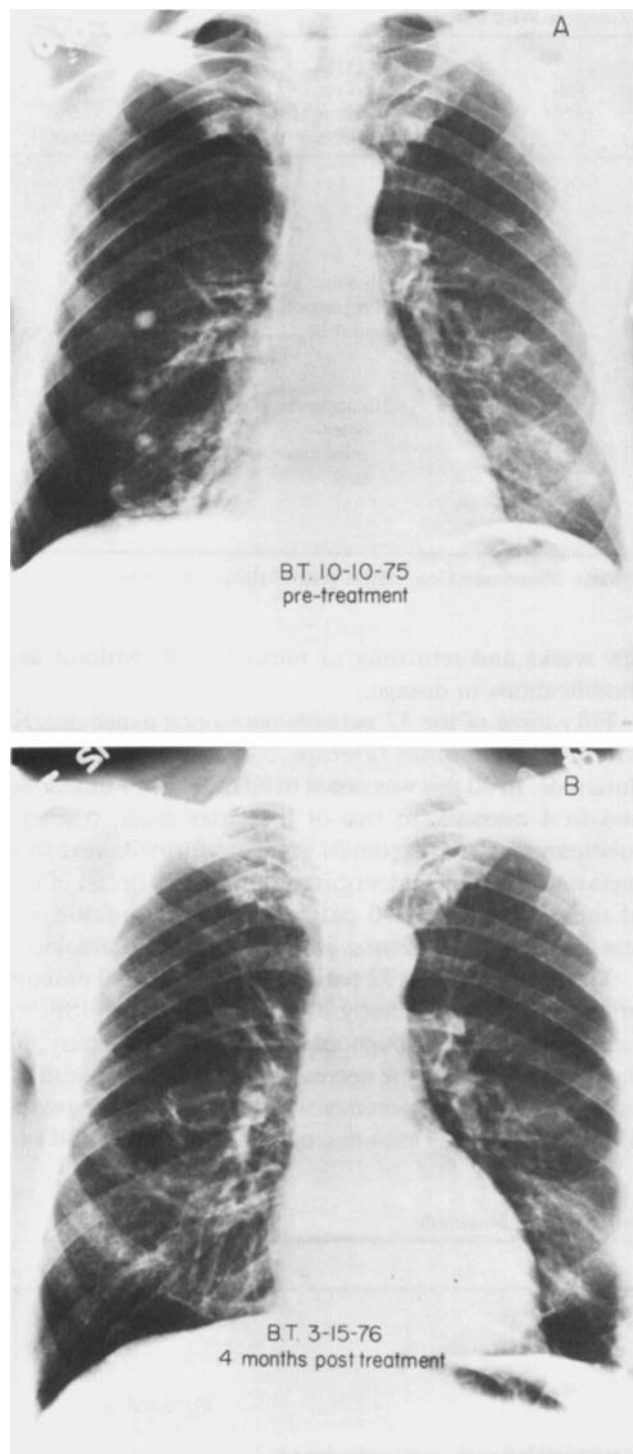
Response in soft tissue metastases could be evaluated more accurately. Of six patients with pulmonary parenchymal metastases (biopsy proven in two cases), three had complete disappearance, one had more than 50% regression, and two showed no significant change, *i.e.*, "stabilization" (Figs. 3A and 3B).

Twenty-two patients (30%), had lymph node metastases as determined by physical examination, chest x-ray, lymphangiogram, or abdominal and pelvic computerized tomography (CT). In five of six patients with measurable peripheral lymph node metastases (biopsy proven in three), the nodes palpably disappeared on flutamide therapy; the other patient had more than 50% regression of bilateral groin nodes. Two of three patients with measurable mediastinal node metastases (biopsy proven in one case) had complete radiographic disappearance, and more than 50% regression occurred in the third. Paraortic and pelvic node metastases were presumed in 13 patients from pedal lymphangiograms and/or CAT. Although these were not or could not be accurately evaluated in all 13 patients, in 4 (30.8%) an obvious regression was noted.

In one patient, a 4 × 2 cm mass due to local extension from the superior aspect of the prostate involving the seminal vesicles and the base of the bladder and causing rectal compression resolved completely.

Obstructive Urinary Symptoms

Twenty patients had symptoms of urinary outlet obstruction prior to starting flutamide. In 13 (65%), these symptoms resolved completely. Two of these patients had needed a urethral catheter for vesical drainage, and in



FIGS. 3A AND 3B. (A) Chest x-ray shows multiple biopsy-proven bilateral lung metastases from prostatic carcinoma. (B) Four months after treatment with flutamide lung metastases have disappeared completely.

both, the catheter was ultimately removed and a normal voiding pattern resulted. Intermittent gross hematuria resolved in one patient. In four patients, the voiding status was believed to have improved more than 50% while no improvement was noted in the remaining three patients.

TABLE 1. Duration of Response With Flutamide

Duration of response	No. of patients
NIL or 3 mo	9
3 to 6 mo	12
6 to 12 mo	27
12 to 24 mo	13
24 to 36 mo	7
36 to 48 mo	2
48 to 60 mo	2
Total	72

General Status

Overall performance status, appetite, and body weight improved in 56 patients (78%), remained stable in 11 (14%), and deteriorated in 5 (7%), with mental depression and progressive loss in appetite and weight correlating with the absence of favorable responses in other parameters.

Based on the parameters specified, 63 of the 72 patients in this trial (87.5%) showed a favorable response in one or more of the defined criteria following treatment with flutamide, and 9 (12.5%) were nonresponders. The duration of response ranged from 3.5 months to 54 months (average, 11.8 months). The number of patients in each response period is shown in Table 1. Fourteen patients are still in remission under treatment for periods ranging from 4 to 46 months (average, 14.9 months).

Details of the response to the various parameters are given in Table 2. An attempt has been made to categorize the responses as good, partial, and poor in Table 3. The criteria are obviously less rigorous and more arbitrary than those usually required in Phase II trials. Forty-nine of the 72 patients (68%) had a good response, 14 (19.4%) a partial response, and 9 (12.6%) a poor response (including the nonresponders).

Tumor grade was documented in 57 of the 72 patients. According to the criteria in Table 3, all 10 patients with grade I, 14 of 23 with grade II (60.8%), 10 of 14 with grade III (71.4%), and 4 of 10 with grade IV (40%) cancers showed a good response. The small numbers of patients in each group prevent definitive correlations between the response to flutamide and the grade of the carcinoma, but it is evident that high tumor grade did not preclude a favorable response.

Subsequent Treatment

Thirty-two patients who relapsed after an initial favorable response to flutamide or were refractory to flutamide were treated with conventional endocrine therapy (diethylstilbestrol and/or bilateral orchiectomy), seven with chemotherapy, and two with chemotherapy after conventional endocrine treatment. Thirteen patients had relief of bone pain for about 2 months, and one for 7 months, but no other evidence of remission according to the stated parameters was noted in any of these cases.

TABLE 2. Evaluation of Tumor Response With Flutamide

Parameter	Bone pain	SAP	Prostatic lesion	Hydro	Bone mets	Lung nodules (mets)	Palpable LNs	Mediastinal LNs	Pelvic and retro-peritoneal LNs	Obst. voiding symptoms	Gen. status
No. of patients	52	53	70	17	55	6	6	3	13	20	72
Complete regression	40	39	14	4	—	3	5	2	Obvious regression in 4	13	Improvement in 56 patients
75% improvement	Partial relief in 5	8	11	—	—	—	—	No accurate determination in 9		—	
50-75% improvement		1	25	1	—	1	1			4	
50% improvement		—	3	14	—	10 possible improvement	—		—	—	
No improvement	5	—	6	6	38 stable disease	2	—	—	No accurate determination in 9	3	Stable in 11 Deterioration in 5
Progression	2	2	—	—	7	—	—	—		—	

SAP: serum acid phosphatase; Hydro: hydronephrosis; LNs: lymph nodes; Mets: Metastases; Gen. status: general status.

Side Effects

No adverse effect on any hematologic values including methemoglobin levels was observed. Blood urea nitrogen, creatinine, and uric acid levels were unaffected. After 3 months on a high dose of flutamide (1500 mg daily), two patients had mild elevation in serum glutamic oxaloacetic transaminase (up to 70 U/l) and lactic dehydrogenase levels without alterations in serum bilirubin and without any clinical manifestations. The drug was discontinued with return of the serum enzyme abnormalities to normal levels within 6 weeks. Flutamide was then restarted at the usual dose (750 mg/d) with remission in the prostatic cancer and without any further abnormalities in liver function in either patient. One other patient on the conventional dose had a mild elevation in SGOT lasting a

few weeks and returning to normal levels without any modifications in dosage.

Fifty-three of the 72 patients developed gynecomastia within 2 to 8 months (average, 3 months) after starting flutamide. In 30 this was noted to be mild, in 19 moderate, and in 4 massive. In two of the latter cases, cosmetic subcutaneous mastectomies were performed, revealing metastatic prostatic adenocarcinoma in one breast of one of these patients. In 50 patients the gynecomastia was associated with tenderness in the nipples and areolae.

Thirty-seven of the 72 patients claimed sexual potency prior to flutamide therapy. Of these, thirty-two (86.5%) remained potent throughout the period of therapy, although 9 reported some decrease in potency. Five patients experienced loss of potency while on flutamide: two at 3 months, one at 9 months, one at 18 months, and one

TABLE 3. Categorization of Response With Flutamide

Response	Criteria	No. of patients
Good	Period of response > 3 mo Complete disappearance in bone pain	49/72 (68%)
	Return of elevated serum acid phosphatase to normal or >75% reduction of pretreatment level	
	>75% improvement in prostatic lesion	
	Complete disappearance or >75% regression of palpable or measurable lymph nodal metastases	
Partial	Disappearance of obstructive voiding symptoms no deterioration of other parameters	14/72 patients (19.4%)
	Period of response > 3 mo Partial relief in bone pain	
	>50% reduction in elevated serum acid phosphatase 50%-75% reduction of prostatic lesion	
	50%-75% regression in soft tissue metastases	
Poor	No deterioration of other parameters Any responses not qualifying as good or partial are included in this category	9/72 patients (12.6%)

at 34 months. Two patients who were impotent prior to starting flutamide reported satisfactory potency during the therapy.

No deleterious effects were noted from flutamide in two patients with a history of myocardial ischemia, two with prior phlebothrombosis of the lower limbs, and one with arteriosclerotic heart disease and recurrent angina. The latter patient developed an acute myocardial infarction immediately after undergoing subcutaneous mastectomies; the flutamide was discontinued for 2 months, and, after satisfactory cardiac evaluation, flutamide was restarted and continued without incident. One patient with far advanced prostatic carcinoma expired from acute cardiorespiratory failure (myocardial infarction or pulmonary embolism) after having relapsed from flutamide therapy and while on combined treatment with flutamide, diethylstilbestrol, and corticosteroids.

Discussion

Flutamide has been found to be a potent antiandrogen functionally specific for androgen-dependent accessory sex structures (seminal vesicles and ventral prostate).^{1,2} The exact mechanism by which it exerts its antiandrogenic effect has yet to be established conclusively. However, evidence suggests that flutamide or its metabolites inhibit the uptake of testosterone, or the binding of testosterone or dihydrotestosterone or both to the nuclear receptor, and thus prevent androgens from exerting their biological effects on the secondary sex structures.^{5,6} Its effects have been extensively studied in experimental animal models. The antiandrogenic action of flutamide administered orally in pharmacologically active doses is evidenced almost exclusively by atrophy of the prostate gland without structural changes in the testes in dogs and rats.^{1,2} When administered to the baboon, marked reduction of the prostatic weight is noted, a reduction that is more profound than that accomplished by castration.⁷ When flutamide is administered to mature animals, a significant decrease in the uptake of radioactive testosterone by the prostatic nuclei is observed.⁷ The functional specificity of the drug for androgen-dependent sex structures is proven by its lack of effect in female rats, in which doses 5 to 10 times the effective antiandrogenic doses in the male fail to affect female sex structures. Its mode of action does not require an intact pituitary or adrenal gland.^{1,2}

In humans, the drug is metabolized rapidly after administration and at high doses produces elevation of serum luteinizing hormone without decrease in the level of plasma testosterone.⁸ In fact, as noted in prior clinical evaluations⁹ and in this study, plasma testosterone actually may increase to high normal or super normal levels during treatment. The therapeutic effect of flutamide is probably not mediated by its effect on cortisol metabolism, since the clinical response does not correlate with the changes

TABLE 4. Results of Various Clinical Trials With Flutamide in Advanced Prostatic Cancer

Reference	Prior endocrine therapy	Responders	
		No.	(%)
Irwin and Prout, 1973 ¹¹	No	8/12	(66)
Stoliar and Albert, 1974 ¹²	Yes*	7/18	(39)
Sogani et al., 1975 ³	Yes	6/26	(23)
Prout et al., 1975 ⁸	No	11/13	(85)
Jacobo et al., 1976 ⁷	No	Low dose: stable for 30 wk High dose: stable for 25 wk	
Sogani et al., 1979 ⁴	No	19/21	(90)
Current study	No	63/72	(87.5)

* Also includes 3 untreated patients.

in cortisol metabolism.¹⁰ A comparison of the pretherapy and posttherapy biopsies of the prostate in humans treated with flutamide has shown sporadic squamous metaplasia and nuclear pyknosis such as occurs with estrogen therapy.⁷

Evaluation of the results of treatment of metastatic prostatic carcinoma is made difficult by the usual absence of the reliable and classic Phase II study indicators of tumor response. The criteria used in this study, although semiarbitrary and by no means ideal, are definable and reproducible. In most patients improvement in all or most of the existing response parameters occurred concomitantly. However, improvement in one parameter did not necessarily involve improvement in each of the other parameters. Within these limitations, this uncontrolled study indicates that flutamide has a favorable effect on the majority of patients with advanced prostatic carcinoma who have not been previously treated with conventional endocrine therapy. The response rate of 87.5% is similar to that of our earlier experience.⁴

Prout and associates reported an 85% response rate in 13 previously untreated patients⁸ and Irwin and Prout a 66% favorable response in 12 patients on flutamide therapy.¹¹ Flutamide after conventional endocrine therapy has not been found to be as effective as in previously untreated patients. Sogani and associates, reported a favorable response of short duration from flutamide in 23% of patients who were refractory to conventional endocrine therapy.³ Stoliar and Albert reported a response rate of 29% in a similar setting, although 3 of the patients had not received prior hormonal therapy.¹² From a small double-blind study comparing the efficacy of flutamide and diethylstilbestrol in advanced, but previously untreated patients with prostatic carcinoma, Jacobo and associates concluded that neither agent displayed significant superiority.⁷ Table 4 lists the results of reported clinical trials with flutamide in advanced prostatic cancer.

No serious side effects were noted in patients during

the course of therapy with flutamide. Three patients had possible drug-related mild hepatic toxicity, but no long-term adverse effect. Because flutamide is an anilide, it has the potential for causing methemoglobinemia. No patient in any of the three clinical trials from MSKCC has shown any increase in methemoglobin levels. The problems of cardiovascular and thromboembolic complications with the use of flutamide cannot be precisely evaluated by such a clinical trial. Two patients had such complications, but a relationship to flutamide is uncertain. None of the patients, however, had recognized problems with fluid retention or congestive heart failure.

Gynecomastia, although common in these patients, was generally mild. The basis for this gynecomastia remains uncertain, although high plasma estrogen could be contributory.⁹ Flutamide has been reported to have no significant adverse effect on libido and potency.^{3,4,8,11,13} In this study, 86.5% of the patients retained their potency during therapy, and three of the five patients who did become impotent, did so quite late.

This study and others⁷ suggest that the qualitative and quantitative responses of patients with Stage D prostatic carcinoma to flutamide are similar to those achieved with conventional hormonal therapy. The exact incidence of thromboembolic complications and effects on libido and potency with estrogens *versus* flutamide are unknown, and thus any comparison between flutamide and estrogen with regard to these side effects is impossible. This experience has clearly shown that flutamide is a safe, oral antiandrogen which is effective in the treatment of patients

with advanced prostatic cancer previously untreated with endocrine therapy.

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