Comparison of Various Hormonal Therapies for Prostatic Carcinoma

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The goals of hormonal therapy for prostatic cancer are to decrease circulating plasma testosterone to castration levels; prevent a rise in or reduce circulating prolactin; and block residual androgen at the cell level. Orchiectomy is very effective but does not prevent residual adrenal androgens from being converted to dihydrotestosterone (DHT); also, it has no effect on plasma prolactin. Estrogen has no known effect on androgen-receptor concentration or DHT binding to receptor and raises plasma prolactin. It also has significant side effects. Megestrol acetate, the only antiandrogen currently available for use in the United States, has been shown to block androgen from all sources. It produces a transient reduction in plasma testosterone to levels somewhat higher than those in castrated men, and it has no effect on plasma prolactin. When used in a dose of 120 mg/day in combination with 0.5 to 1.5 mg of estradiol per day, it acts synergistically to suppress pituitary gonadotropins and maintain plasma testosterone at castration levels for periods of up to 1 year. Newer therapies being studied include flutamide, a nonsteroidal antiandrogen, and luteinizing hormone-releasing hormone (LHRH). Data on these agents are limited and comparisons with standard therapies are needed.

THERE ARE at least two major reasons why hormonal or ablative therapy is widely used in patients with prostate cancer: (1) between 80% and 90% of patients have metastatic disease and are not curable by surgery at the time of discovery of their tumors; they will require palliative therapy with hormones at some time during their disease,[1] and (2) of prostate cancers, 80% are hormone dependent in varying degrees;[1] therefore, it makes sense to block androgens with orchiectomy or antiandrogens in metastatic disease.

Virtually all patients with stage D_2 prostate cancer (widespread metastasis with increased acid phosphatase) should receive hormonal therapy or ablative therapy (orchiectomy). It has recently been shown that in stage C and D_1 disease, with severe obstructive symptoms, it might be better to treat with hormonal therapy and radiation rather than a palliative transurethral resection of the prostate (TURP), since survival studies are better with the former, implying that surgery may actually spread the tumor.[2]

There are at least two prognostic indices proposed to predict the response to hormonal treatment in prostate cancer: (1) histologic grading and (2) biochemical parameters mediating androgen action, including tissue dihydrotestosterone (DHT) levels and androgen receptor concentration.

It is generally felt that, as in breast cancer,[3] biochemical parameters may provide more useful information for the prediction of response to hormonal therapy than histologic grading. Until the experimental evidence for the usefulness of receptor and/or DHT in the prediction of response to hormonal therapy has been confirmed, all prostate cancers should be given a trial of endocrine therapy since overall 80% will respond.

SELECTING THE IDEAL ANTIANDROGEN

The mechanism of action of androgen on target tissue, as depicted in Fig. 1, may help us define the goals of hormonal therapy and select an ideal antiandrogen. These goals include the following: (1) to decrease circulating plasma testosterone to castration levels; (2) to reduce adrenal androgens to negligible levels; (3) to prevent a rise in or to reduce circulating prolactin; and (4) to block any residual androgen at the cell level by decreasing DHT binding to receptor by competitive inhibition, decreasing receptor concentration, and decreasing 5α-reductase activity.

There are a multitude of antiandrogen programs for the management of advanced prostate cancer. These include the traditional standbys proposed by Huggins and Hodges[4] of orchiectomy and estrogen therapy. The newer therapies

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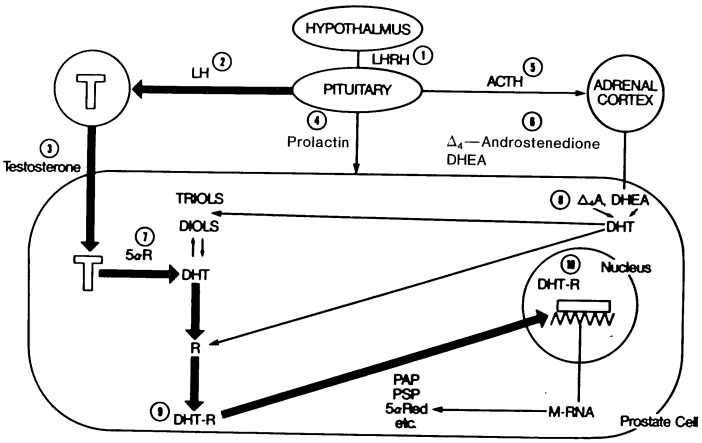

Fig. 1. This figure depicts the mechanism of action of androgen on target tissues. The plasma factors affecting androgen action are shown by numbers: 1-LHRH, 1-LH, 3-testosterone (T), 4-prolactin, 5-ACTH, and 6-adrenal androgens (Δ_4-androstenedione and DHeA and DHeA sulfate); intracellular-mediated androgen action is shown by the various symbols depicted within the prostate cell. These include T conversion to DHT by 5α-reductase (7); conversion of adrenal androgens Δ_4 androstenedione and DHeA to DHT (8); binding of DHT derived from T and DHT derived from adrenal androgens to receptor to form the DHT-receptor complex (9); translocation of DHT-receptor complexes to nucleus and binding to acceptor site (10); new protein synthesis is shown by M-RNA and PAP, PSP, 5α-reductase, etc.

Table 1. The Effect on Plasma Hormones of Various Regimens

Hormone	Megestrol Plus Estradiol*	DES†	Castration	Injected LHRH Agonist	Flutamide‡
LH	↓	↓	↑	↓	↑
Plasma testosterone, sustained reduction to castrate levels	↓	↓	↓	↓	→ or ↑
Adrenal androgen	↓	→	→	→	→
Prolactin	↑	↑	→	→	→

*Megestrol, 120 mg/day, plus estradiol, 0.5 to 1.5 mg/day.
†DES, 3 mg/day.
‡Flutamide, 750 mg/day.

include the use of antiandrogens alone or combined with estrogen, the nonsteroidal antiandrogen flutamide, and luteinizing hormone-releasing hormone (LHRH).

Orchiectomy is a very effective tool for the elimination of the major biologically active androgen, testosterone. It is an effective treatment but it does not fulfill the requirements of the ideal drug because of its lack of effect on adrenal androgens and its inability to prevent residual adrenal androgens from being converted to DHT at the level of the prostate (Table 1). It has no effect on plasma prolactin.

Estrogen therapy indirectly suppresses testosterone production by inhibiting gonadotropins; it also has some direct suppressive effects on the production of testosterone. Diethylstilbestrol (DES), 3.0 mg/day, will suppress plasma testos-

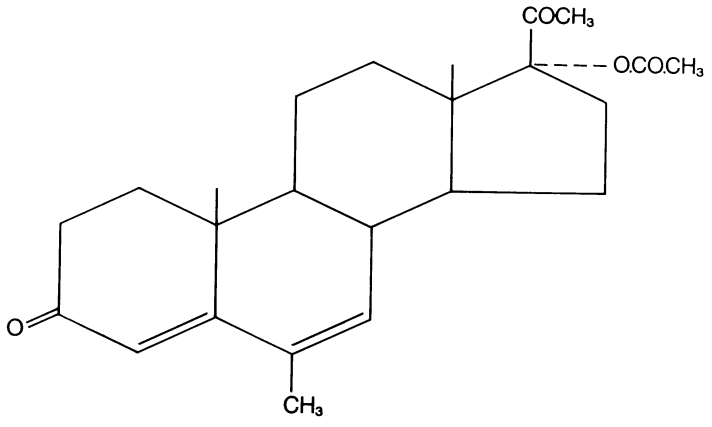

Fig. 2. This figure depicts the structure of megestrol acetate.

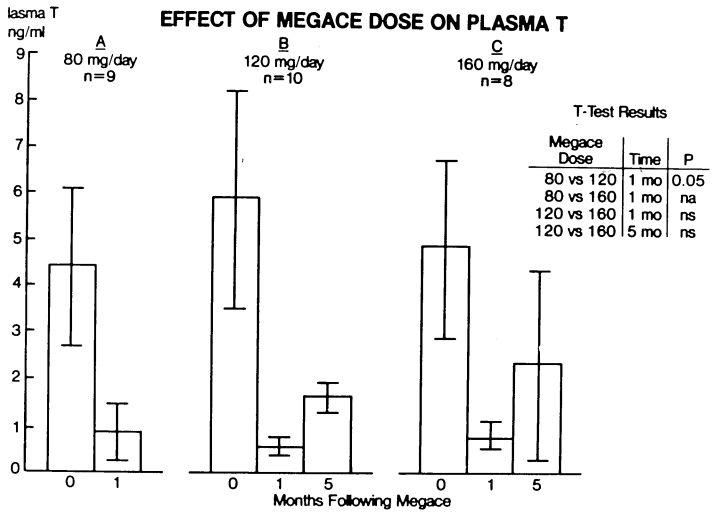

Fig. 3. Relationship of plasma testosterone levels (ordinate) to varying doses of megestrol (A, B, C) administered to patients for 1 to 5 months. Numbers under bars indicate months following start of drug administration. Horizontal lines above and below the top of each bar indicate 1 SD. Statistical comparisons of the various doses are shown under *t* test results on the upper right section of the bar graph.

terone to castration levels. Estrogen has some modest suppressive effects on 5α-reductase activity but no known effect on androgen-receptor concentration or significant competitive inhibition on DHT binding to receptor. Estrogen raises plasma prolactin, and since prolactin potentiates androgen transport into cells and androgen metabolism, this may be considered an unwanted effect. Estrogen also has significant side effects, which include increased thromboembolism, gynecomastia, and salt retention. Therefore estrogen by itself is not an ideal agent for the management of prostate cancer.

Only one antiandrogen is currently available for use in the United States. It is a steroidal antiandrogen, megestrol acetate,* available by prescription but not yet approved by the FDA for use in prostate cancer (Fig. 2).

EFFECT OF MEGESTROL ACETATE ON PLASMA HORMONES

Administration of megestrol acetate has diverse biochemical effects. Studies of the effect on plasma hormones of 80 to 160 mg of megestrol acetate daily for 2 weeks to 5 months show there is a transient reduction in plasma testosterone to levels somewhat higher than those that occur in the castrated men.[5] These levels tend to return towards the normal range by 4 to 6 months after the administration of each dose (Fig. 3). There are transient decreases in plasma luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which also tend to return towards normal after 4 to 6 months of megestrol acetate therapy.[5] Adrenal androgens, including androstenedione and DHEA sulfate, significantly decrease, and this decrease is sustained for periods of up to a year[5] (Fig. 4). There is no effect on plasma prolactin.[6]

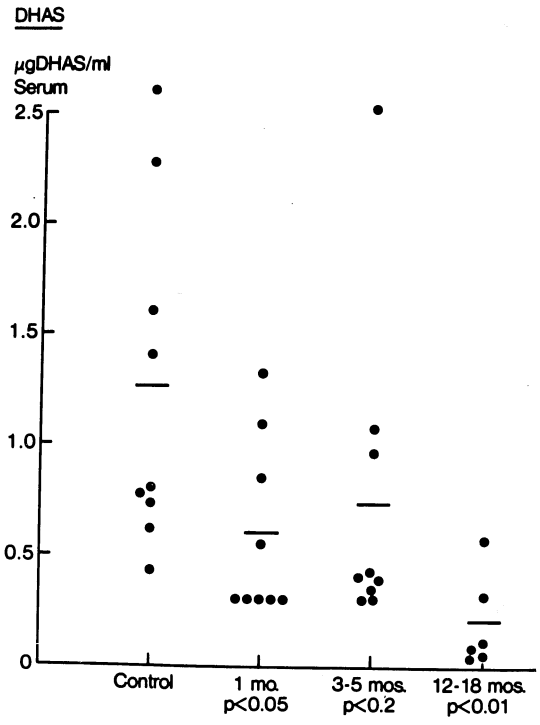

Fig. 4. DHeA sulfate (DHAS) values are shown for previously untreated patients with prostate cancer at varying time intervals following megestrol therapy. *P* values refer to comparison of each time point with control values.

*Megace®, Mead Johnson Pharmaceutical Division, Evansville, Ind.

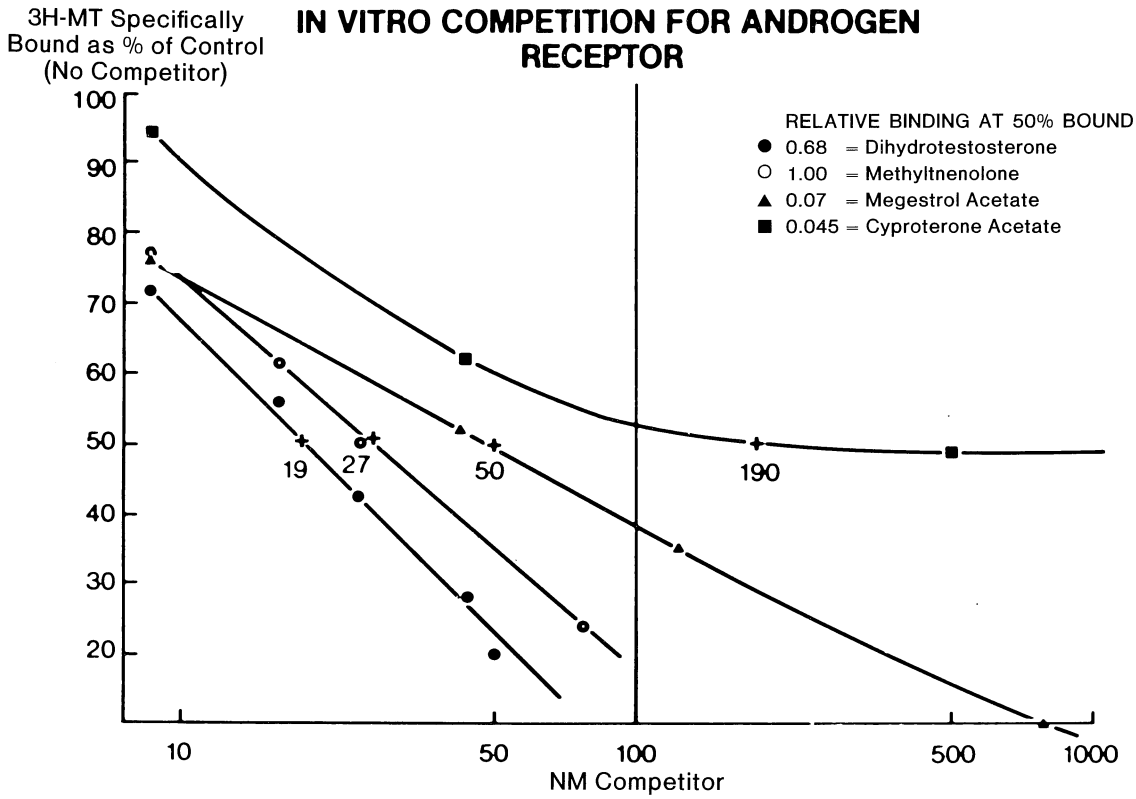

Fig. 5. This figure depicts the competition by various steroids for the cytosol androgen receptor. In this study, each incubation contained 7 nmol/L ^{3}H-R 1881 (methyltrienolone) added to cytosol derived from human benign prostatic hypertrophy (BPH) in a total volume of 220 μL. Incubations were performed overnight at 15°C with and without various concentrations of cold competitors (10 to 1000 nmole/L) incubated with 7 nmol/L-labelled ^{3}H-R 1881. Nanomolar concentrations of competitor are shown on the abscissa. After incubation, bound ^{3}H-R 1881 was separated and measured. Competition for the androgen receptor was determined by plotting inhibition binding of ^{3}H-R 1881 at varying concentrations of competition and determining the concentration of cold steroid required to decrease relative binding to 50%. Note that megestrol acetate has a relative binding inhibition of approximately 0.07.

There are significant effects of megestrol acetate on the intracellular biochemical mechanisms that mediate androgen action. These include a modest inhibition of 5 α-reductase of approximately 50% to 70%[6]; a competitive inhibition of DHT binding to the cytosol androgen receptor as shown in vitro (Fig. 5); a decrease in both nuclear and cytosol androgen-receptor synthesis and/or metabolic degradation[7] (Fig. 6); and decreases in tissue DHT levels to values less than 2.4 ng/g[6] (Fig. 7).

In view of the notable effects of megestrol acetate on inhibiting both circulating androgens and androgen-mediated action at the cellular level, it was decided to treat prostate cancer with megestrol acetate alone in doses of 120 to 160 mg/day. Table 2 summarizes the data from this and two other studies[8,9] using megestrol acetate in advanced prostate cancer.

MEGESTROL ACETATE IN COMBINATION WITH 17-β-ESTRADIOL

Megestrol acetate (120 mg/day) has been combined with small doses of 17-β-estradiol (0.5 to 1.5 mg/day) for advanced metastatic prostate cancer. One objection to the use of megestrol acetate alone for advanced prostate cancer is that plasma testosterone rebounds towards the normal range following 4 to 6 months of treatment. We have found that a combination of small, daily doses of estradiol (0.5 to 1.5 mg/day) together with 120 mg of megestrol acetate acts synergistically to suppress pituitary gonadotropins and maintain plasma testosterone at castration levels for periods of up to 1 year (Figs. 8 and 9).

Of 10 patients treated with megestrol acetate and estradiol to date, eight have had stage C disease and two have had stage D. Three of the

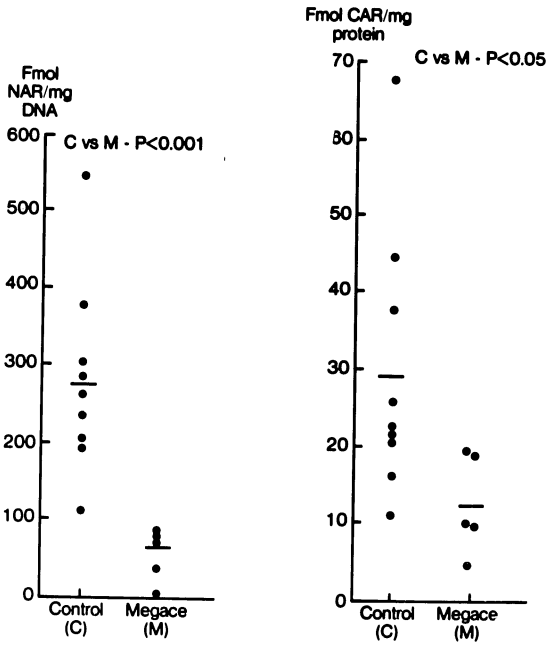

Fig. 6. On the left side of the figure are shown data for nuclear androgen receptor; individual values are indicated by solid dots and the mean is indicated by a horizontal line for TURP specimens from control patients and patients treated with megestrol. The vertical axis is calibrated in femtomoles of cytosol receptor per milligram of protein. Statistical comparisons of the two groups are shown in the top part of the figure. On the right hand side of the figure, similar symbols are used to show results for cytosol androgen receptor; the vertical axis is calibrated in femtomoles of cytosol receptor per milligram of protein. Statistical comparisons of the two groups are shown in the top of the figure.

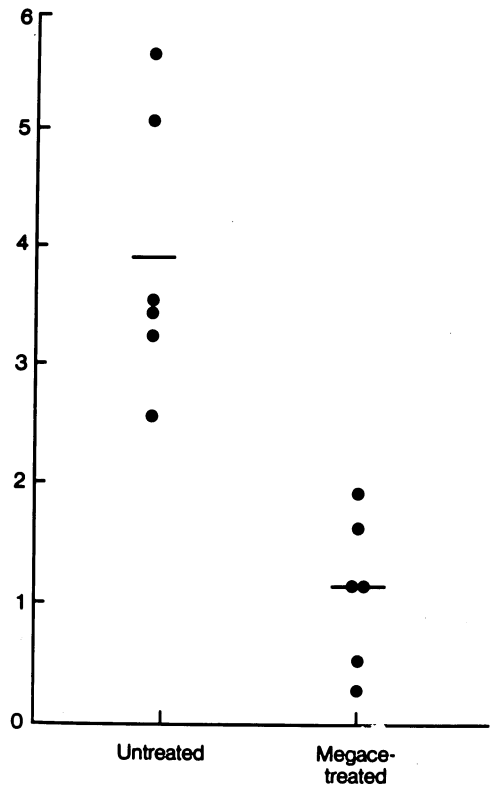

Fig. 7. The mean (horizontal line) and individual values (solid dots) for endogenous DHT in the prostate are shown on the ordinate for patients with untreated BPH and patients with BPH treated with megestrol, 80 mg/day for 1 to 25 days prior to TURP.

patients died of causes unrelated to prostate cancer at 9, 12, and 13 months following initiation of the megestrol acetate–estradiol program. The other seven patients remain objectively stable for from 19 to 23 months. Seven of the 10 patients have been maintained at castrate plasma testosterone levels on 0.5 mg of estradiol together with 120 mg of megestrol acetate (Fig. 8). Two of the other three patients have required 1.0 mg/day of estradiol to maintain a castrate level of plasma testosterone (less than 0.4 ng/ml) while one patient has required 1.5 mg/day of estradiol along with 120 mg of megestrol acetate (Fig. 9).

In several patients on the estradiol–megestrol acetate program, after 1 year of stable castrate levels of plasma testosterone the megestrol acetate dosage has been reduced to 80 mg. Sustained lowering of plasma testosterone has been maintained on this megestrol acetate dosage in two of three patients studied thus far for up to 6 months following the decrease in megestrol acetate dosage (Fig. 8).

Table 2. Summary of Clinical Effect of Megestrol Given as Initial Therapy in Advanced Prostate Cancer

	Number of Patients Studied	Objective*			Subjective*	
		Partial Regression	Stable	Progression	Good Response	Poor Response
Geller et al	9	4 (30)	4 (11)	1	—	—
Johnson et al[8]	13				12 (11)	1
Block et al[9]	9	5 (14)	2 (9)	2		

*Values shown are numbers of patients responding, with average time of response in months shown in parentheses.

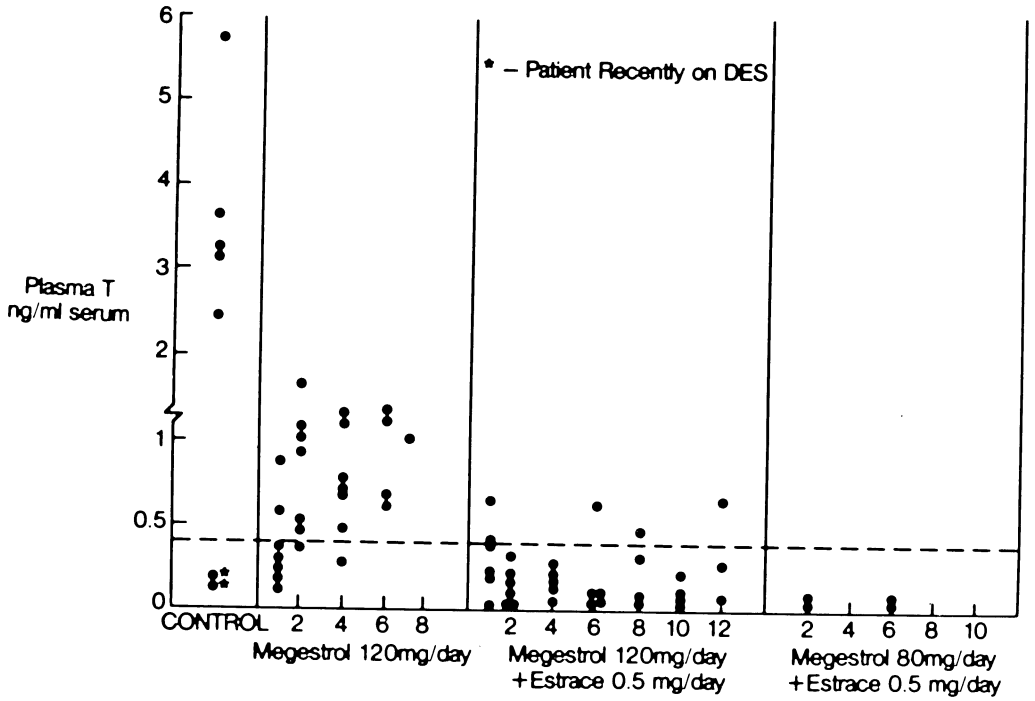

Fig. 8. The individual values for plasma testosterone in seven patients who were eventually maintained at castrate levels with megestrol 120 mg/day and estradiol 0.5 mg/day are shown sequentially from left to right according to different dosing programs. The different drug regimens are indicated beneath the horizontal axis while the plasma testosterone level is shown in nanograms per milliliter along the vertical axis. The horizontal dashed line across the figure indicates the maximum value of testosterone acceptable as a "castrate" level. To the left of the graph are shown the individual dots for patients whose plasma testosterone was measured prior to institution of megestrol 120 mg/day. Notice that two of the patients had recently been receiving DES 3.0 mg/day, and their plasma testosterone levels are initially depressed. Following institution of megestrol (second panel from left) plasma testosterone levels, shown by individual dots, progressively rise over 2 to 7 months; when plasma testosterone levels remained above 0.8 mg/mL on two consecutive occasions, 0.5 mg of estradiol was added as shown in the third panel from the left. Patients were maintained on this dosage 10 to 12 months. NOTE: The panel to the far right depicts plasma testosterone levels in patients who, after 10 to 12 months of therapy, had their megestrol dosage lowered from 120 to 80 mg/day and continued with 0.5 mg/day of estradiol.

OTHER THERAPEUTIC AGENTS

Other therapies effective in prostate cancer include flutamide, a nonsteroidal antiandrogen that exerts its action by competition for the androgen receptor and LHRH. Flutamide is currently undergoing clinical trials in prostate cancer patients and is not yet available for general use. Narayama et al[10] used flutamide in 12 patients with prostate cancer metastatic to bone. All patients became clinically stable for 3 months, but by 6 months all but three patients had progressed; these three patients each remained stable for 61 to 120 weeks.

Sogani and Whitmore[11] treated 21 previously untreated patients who had stage D prostate cancer with 750 mg/day of flutamide. Nineteen of 21 patients had responses. Of the 10 patients who relapsed following initial response, the average time of disease-free interval was 11.4 months with a range of 6 months to 2½ years. The advantage of flutamide is that it may not decrease libido since plasma testosterone is slightly increased or unchanged. A disadvantage is the significant gynecomastia that has been reported in some cases. Finally, disease-free interval and survival during flutamide therapy has not yet been compared with other standard therapies.

Potent agonist analogs of LHRH have been tried in metastatic prostate cancer. These compounds desensitize pituitary gonadotropins by decreasing the receptors for LHRH in the pituitary; they also decrease the LH receptor in the Leydig cells of the testis. The net result of these effects is to achieve castration levels of plasma testosterone.

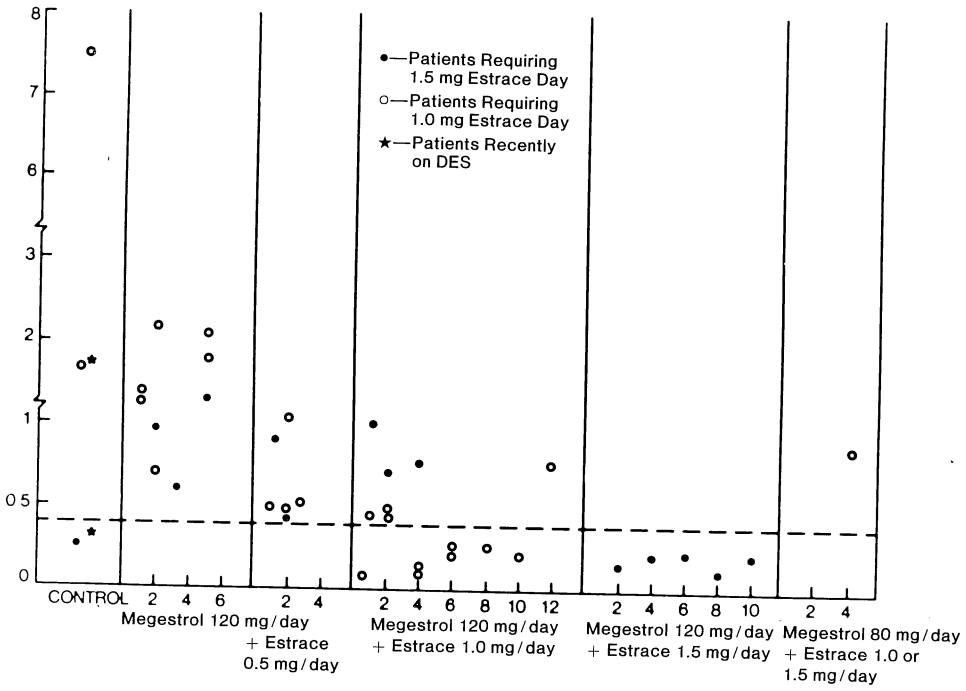

Fig. 9. This figure depicts plasma testosterone levels during sequential therapy with megestrol alone, then megestrol combined with estradiol for patients requiring more than 0.5 mg of estradiol (three patients). The solid dots indicate the one patient requiring 1.5 mg of estradiol per day, while the circles indicate patients requiring 1.0 mg of estradiol per day. Beginning from left to right is shown sequential plasma testosterone levels during various drug regimens, starting with control. On the far left is shown megestrol alone; next from the left, megestrol plus estradiol 0.5 mg/day; third from left, megestrol 120 mg/day plus estradiol 1.0 mg/day, followed by megestrol 120 mg/day plus estradiol 1.5 mg/day. To the far right is shown a plasma testosterone level at 5 months in one patient who was on megestrol 120 mg/day plus estradiol 1.0 mg/day for 1 year and then on a reduced megestrol dose of 80 mg/day with the same dose of estradiol.

To date, 117 patients have been treated with leuprolide, an LHRH analog.[12] Of 30 previously untreated patients followed long enough to be evaluated, 70% had complete or partial remissions initially, and 27% were objectively stable. Serum testosterone levels decreased to the castrate range by 4 weeks in all patients. The long-term survival and the disease-free interval are not yet known for these patients.

Disadvantages of leuprolide appear to be initial transient increases of plasma testosterone prior to the desensitization effect with an increase in symptoms of bone pain in some patients. Cost is currently excessive. Also, the medication must be given by daily injection, which is inconvenient, or by the intranasal route, which requires large doses and may not be dependable. The advantages of leuprolide are the

Table 3. Effects on Intracellular Biochemical Steps Mediating Androgen Action of Various Regimens

Biochemical Step	Megestrol Plus Estradiol*	DES†	Castration	Injected LHRH Agonist	Flutamide
5α-Reductase	↓	↓	→ ?	?	→
5α-DHT concentration in prostate	↓↓	↓	↓	? (Probably ↓)	↓, but not to castrate levels
Synthesis of androgen receptor	↓	?	?	?	?
Competitive binding for androgen receptor	Competes	Little or no competition	No effect	?	Competes

*Megestrol, 120 mg/day, plus estradiol, 0.5 to 1.5 mg/day.
†DES, 3 mg/day.

Table 4. Major Clinical and Endocrine Effects, Side Effects and Cost of Drugs and Surgery for Prostate Cancer

	Megestrol Plus Low-Dose DES or Estradiol	Castration	DES	Injected LHRH Agonist	Flutamide	LHRH Agonist Plus Antiandrogen
Gynecomastia*	+	0	++++	?	++	?
Loss of libido	Yes	Yes	Yes	Yes	No	Yes
Sustained decrease in plasma T	Yes	Yes	Yes	Yes	No	Yes
Blockade of adrenal androgens	Yes	No	No	No	Yes	Yes
Salt retention	No	No	Yes	No	No	No
Thromboembolism	No	No	Yes	?	No	?
Convenience	Yes	No	Yes	No daily injections	Yes	No
Cost	$60/month	One-time cost only	Cheap	$1200/month	?	? High

*Intensity: 0 to ++++.

lack of side effects such as gynecomastia, thromboembolism, and fluid retention seen with some of the other hormonal therapies. Recently, a combination of LHRH with a pure antiandrogen, RU 23908, has been shown to be effective in preliminary trials in prostate cancer.[13] This therapy has many of the theoretical advantages of megestrol acetate–estradiol, but cost and convenience remain negative factors.

Comparisons of the effects of the various therapeutic programs outlined on plasma hormones, intracellular biochemical steps mediating androgen action, and side effects and costs are shown respectively in Tables 1, 3, and 4.

CONCLUSIONS

On the basis of its ability to block androgen from all sources, minimal side effects, relative simplicity of administration, side effects limited to loss of libido, and moderate cost, it appears that the combination of megestrol acetate, 120 mg/day, together with estradiol, 0.5 to 1.0 mg/day, is currently the optimal effective therapy for metastatic prostate cancer.

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