Henry Ford Hospital Medical Journal

Volume 40 | Number 1 Article 27

3-1992

Maximal Androgen Ablation: A Review

Brian J. Miles

Joseph Babiarz

Maximal Androgen Ablation: A Review

Brian J. Miles, MD,* and Joseph Babiarz, MD†

Primary management of advanced (stage D) adenocarcinoma of the prostate is androgen ablation. Since this principle was discovered in the early 1940s, therapeutic alternatives and "progress" have centered around different ways to obtain castrate levels of androgens. The role of adrenal androgens in supporting prostate or prostatic cancer growth has been debated for decades and until recently was believed to be minimal. In the 1980s the concept of maximum androgen suppression, involving both the testes and adrenal glands, was reintroduced with some investigators claiming exceptional results. We review studies that have examined this concept, with emphasis on the largest trial which was carried out by the National Cancer Institute. (Henry Ford Hosp Med J 1992;40:114-7)

In 1941 Huggins and Hodges (1) published their landmark paper on the effects of androgen withdrawal on advanced adenocarcinoma of the prostate. This early work was the first to establish the hormone dependency of a human cancer. Since then, the endocrine physiology of the prostate has been well defined (Fig 1) (2). The testes, under direct control of the pituitary, produce testosterone, the main androgen support of the prostate. The remaining androgens in males are produced by the adrenal glands primarily as androstenedione. A total of 95% of circulating androgens are in the form of testosterone. The therapeutic options to ablate or suppress androgens include bilateral orchiectomy (castration) and administration of estrogens, luteinizing hormone-releasing hormone (LHRH) agonists, or various antiandrogens.

Bilateral orchiectomy has been the mainstay of therapy for advanced prostate carcinoma since the time of Huggins and Hodges. The procedure is simple, effective, and immediate. The major difficulty has been the psychological effect of significant body image changes associated with this procedure. Estrogen therapy had been the main alternative to castration until the past five years.

Estrogen therapy induces a "pharmacological castration" by suppressing the hypothalamic-pituitary stimulation of the testis. A number of studies have shown that the cardiovascular side effects of estrogens in males are severe, with cardiovascular death occurring in up to 15% of patients (3,4). LHRH agonists have become the main alternative to castration because with their use cardiovascular toxicity is essentially zero (5). The pituitary is responsive to intermittent stimulation by LHRH from the hypothalamus, but when subjected to constant stimulation by LHRH (or a long-acting LHRH agonist) the pituitary is desensitized and stops secreting luteinizing hormone (LH). Accordingly, LHRH agonists have the paradoxic effect of suppressing LH production, inducing pharmacologic castration.

Antiandrogens have various mechanisms of action. The most popular, flutamide, competitively inhibits the uptake of dihydrotestosterone (the active form of testosterone) by the prostate nuclear receptor (6). Because the prostate cells cannot bind dihydrotestosterone, DNA transcription cannot take place and cellular reproduction is prevented. Because the agent is a competitive inhibitor, it acts to release the "balanced" levels of LH and serum testosterone rises. Flutamide has not been approved as monotherapy owing to concerns that its competitive inhibiting effects might be overcome by increasing testosterone. Such result has not yet been observed in small, nonrandomized clinical trials. An advantage of flutamide as monotherapy is due to the fact that serum testosterone levels remain in the upper normal range and sexual libido is not impaired.

All primary methods to achieve androgen deprivation in patients with advanced prostate carcinoma are equally effective as monotherapy, with approximately 80% objective response rate (7). In 10% of patients the disease progresses as if they had received no treatment, but 10% survive 10 or more years with no evidence of progressing disease. Generally, even in patients who respond, the disease progresses at a median of 18 months to 2 years, and median survival is approximately 30 months.

The reason patients fail androgen ablation has been the source of much investigation. Huggins and Scott (8) suggested that adrenal androgens must be supporting the prostate carcinoma and they attempted bilateral adrenalectomy in patients whose disease progressed after castration. Along with other investigators, however, they demonstrated that either hypophysectomy or adrenalectomy was ineffective with objective response rates of only 6% to 7% (7).

Patients who fail primary ablation of testicular androgen must do so either because the cancer includes an androgen-independent clone of cells or, alternatively, a clone which is "supersensitive" to androgen has been selected and proliferated (9). If

Submitted for publication: July 31, 1991.
Accepted for publication: September 23, 1991.
*Formerly Department of Urology, Henry Ford Hospital. Currently Desert Valley Medical Group, Apple Valley, CA.
†Department of Urology, Henry Ford Hospital.
Address correspondence to Dr. Miles, Desert Valley Medical Group, 18219 Highway 18, Suite 1, Apple Valley, CA 92307.

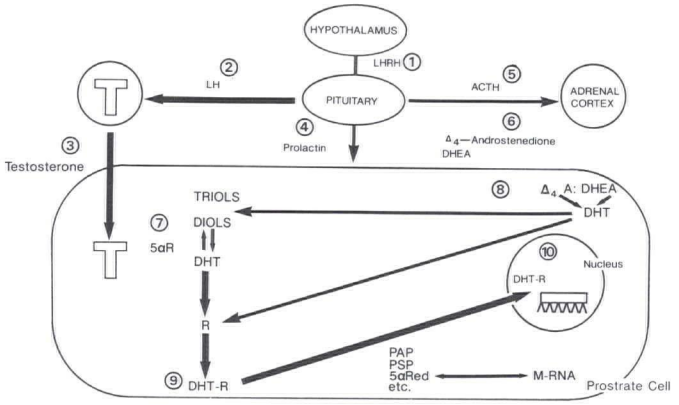

Fig 1—The mechanism of action of androgen on target tissues. The plasma factors affecting androgen action are shown by numbers of 1) luteinizing hormone-releasing hormone (LHRH), 2) luteinizing hormone (LH), 3) testosterone (T), 4) prolactin, 5) ACTH, and 6) adrenal androgens—Δ_4-androstenedione and dehydroepiandrosterone (DHEA and DHEA sulfate). Intracellular-mediated androgen action is shown by the various symbols depicted within the prostate cell. These include T conversion to dihydrotestosterone (DHT) by 5α-reductase, 7) conversion of adrenal androgens, Δ_4-androstenedione and DHEA to DHT, 8) binding of DHT derived from T and adrenal androgens to receptor to form the DHT-receptor complex, and 9) translocation of DHT-receptor complexes to nucleus and binding to acceptor site; 10) new protein synthesis is shown by M-RNA and prostate acid phosphatase (PAP), prostatic specific protein (PSP), 5α-reductase, and so forth. (From Geller J. Megestrol acetate plus low-dose estrogen in the management of advanced prostate carcinoma. Urol Clin North Am 1991;18:83-91. Reprinted with permission.)

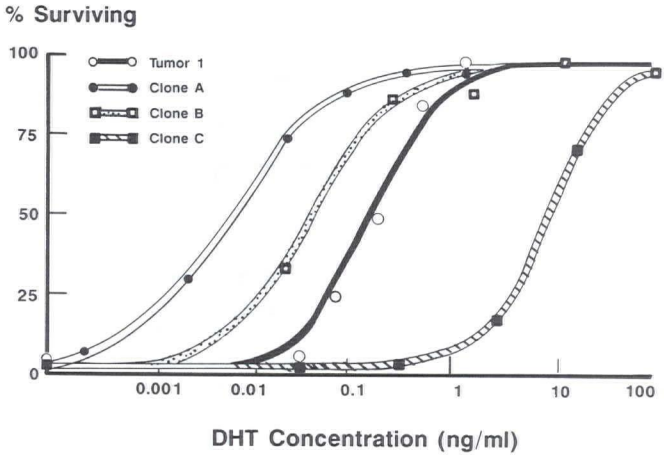

Fig 2—Response of four clones of cells to differing DHT levels in Shionogi mouse mammary tumor. (From Labrie F, Veilleux R. A wide range of sensitivities to androgens develops in cloned Shionogi mouse mammary tumor cells. Prostate 1986;8:293-300. Reprinted with permission.)

minimally androgen-dependent clones do prevail, stimulation by adrenal androgens could be supporting cellular growth. Labrie and Veilleux (10) showed varying degrees of androgen sensitivity in the Shionogi mouse model of prostate carcinoma (Fig 2). Geller and associates (11) also demonstrated that while castration reduced the level of serum testosterone ≥ 95%, intracellular dihydrotestosterone decreased by only approximately 60%. These data suggest that adrenal androgens have a more important role than was postulated by earlier investigators.

Based on the above studies, and because all earlier studies on the effect of ablating adrenal androgens were performed *after* primary testicular ablation had failed, Labrie recommended that primary treatment of advanced prostate cancer include simultaneous ablation of both testicular and adrenal androgens. It was believed that such treatment would eradicate all clones of cells, even with varying androgen sensitivity. This theory was not widely accepted by the urologic community because much data existed, both animal and human, which showed no benefit from combined androgen ablation. At least two animal studies utilizing rat Dunning prostate cancer models should be cited: 1) castration alone versus castration plus cyproterone acetate (an antiandrogen), and 2) LHRH agonist alone versus an LHRH agonist plus flutamide. No change in tumor weight was observed either with the monotherapy androgen ablation or with the combination therapies (12,13). A few small clinical trials (fewer than 20 patients in each arm) have evaluated the possible benefit of complete androgen blockade. In these studies the rate of progression one year after castration was the same in patients receiving an LHRH agonist, an antiandrogen, or no adjuvant therapy at all (7).

Nonetheless, Labrie et al (14-16) also conducted clinical trials and claimed impressive results. These data and public pressure led the National Cancer Institute (NCI) to begin a large multicenter intergroup study of combined therapy enlisting the efforts of the National Prostate Cancer Project, Southwest Oncology Group, Northern California Oncology Group, Mid Atlantic Oncology Program, and the North Central Cancer Treatment Group (17). A total of 617 patients with newly diagnosed stage D2 adenocarcinoma of the prostate were randomized in a double-blind fashion to receive either an LHRH agonist (leuprolide) plus placebo, or leuprolide plus the antiandrogen flutamide. There were 306 patients randomized to placebo and 311 to flutamide. Three patients in each arm were randomized to receive no treatment. Evaluable patients included 272 from the placebo arm and 282 from the flutamide arm. Endpoints of the study were response, time to first evidence of failure, and survival. Patients were evaluated every three months by bone scan, serum acid phosphatase level, and performance status. Progression was defined as objective evidence of new disease in bone or soft tissue or a measurable increase in old disease. Patients were stratified by extent of disease and performance status: minimal disease included those with axial, skeletal, and pelvic involvement only; extensive disease included patients with long bone, skull, rib, or visceral/soft tissue (lung) metastases.

The results demonstrated a significant improvement in progression-free survival (16.5 versus 13.9 months) as well as in ul-

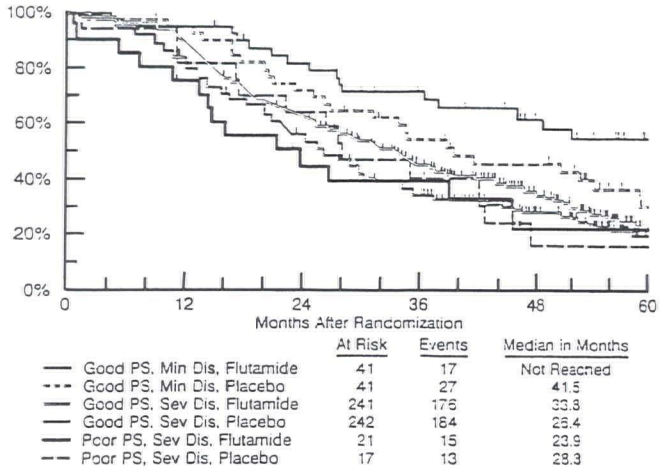

Fig 3—National Cancer Institute Intergroup Protocol 0036: Survival classified by stratification and randomized treatment (December 1990). (Crawford ED, Eisenberg MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med 1989;321:419-24. Reprinted with permission.)

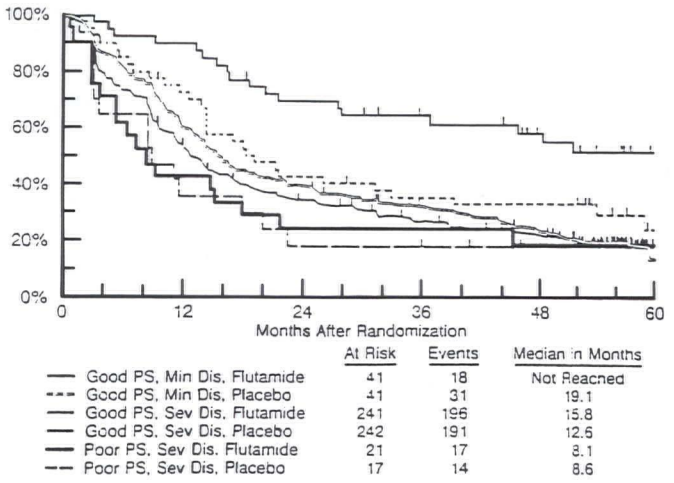

Fig 4—National Cancer Institute Intergroup Protocol 0036: Progression-free survival classified by stratification and randomized treatment (December 1990). (Crawford ED, Eisenberg MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med 1989; 321:419-24. Reprinted with permission.)

timate survival (35.6 versus 28.3 months) for the flutamide group (Figs 3 and 4) (P value for each evaluation < 0.01). Although they are statistically significant, the results have been considered to be clinically insignificant by the medical community. However, the results do indicate that, in the good performance status, minimal disease group, combination therapy was associated with dramatically improved results compared to the group receiving placebo. At 60 months the median progression-free survival had not been reached in the flutamide group, but was only 19.1 months in the placebo group. Median survival was 39.6 months for the placebo group, but, at 60 months, had not yet been determined for flutamide treated patients. Although the number at risk is small, these results warrant further investigation.

Other randomized trials of maximal androgen ablation have been carried out in Canada and Europe. All the studies have problems with design and endpoint evaluation, and therefore are not comparable to the NCI study. The International Prostate Study Group, with 568 patients randomized, is the only other large study (18). Unfortunately, patients with locally advanced disease but without metastatic disease were included. A total of 65% of the patients did have metastatic disease. The patients were randomized in an unblinded fashion to receive either the LHRH agonist zoladex alone or zoladex plus flutamide. The preliminary results, presented only in abstract form, show no statistically significant difference in objective response rate or in time to progression, at a median follow-up of 30 weeks. The report does not state how many patients were followed, how many were excluded, or for what reasons.

The Canadian study compared patients after bilateral orchiectomy who received the antiandrogen nilutamide to patients after orchiectomy who received placebo (19). There were 97 evaluable patients who received antiandrogen and 96 who received the placebo. The results showed an 87% response for the nilutamide group and 61% for the control group (P = 0.013). Median time to progression was 11.7 months for the placebo group and 12.4 months for the nilutamide group, not a statistically significant difference. Similarly, the 5.4-month survival advantage (24.3 versus 18.9) for the group receiving nilutamide was not significant. The study was designed to evaluate best response, not progression or survival. To evaluate all of these parameters, the study would have to include at least three times as many subjects (20).

In France, Brisset et al (21) conducted a randomized, prospective, blinded trial comparing orchiectomy and placebo versus orchiectomy and anandron 150 mg daily or orchiectomy and anandron 300 mg daily. Patients were evaluated for best response, progression-free survival, and ultimate survival. A total of 160 patients were studied in the three groups. Thirty-three patients were not evaluable because they were shown to have had no metastasis on entry, had been lost to follow-up, or had medications beginning later than three months after orchiectomy. Of the 127 patients for evaluation, 43 were in the placebo group, 46 in the 150 mg anandron group, and 38 in the 300 mg anandron group. The objective response rate was 61% in each of the two anandron-treated groups, compared to 33% in the placebo group. This is stated to be statistically significant, but a P value is not given. Progression-free survival and ultimate survival were similar in all three groups. Median time to progression was 13 months in all groups, and the median time to death was 22 to 24 months in all three. The number of patients involved in this three-arm study is small, enough to evaluate response but not nearly enough to evaluate progression and/or survival.

The European Organization of Research and Treatment of Cancer (EORTC) conducted a clinical trial comparing orchiectomy versus orchiectomy plus cytoproterone acetate versus 1

mg/day of diethylstilbestrol (DES) (22). This was an unblinded, prospective, randomized study. A total of 350 patients were entered from 16 European institutions. Eleven patients were determined to be ineligible and six were removed from the study because of treatment toxicity. Four of these six had received DES and developed cardiovascular disease. Preliminary evaluation of 241 patients showed no difference in time to progression or in length of survival for any of the three methods of treatment. Best response to therapy was not reported, but the data appear to support the contention that there is no benefit from such combined androgen ablation. As with other evaluations, the EORTC study is not large enough to reveal the desired endpoints in a statistically significant manner.

The EORTC is currently engaged in an unblinded randomized trial of orchiectomy versus flutamide plus the LHRH agonist zoladex (23). A total of 149 patients have been entered in the combination arm and 148 in the orchiectomy arm. Best response, measured by bone scan, was 67% for orchiectomy and 79% for combination therapy. Median time of progression was 18 months for the orchiectomy group and 26 months for the combined therapy group (P = 0.03). In time to death, both groups were essentially the same with a median of approximately 30 months. This study may be criticized for a number of reasons. First and most important is that the investigators are not comparing similar groups but two entirely different treatments. Although there is suggestive indirect evidence, there is no direct data showing equivalent effects from orchiectomy and the administration of LHRH agonists. Comparing this combination therapy to orchiectomy is not meaningful. Furthermore, this study, while large enough to evaluate best response, is also too small to evaluate progression and survival statistically.

This compendium of apparently conflicting data demonstrates the difficulty of deriving meaningful conclusions. Evidence suggests a more favorable response to maximal androgen ablation and, for patients with "minimal" disease, the chance of improved progression-free survival as well as ultimate survival. However, too few patients have been evaluated to provide statistical significance to the results of various treatment regimens. Currently the NCI is sponsoring another double-blinded intergroup trial comparing orchiectomy plus flutamide to orchiectomy plus placebo to see if the favorable results of the first trial can be reproduced. This study will involve over 1,200 patients, which should provide enough patients in each group to obtain significant results for all parameters.

References

1. Huggins C, Hodges CV. Studies on prostatic cancer: Effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941;1:293-7.

2. Geller J. Megestrol acetate plus low-dose estrogen in the management of advanced prostate carcinoma. Urol Clin North Am 1991;18:83-91.

3. De Voogt HJ, Smith PH, Pavone-Macaluso M, et al. Cardiovascular side effects of diethylstilbestrol, cyproterone acetate, medroxyprogesterone acetate and estramustine phosphate used for the treatment of advanced prostatic cancer: Results from European Organization for Research on Treatment of Cancer Trials 30761 and 30762. J Urol 1986;135:303-7.

4. Henriksson P, Edhag O. Orchiectomy versus oestrogen for prostatic cancer: Cardiovascular effects. Br Med J 1986;293:413-5.

5. Leuprolide Study Group. Leuprolide versus diethylstilbestrol for metastatic prostate cancer. N Engl J Med 1984;311:1281-6.

6. Neri R, Kassem N. Biological and clinical properties of antiandrogens. Prog Cancer Res Ther 1984;31:507-18.

7. Schulze H, Isaacs JT, Coffery DS. A critical review of the concept of total androgen ablation in the treatment of prostate cancer. In: Murphy GP, Khoury S, Kuss R, et al, eds. Prostate cancer. Part A: Research, endocrine treatment and histopathology. New York: Alan Liss, Inc., 1987:1-19.

8. Huggins C, Scott WW. Bilateral adrenalectomy in prostatic cancer: Clinical features and urinary excretion of 17-ketosteroids and estrogens. Ann Surg 1945;122:1031-44.

9. Isaacs JT, Coffey DS. Adaptation versus selection as the mechanism responsible for the relapse of prostatic cancer to androgen ablation therapy as studied in the Dunning R-3327-H adenocarcinoma. Cancer Res 1981;41:5070-5.

10. Labrie F, Veilleux R. A wide range of sensitivities to androgens develops in cloned Shionogi mouse mammary tumor cells. Prostate 1986;8:293-300.

11. Geller J, de la Vega DJ, Albert JD, Wachtsheim DA. Tissue dihydrotestosterone levels and clinical response to hormonal therapy in patients with advanced prostate cancer. J Clin Endocrinol Metab 1984;58:36-40.

12. Ellis WJ, Isaacs JT. Effectiveness of complete versus partial androgen withdrawal therapy for the treatment of prostatic cancer as studied in the Dunning R-3327 system of rat prostatic adenocarcinomas. Cancer Res 1985;45: 6041-50.

13. Isaacs JT. Hormonally responsive versus unresponsive progression of prostatic cancer to antiandrogen therapy as studied with the Dunning R-3327-AT and -G rat adenocarcinomas. Cancer Res 1982;42:5010-4.

14. Labrie F, Dupont A, Belanger A. A complete androgen blockade in the treatment of prostate cancer. In: de Vita VT, Hellman S, Rosenberg SA, eds. Important advances in oncology. Philadelphia: JB Lippincott, 1985:193.

15. Labrie F, Dupont A, Belanger A, et al. New hormonal therapy in prostatic carcinoma: Combined treatment with an LHRH agonist and an antiandrogen. Clin Invest Med 1982;5:267-75.

16. Labrie F, Dupont A, Belanger A, et al. New approach in the treatment of prostate cancer: Complete instead of partial withdrawal of androgens. Prostate 1983;4:579-94.

17. Crawford ED, Eisenberg MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med 1989;321:419-24.

18. Altwein JE, Klippel KF, Holdaway IM, et al. A multicenter randomised trial comparing the LHRH agonist zoladex with zoladex in combination with flutamide in the treatment of advanced prostate cancer (Abstract). J Urol 1989;141:310A.

19. Beland G, Elhilali M, Fradet Y, et al. A controlled trial of castration with and without nilutamide in metastatic prostatic carcinoma. Cancer 1990;66:1074-9.

20. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Br J Cancer 1976;34:585-612.

21. Brisset J-M, Boccon-Gidob L, Botto M, et al. Anandron (RU23908) associated to surgical castration in previously untreated stage D prostate cancer: Multicenter comparative study of two doses of the drug and of a placebo. In: Murphy G, Khoury S, Kuss R, et al, eds. Prostate Cancer. Part A: Research, endocrine treatment and histopathology. New York: Alan Liss, Inc., 1987:411-22.

22. Robinson MRG. Complete androgen blockade: The EORTC experience comparing orchiectomy versus orchiectomy plus cyproterone acetate versus low-dose stilbestrol in the treatment of metastatic carcinoma of the prostate. In: Murphy G, Khoury S, Kuss R, et al, eds. Prostate cancer. Part A: Research, endocrine treatment and histopathology. New York: Alan Liss, Inc., 1987:383-90.

23. Denis L, Smith P, Carneiro JL, et al. Total androgen ablation: European experience. Urol Clin North Am 1991;18:65-73.