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Perspectives and Commentaries

Adrenal Androgen Blockade in Relapsed Prostate Cancer

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(A COMMENT ON: Murray R, Pitt P. Treatment of advanced prostatic cancer, resistant to conventional therapy, with aminoglutethimide. *Eur J Cancer Clin Oncol* 1985, **21**, 453-458.)

AT THE time of discovery, prostate cancer is usually metastatic and 10% or less of patients are suitable for curative total prostatectomy. Since approximately 80% of prostate cancers are androgen-sensitive, hormonal or ablative therapy is widely used in the initial treatment of metastatic disease. Several key questions are still unresolved in the management of metastatic prostate cancer with anti-androgen therapy. These include:

1. Does early and aggressive therapy with total simultaneous androgen blockade (testicular and adrenal) increase survival and disease-free interval in prostate cancer?
2. Do adrenal androgens significantly stimulate tumor growth and should suppression of adrenal androgens be undertaken following relapse after castration or estrogen therapy?

The first question, although somewhat tangential to our main theme, is provocative and of great potential clinical importance. Both Labrie [1] and Geller and Albert [2] have reported encouraging preliminary results using different drug combinations which suppress all androgens at the initiation of therapy for metastatic prostate cancer. Labrie uses GNRH and a pure anti-androgen, while Geller uses daily oral treatment with megestrol acetate 120 mg a day and 0.1 mg of DES. Labrie's dramatic results of 97% remission rate in 30 patients followed for 18 months will bear careful watching over a 5-yr period.

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The second question addresses a major practical problem facing most clinicians in the management of prostate cancer in relapse following castration or estrogen. We will review the evidence for the effectiveness of blockade of adrenal androgens in managing relapsed prostate cancer. Let us first enumerate the major adrenal androgens and the amounts secreted daily. Androstenedione (Δ_4) blood production rates average approximately 4.0 mg/24 hr; DHeA averages 8.0 mg per day while DHeA sulfate has a blood production rate of approximately 20-30 mg per day. The adrenal also secretes small amounts of testosterone (T), ranging from 0.02 to 0.2 mg per day. Approximately 0.2-0.3 mg of T result from peripheral conversion of Δ_4. Dihydrotestosterone (DHT) is the major intranuclear androgen in prostate cells and the stimulus for growth and replication of the prostate. Exemplifying this is nature's experiment with 5α-reductase deficiency, in which DHT cannot be formed from T. Patients with this syndrome either have no prostate or only a remnant present. In castrated patients therefore the question is can adrenal androgens be converted into significant amounts of DHT in the prostate? Both aspects of this question are important, namely, conversion of adrenal androgens to DHT and the question of what constitutes significant amounts. There is some direct evidence indicating that prostatic DHT in the human prostate can indeed be derived from adrenal androgens. Harper *et al.* [3] infused equimolar amounts of labeled T, Δ_4 and DHeA sulfate into patients half an hour before

prostatectomy and measured radioactive androgen metabolites in the prostate. They found an average of 63% of ^3H in the prostate as DHT. In the case of Δ_4, [^3H]DHT comprised 9% of the ^3H label, while in the case of DHeA sulfate the average conversion to [^3H]DHT of the label was 2%. If we assume that the blood production rates for Δ_4 and DHeA sulfate are approximately one-half and four times that respectively of testosterone, then based on these figures, Δ_4 and DHeA sulfate would provide approximately one-fifth as much prostatic DHT as would average secreted amounts of testicular testosterone.

In addition, Geller *et al.* [4] showed that 3/28 castrated patients who required subsequent prostate resection for prostate cancer had greater than 2.4 ng/g of prostatic DHT, significantly more than is found in non-androgen target tissues in patients with intact testes. The implication is that adrenal androgens accounted for this increased level of DHT (greater than 2.4 ng/g) in these three patients. Although the studies by Harper *et al.* [3] and Geller *et al.* [4] established that there is conversion of adrenal androgens into DHT in the prostate, what about the quantity of prostatic DHT available from adrenal androgens? Based on Harper *et al.*'s [3] data that adrenal androgens might contribute as much as one-fifth of the total amount of prostatic DHT as T, the question is: is this amount biologically important for the growth of the tumor? Geller *et al.*'s [4] three patients each had amounts of DHT similar to values found in untreated BPH. There are no direct human data available to answer this question. Bartsch *et al.* [5], however, in rats, showed that administration of T to castrate rats in amounts equal to 1/100 of the secretory rate for testosterone significantly increased prostatic weight above castrate levels. Perhaps the question of the biological importance of the contribution of adrenal androgen conversion to DHT in the prostate to prostate growth can be best appreciated by studies of the effects on prostate cancer in relapse when adrenal androgens are blocked. Studies of this type have been done and correlated with clinical response of tumors in patients treated with either adrenalectomy, inhibition of adrenal androgen synthesis as reported in the article by Murray and Pitt [6] in this same issue or by peripheral blockade of adrenal androgens with anti-androgens. Adrenalectomy for prostate cancer was first reported by Huggins *et al.* in 1945. A review by Bhanalaph *et al.* [7] in 1972 of 16 patients with D_2 prostate cancer who had relapsed following estrogen or castration and had surgical adrenalectomy showed that, on average, subjective improvement and survival for the entire group was 4.8 and 8.2 months respectively. In a subset of four patients (25%), subjective improvement was in excess of 1 yr. By contrast, Bhanalaph *et al.* [7] indicated average subjective improvement and survival of 1.6 and 6.8 months respectively in patients who relapsed following castration or estrogen plus hypophysectomy. As regards the objective changes, Bhanalaph *et al.*'s [7] data are difficult to interpret since he admixed five patients who were adrenalectomized while still in remission with 16 patients in relapse. Bhanalaph *et al.* [7] also review 100 previously reported patients in the literature who were adrenalectomized. Overall approximately 50% of these showed subjective improvement while only 6% showed objective improvement. The mean value for the longest survival in these summarized reports of 100 patients is 13 months. There was approximately 10% surgical mortality in this group.

In summary, surgical adrenalectomy is associated with a high incidence of short (average < 6 months) subjective remissions for the group as a whole with rare objective remissions. Subsets of up to 25% of patients may show subjective remissions and survivals of > 1 yr duration. If historical controls or hypophysectomized, castrated patients are used, one can claim a definite albeit short remission following surgical adrenalectomy in patients with carcinoma of the prostate in relapse following castration or estrogen therapy.

Anti-androgens, which block the effects of androgen on target cells also have been evaluated for their clinical effects in prostate cancer in relapse following estrogen or castration. Sogani and Whitmore [8] reported short remissions (time not specified) in 6/23 patients treated with flutamide, a nonsteroidal anti-androgen. Stoliar and Albert [9] reported 39% response rate to flutamide in patients with prostate cancer in relapse following castration or estrogen. Both of these studies lack specific data to determine whether there was subjective responses only or whether they included objective changes.

Geller *et al.* [10] treated 11 relapsed patients with stage D_2 cancer of the prostate with megestrol acetate, 160 mg per day. All patients had previously been treated with either orchiectomy or estrogen therapy. On megestrol acetate therapy, 1/11 patients had a partial objective regression and his PAP returned to normal values; he remained in remission for 16 months. Eight other patients were objectively stable and had an average remission time of 7 months on the megestrol acetate; two patients showed objective progression of disease.

Smith *et al.* [11] administered 300 mg a day of cyproterone acetate, a steroidal anti-androgen, to

28 evaluable patients with prostate cancer in relapse following castration or estrogen. Based on the criteria of relief of bone pain (12/19), improved weakness (5/13), relief of hydronephrosis (2/3) and decreased size of the prostate (12/28), 19/28 (67%) of patients showed a response for a mean time of 14 months. Three out of eight patients with increased prostatic acid phosphatase also showed significant decreases and bone X-rays improved in four patients. This report includes a large amount of objective data. However, bone scans were not used and the radiologic techniques used, according to the authors, were unreliable in evaluating changes in bone metastases. Finally, the effect of aminoglutethimide, an inhibitor of adrenal androgen synthesis that blocks the conversion of cholesterol to pregnenolone, has now been reported in metastatic prostate cancer by at least four different groups. Rostom *et al.* [12] reported the effects of 750–1250 mg per day of aminoglutethimide in 12 patients with advanced prostate cancer. Using performance status and analgesic requirements, 75% of their patients showed subjective improvement following aminoglutethimide and 50 mg a day of cortisone acetate; mean survival following treatment was 6.54 months (range 3–13.5 months for the entire group). No objective changes were noted. Very few side-effects were also noted. Drago *et al.* [13] also reported on the effects of aminoglutethimide in 43 stage D_2 patients with prostate cancer who had been previously castrated and relapsed. They noted a 40% objective response rate using NPCP criteria [14] following 1000 mg of aminoglutethimide per day and hydrocortisone 40 mg per day. One patient had a complete objective regression lasting 290 weeks at the time of the writing, six others enjoyed partial objective regressions ranging from 24 to 167 weeks and ten patients were objectively stable for a mean time of 35 weeks. The majority of the patients were ambulatory prior to therapy.

Block *et al.* [15] found no effect of aminoglutethimide and cortisone acetate 40 mg per day in 20 patients with metastatic prostate cancer in relapse. More than half of the patients were ambulatory at the onset of therapy; the authors attributed the poor results to the fact that the majority of the patients had received two or more systemic treatments prior to aminoglutethimide, including seven who received prior chemotherapy. Doses of aminoglutethimide were titrated to control levels of DHeA sulfate and patients received doses of up to 1750 mg per day in order to decrease DHeA sulfate to less than 5% of basal levels. The authors measured blood levels of aminoglutethimide and noted a marked variation in pharmacokinetics of the drug. The largest study of aminoglutethimide in prostate cancer in relapse following estrogen or castration is reported by Murray and Pitt [6]. They report on 58 patients treated with 250 mg four times a day of aminoglutethimide, 37.5 mg per day of cortisone acetate and fludrocortisone 0.1 mg per day. They used skeletal surveys, bone scans and liver scans to monitor patients every 3 months as well as routine biochemical parameters every month. They used objective criterion established by the NPCP for evaluation of response. Eleven out of 58 or 19% of patients had objective responses to treatment and 14% stablization of disease. The mean duration of remission to date is greater than 10 months (still continuing for some patients) in the partial objective response group and 7 months for those who were objectively stable. Survival times are 15 months in the group with partial objective regression, 9.3 months in those objectively stable and 4.7 months in patients not responding. There were no differences in the characteristics of the three different groups that would allow prediction of response, including interval between time of diagnosis of metastatic disease and starting of aminoglutethimide. Subjective responses accompanied objective response in all patients with partial objective regression or who were objectively stable except for two in the latter group. The drug was generally well-tolerated, with a skin rash being the major complication in 14% of patients. The drug was not discontinued in any patient.

Thus many lines of evidence indicate that surgical ablation or medical blockade of adrenal androgens may lead to significant objective and subjective benefits and increased survival in patients with carcinoma of the prostate in relapse following castration or estrogen. Such therapy appears to benefit a significant subgroup of patients who cannot be predicted in advance based upon prior response to other therapies or the extent of metastatic disease. The best objective scientific studies and the largest series of patients reported to date are the group of 58 patients reported following treatment with aminoglutethimide by Murray and Pitt [6] in this journal and the study of 43 patients by Drago *et al.* [13] using the same drug. The studies are compelling in their support to initiate aminoglutethimide in patients who have relapsed following castration or estrogen since objective remission rates ranged from 33 to 40% and survival was approximately 1 yr in responders and only 4.7 months in nonresponders.

SUMMARY

The effectiveness of aminoglutethimide as an adrenal inhibitor has been well-documented by

decreases in plasma testosterone and Δ_4 levels, which fall significantly following the drug in previously orchiectomized patients. The use of cortisone or cortisol along with aminoglutethimide complicates the interpretation of the role of aminoglutethimide in effecting clinical responses. However, since physiologic replacement doses were used in most cases, a significant role for cortisone in effecting a clinical response is unlikely. Aminoglutethimide does have side-effects including rash and lethargy. It requires administration of replacement doses of cortisone and sometimes mineralocorticoid as well since it inhibits adrenal steroid synthesis in all pathways. Peripheral adrenal androgen inhibitors, such as flutamide, Megace®, cyproterone acetate or 5α-reductase inhibitors, in the future may be equally effective and simpler to administer than aminoglutethimide but objective and adequate numbers of studies using acceptable objective criteria must be done in order to adequately compare these drugs to aminoglutethimide.

There appears to be approximately a 33% response rate (partial objective regression and objectively stable) following blockade of adrenal androgens in patients in relapse after castration. Blockade of adrenal androgen is certainly more tolerable and has many fewer side-effects than the alternative of chemotherapy which does not give response rates in most cases that are significantly different from those noted with aminoglutethimide. Murray's paper, combined with prior studies by Drago *et al.*, goes a long way in establishing adrenal androgen blockade with that drug as the next step to be taken in patients following relapse from prior castration (medical or surgical). The most important question revolves around the timing of adrenal androgen blockade. As stated by Murray, will adrenal androgen blockade provide better survival if given earlier following relapse? The answer is not known yet. The answer may come from the work of Labrie [1], Geller and Albert [2] and others, who suggest that total survival in prostate cancer may be improved with blockade of adrenal androgens not after relapse following castration, but with panandrogen blockade at the time of initial therapy for prostate cancer.

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