Dihydrotestosterone Concentration in Prostate Cancer Tissue as a Predictor of Tumor Differentiation and Hormonal Dependency

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Abstract

Tissue dihydrotestosterone and 5a-reductase (\(\Delta^1\)-3-ketosteroid-5a-oxidoreductase) levels have been measured in prostates of patients with cancer and benign prostatic hypertrophy; significant decreases in average values for both of these biochemical parameters were noted in prostate cancer compared to benign prostatic hypertrophy, although individual values overlapped in both groups. Prostate cancer tissue dihydrotestosterone levels appeared to correlate better than did either histological tumor grading or 5a-reductase with the ultimate clinical response to antiandrogen therapy. These results suggest that assay of tissue dihydrotestosterone levels in prostate cancer should be further explored as a possible marker for tumor differentiation.

Introduction

Although measurement of the estrogen receptor in breast cancer tissue is now a well-established technique for predicting responsiveness to endocrine or ablative treatment, a similar approach has not yet been developed for prostate tumors. Although there is abundant evidence that a high-affinity, low-capacity receptor protein similar to that found in the rat exists in human prostate cytosol and purified nuclei (6-10, 12), uniform detection of such a receptor in human BPH\(^3\) tissue has not yet been accomplished by any group that has studied more than 10 prostates (2). This is attributed to the difficulty of separating cytosol receptor from testosterone- and estradiol-binding globulin (7), reduction of \([\text{\textsuperscript{3H}}]\)DHT at 0-4\(^\circ\), the lability of DHT receptor complex to shearing (9) and temperature changes (9), the near saturation of endogenous cytosol receptor with DHT (12), and the slow dissociation of DHT from receptor (2), negating a possible exchange assay. DHT, which can be measured in a 50-mg biopsy sample of prostate (1), may represent a suitable alternative to the cytosol receptor as a biochemical marker for tissue differentiation, since DHT levels are significantly higher in androgen target tissues. Histological tumor grading of 1 and 2 (Fig. 1A) was considered to be poorly differentiated tumor.

Results

Comparison of 5a-Reductase and DHT Levels in Patients with Prostate Cancer and BPH. In Chart 1, it can be seen that tissue DHT levels were significantly less (\(p < 0.05\)) in patients with cancer of the prostate, as compared to those with BPH, although there was a considerable overlap. In 4 patients with prostate cancer (Chart 1), in whom both DHT levels and 5a-reductase were measured in the same tissue tumor samples, there was no difference in DHT levels compared to those of BPH tissue, although 5a-reductase levels were significantly reduced in 3 of these patients. These 3 patients (7, 8, and 9 in Table 1), who have been followed clinically for at least 6 months, have responded favorably to antiandrogen treatment.

Correlation of Tissue DHT Levels and Histological Grading with Clinical Response to Therapy (Table 1; Chart 1, A and B). In 9 patients with previously untreated Stage D prostate cancer, response to antiandrogen therapy has been retrospectively correlated with both tissue DHT levels and histological grading. We have designated prostate DHT levels \(>2.0\) ng/g as “differentiated,” since this value is more than 2 S.D. above the mean of non-androgen target tissues. Histological tumor grading of 1 and 2 (Fig. 1A) was used to indicate well- and moderately differentiated tumors, respectively (Figure 1A); tumors with greater than Grade 2 histological changes (Fig. 1B) were considered to be poorly differentiated.

Materials and Methods

Clinical. Patients with previously untreated Stage D prostate cancer who underwent transurethral resection of prostate and in whom 75% or more of the resected tissue was cancer were selected for study. Tissue was utilized for histological study and biochemical assays. Patients were followed, whenever possible, by objective parameters for tumor responsiveness, as outlined by Schmidt et al. (13). Antiandrogen therapy consisted of either castration, diethylstilbestrol (3 mg or more per day), or megestrol acetate (Megace; 160 mg/day). Parameters used to follow patients included bone scan, prostatic acid phosphatase, and prostatic size. In some patients, objective data were not available and subjective evidence such as change in weight, pain, appetite, and activity was utilized. Prostate DHT levels and histological grading were retrospectively correlated with tumor response.

Tissue DHT and 5a-reductase (\(\Delta^1\)-3-ketosteroid-5a-oxidoreductase) concentrations were measured according to previously reported methods (3). Prostate cancer was graded histologically, with the use of a scale of 1 to 3, with 3 representing an undifferentiated tumor and 1 a well-differentiated tumor.

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2 To whom requests for reprints should be addressed.
3 The abbreviations used are: BPH, benign prostatic hypertrophy; DHT, 17\beta-hydroxy-5a-androstan-3-one.

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Data for objective evaluation were not available. Among 8 patients who had either partial or complete regressions or subjective remissions, or who were objectively stable on therapy, 7 had DHT levels > 2.5 ng per g of tissue, while only 3 of these 8 patients were classified as Grade 1 or 2 microscopically differentiated; one patient had objective progression of his disease on treatment and had a DHT level below 1.8 ng/g and histological Grade 3 tumor.

Discussion

DHT is found in significant amounts only in androgen target tissues, as demonstrated in previous studies (4). This selectivity is due to requirements for $5\alpha$-reductase, DHT-binding cytosol receptor, and nuclear acceptor in these specialized tissues. That $5\alpha$-reductase and the receptor are critical for biological activity of androgens is indicated by some of nature's experiments, including male pseudohermaphroditism Type II and testicular feminization, in which $5\alpha$-reductase in the former and cytosol receptor in the latter are virtually absent and prostate and male secondary sex structures are absent or ambiguous. It is presumed that DHT, the biologically active androgen in most target tissues, is also very low in tissues of these patients. Tissue DHT levels depend upon multiple factors. These include levels of plasma testosterone, a major substrate for DHT, and 3-hydroxysteroid dehydrogenase, which removes DHT by reduction, in addition to previously mentioned $5\alpha$-reductase and receptors.

We have attempted to study the relative importance of some of these various biochemical factors as regulators of tissue DHT. In previously reported studies of patients with BPH in which we acutely perturbed plasma testosterone, $5\alpha$-reductase, and cytosol receptor with either Megace, an antiandrogen, or polyestradiol phosphate (Estradurin), tissue DHT levels appeared to correlate best with change in cytosol receptor binding of DHT (5). This conclusion was based on the fact that Megace and Estradurin had similar quantitative inhibitory effects on $5\alpha$-reductase and plasma testosterone, but only Megace, which also decreased receptor binding of DHT, significantly decreased tissue DHT levels.

In this study, we have shown in Chart 1 that among 4 patients with prostate cancer with DHT levels similar to those of the BPH group, 3 had low values of $5\alpha$-reductase (see Chart 1). The fact that these 3 patients responded favorably to antiandrogen therapy supports the hypothesis that DHT is a better biochemical marker of tumor differentiation than is $5\alpha$-reductase. In 9 patients with prostate cancer studied to date, tissue DHT also appears to correlate better with the ultimate response to antiandrogen therapy than histological grading (Table 1). Extension and confirmation of these studies in a much larger series of patients is necessary, however, before any final conclusions can be reached.

It would thus appear that levels of DHT in prostate cancer tissue may provide a biochemical index for tissue differentiation in previously untreated patients. Tumor DHT assay also represents a practical approach to clinical limitations on tissue availability, since assay of a 50-mg sample of tumor can accurately and precisely detect as little as 100 pg of DHT or 2 ng of DHT per g wet weight of tissue, the lower limit set for DHT content in differentiated tumors. Previous therapy for prostate cancer with drugs or surgery, which decrease plasma testosterone, invalidates the usefulness of DHT for study of differentiation. In treated patients with low endogenous steroid testosterone, cytosol receptor assay, when a reproducible method has been developed, might provide a reliable index of tumor differentiation, as recently suggested by Mobbs et al. (11).

Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Histological grade</th>
<th>ng DHT/g tissue</th>
<th>Clinical response to therapy</th>
</tr>
</thead>
</table>
| 1       | 2                  | 0.97           | Partial objective regression
| 2       | 2                  | 2.7            | Objectively stable
| 3       | 3                  | 1.1            | Objective regression
| 4       | 2-3                | 2.5            | Partial objective regression
| 5       | 2-3                | 2.8            | Partial objective regression
| 6c      | 3                  | 5.9            | Remission
| 7       | 2-3                | 3.6            | Remission
| 8       | 2-3                | 5.5            | Remission
| 9       | 2                  | 8.7            | Partial objective regression

a Values > 2.0 ng/g indicate differentiated.
b Refers to use of objective criteria for evaluating response, including changes in bone scan, tumor mass, and prostatic acid phosphatase.
c Lymph node replaced by prostate cancer tissue.
d Refers to use of subjective and clinical criteria for response; adequate data for objective evaluation were not available.

differentiated. Among 8 patients who had either partial objective regressions or subjective remissions, or who were objectively stable on therapy, 7 had DHT levels > 2.5 ng per g prostate (biochemically differentiated), while only 3 of these 8 patients were classified as Grade 1 or 2 microscopically differentiated; one patient had objective progression of his disease on treatment and had a DHT level below 1.8 ng/g and histological Grade 3 tumor.

References


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Fig. 1. A. moderately well-differentiated prostate cancer (Grade 2). The tumor appears to be forming glands, cells are uniform without evidence of anaplasia or pleomorphism, and there is fibrosis of the stroma. B, a fully differentiated prostate cancer (Grade 3). The tumor appears as solid sheets of pleomorphic anaplastic cells. There is no gland formation.
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