Continuous Finasteride Therapy for Benign Prostate Hypertrophy Upgrades Both Neuroendocrine Differentiation and Aggressive Prostate Cancer

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Abstract. Finasteride has been recognized as a drug suitable for the chemoprevention of prostate cancer (PC) by reducing intracellular dihydrotestosterone (DHT) levels. The Prostate Cancer Prevention Trial (PCPT) database on continuous finasteride treatment of almost 19 thousands patients indicated the reduction in cancer prevalence by about 25%. However, in this same study more than a twofold increase in high grade aggressive prostate tumors was recorded when compared to controls thus arising serious doubts upon the real benefits of the protocol. Here, our investigation was performed three years on a continuous versus intermittent (six month treatment followed by 6 months resting period) finasteride treatment in 125 BPH patients (pts) each. The overall PC prevalence in both finasteride-treated groups was lower that in untreated controls and thus being in accordance with the PCPT data. However, continuous therapy gave significantly higher incidence in Gleason score (GS)>6 carcinomas compared to intermitted therapy and controls (44.5%, 25% and 18.2% of total acquired PC, respectively). In addition, the acquired elevated chromogranin A (CgA) values were also more than doubled in pts treated continuously compared to the other two groups (13.6%, 5.6% and 6.4%, respectively). Acquired PC GS>6 recorded in pts with a raise in CgA was higher in continuously treated pts (50%) than in the other two studied groups (20% and 25%, respectively). In pts with the retained normal CgA concentration highest PC incidence was found in controls (5.1%) and lower prevalence was recorded in continuously (2.8%) and intermittently treated pts (2.5%) while the respective PC GS>6 incidence was lower in controls than in treated pts. Seemingly, finasteride treatment reduces PC prevalence in pts free of NED but elevates the number of aggressive carcinomas in CgA-positive pts only if continuous treatment is applied. In conclusion, current chemoprevention protocols need to be carefully reconsidered prior to the selection between continuous and discontinued finasteride treatment.

The conservative approach to benign prostatic hypertrophy (BPH) treatment frequently involves the use of 5alpha reductase inhibitors and the most widely applied drug being finasteride. More recently dutasteride has also been frequently used. Such therapy leads to an intraprostatic dihydrotestosterone (DHT) deficiency (1). Finasteride is also rather often used as a supplement to either androgen deprivation therapy or a maximal androgen blockade (Mab) (2, 3). Finasteride treatment applied to BPH patients with a large prostate facilitates an early detection of prostate cancer (PC) (4). An increase in circulating chromogranin A (CgA) level was recorded during prolonged antiandrogen therapy for PC indicating the appearance of neuroendocrine differentiation (NED) (5). In parallel, NED within the prostate was recognized as a risk factor for developing aggressive PC (GS>6) being of poor prognosis (6,7). Relatively low testosterone levels are found in first presented patients with higher Gleason score (GS) PC (8). Seemingly, an androgen deficient environment provokes the differentiation of NE cells and thus the raise in serum CgA level. An increased volume of evidence indicates NED as one of the critical events in the development of hormone-refractory prostate cancer (HRPC) (9) possibly playing a role in the onset and regulation of apoptosis in PC (10).

The efficiency of finasteride in descending the most potent androgen (DHT) level in BPH patients initiated a PC Prevention Trial (PCPT) related to the use of this agent for the chemoprevention of PC (11). The 24.8% reduction in prevalence of PC during the seven-year trial was recorded in finasteride treated subjects versus placebo branch. However tumors of GS 7-10 were more common in the finasteride group (37.0% of PC) than in the placebo group (22.2%, respectively). An overall 25% risk reduction in the finasteride preven...
The chemoprevention trial was accompanied with approximately 25% increase in the incidence of high-grade tumors. That increase was speculated to be due to ascertainment bias since finasteride treatment reduces the size of the prostate by about 25% and thus biopsy needles are correspondingly more likely to sample any present high-grade tumors. The use of finasteride may also increase the diagnostic accuracy of prostate specific antigen (PSA) for finding high-grade disease in the PCPT. Together, these phenomena may explain the increased incidence of high-grade disease in the finasteride arm. Nevertheless, a true biologic effect of finasteride on the raise in high-grade PC is still under consideration and despite strong recommendations in support of the proposed PC chemoprevention procedure serious doubts still remain (12).

By the time the PCPT article was published the present study on finasteride chemoprevention capability had been ongoing and the progress report was published soon thereafter (13). Being aware of the importance of NED in androgen deficient environment (5) investigations were performed on continuous versus intermittent finasteride treatment in BPH patients following the acquisition of PC and the elevation in serum CgA values.

Due to the much lower number of patients investigated in this study compared to the PCPT study this article might be considered as an initiative aimed at the thorough investigation of NED and its role in androgen deprivation protocols.

Patients and Methods

Patients were continuously treated with 5 mg finasteride daily over 36 months (group A, n=125) or in an intermitting manner over 6 months followed by a 6 months resting period, for an overall of 36 months (group B, n=125). The treatment period in group B was chosen in accordance with the literature data (14). Clinical benign prostate hypertrophy (BPH) was diagnosed in all subjects (DRE, TRUS and laboratory data). Prostate volume ranged 20-60 cc. The control group C (n=125) received 100 mg of aspirin several times a week (as did patients in groups A and B).

Patients were free of acute prostate inflammation (checked by bacteriological analysis of ejaculate and/or inspection of prostatic excretion), renal insufficiency (normal serum creatinine level), any malignant tumor and were recorded serum CgA<80 ng/mL, total PSA <2.5 ng/mL (ongoing PC chances <2%) and % FPSA>18%. Every 6 months patients treated with finasteride and those in the control group were evaluated clinically and biochemically (PSA, %FPSA and CgA) in a described manner (4). Biopsy was performed in all patients with CgA elevation and in all clinically and/or biochemically suspected subjects. Patients with proven prostate cancer (PC) quitted periodical study exams but were included in the final number of presented patients.

The progress report on this investigation was published with a lesser number of patients (13). The study continued until an equal number of pts (125) in all studied groups was reached for the sake of a more transparent data analysis. A total of 518 patients initially entered this study but 143 of them (27.6%) were lost for various reasons.

Statistical analyses were performed by applying Macintosh software and a t-test. Probability values <0.05 were considered statistically significant.

Results

The elevation of the CgA marker was almost identical in the control group C and in patients treated discontinuously with Finasteride (8/125 and 7/125, respectively) but was more frequent in group A among patients treated with Finasteride in an uninterrupted manner (17/125). The differences between these two sets of data are significant (p<0.01).

Contrary, the percentage of acquired PC cases among patients with elevated CgA concentration was much lower in group A (6/17, 35.3%) than it was in groups B and C (71.4% and 62.5%) (p<0.05). Respective outcome in group A was numerically the highest. In addition, GS>6 was found in 50% of patients in group A (GS 6 was attributed to other 50% of patients) while in groups B and C PC GS>6 was recorded in 20% and in 25% of patients, respectively (p<0.01).

PC was found also in patients with retained normal CgA level and the respective percentages differ significantly among groups A and B versus C (3/108, 2.8%; 3/118, 2.5%; 6/117, 5.1%, respectively). In parallel, GS>6 data were numerically identical in all groups (but not in percentages, Table I) while GS 6 results again differ markedly in groups A and B versus C (2/3, 66.7%; 2/3, 66.6% and 5/6, 83.3%, respectively).

Overall, PC GS >6 was found in 44.5% of patients (4/9) within group A, as well as in 25% of patients (2/8) in group B and in 16.6% of patients (2/11) in group C (Table I).

A total of 7.2% PC patients were detected in group A, 6.4% in group B and 8.8% in group C, all based on 125 patients studied (Table I). The reduction in PC acquisition in group A versus group C was 37.5% and in group B versus C was 22.2%. Both differences are statistically significant (p<0.05).

Serum PSA data were out of consideration of this study and thus have not been tabulated in Table I. These results were in line with the clinical findings in cases of PC diagnosis. Elevated CgA recordings (normal range 0-80 ng/mL) were over 100 ng/mL. Respective mean value in groups A-C (± SD) was 139±27 ng/mL, 126±20 ng/mL and 111±5 ng/mL. Normal mean CgA level in all groups was 51±21ng/mL.

Discussion

Maximal effect of finasteride on prostate volume and prostate-specific antigen value is achieved within a period of 6 to 9 months (4) thus being in accord with clinical standards for BPH therapy (14, 15). Conjointly, the acquisition of NED during Mab (5), expressed as the significant elevation in CgA
concentration, was ratified after 9 months of study and respective data were fully documented after 15 months of the therapy taken for an overall period of 3 years (5). Since finasteride treatmet changes androgen environment within the prostate, although differently than Mab, it was decided to mimic the conditions required for finasteride efficiency in intermittendly treated subjects (4, 14, 15) and to hold them sufficiently long for the possible NED expression to take place during continuous therapy (5). Thus, both acquisition data of NED and PC together with the respective GSs in resulting PC patients were identically compared in group A patients as well as in group B BPH patients. Placebo-referred BPH patients served as controls (group C). Data from 125 patients in all groups during the 3-years study are presented in Table I.

Tabulated data (Table I) were discussed here in terms of the acquisition of both PC and CgA-elevation, the distribution of GS 6 and GS>6 in acquired PC throughout studied groups and the relationship of acquired PC in patients with elevated versus patients with normal CgA concentration in all three groups. Finally, the above data were compared with the PCPT results (11).

Intermittent therapy (group B) yielded an even lower cancer incidence (37%) compared to controls. This result might be potentially important and should be controled by a comprehensive and multicentric study. Overall incidence of PC GS>6 is highest in continuously treated patients (44.5%) and lowest in controls (18.2%) (<0.01) thus also resembling PCPT data (11) rather closely.

The acquired NED is markedly higher in group A (13.6%) than in groups B and C (5.6% and 6.4%, respectively) indicating continuous finasteride therapy as a possible if not a critical reason for an increase in NED compared to discontinuous treatment.

In patients with the raise in CgA concentration the percentage of acquired PC was smallest in group A (35.3%) and rather higher in groups B and C (71.4% and 63.5%, respectively). However, the PC GS> distribution among these patients was highest in group A (50%) and significantly lower in the two other groups (20% and 25%, respectively). Thus the capacity of NED provoked by a continuous finasteride therapy seems to be responsible for a decrease in PC prevalence and possibly, due to higher incidence in serum CgA elevation, for the promotion of aggressive PC.

To understand more closely the interrelationship between the two modes of therapy and untreated patients the acquired PC and the distribution of respective GS in patients with the retained normal CgA level should be analyzed.

### Table I. Study of the acquisition of PC, respective Gleason score distribution and serum Chromogranin A (CgA) elevation in BPH pts refered for 3 years to continuous finasteride therapy (A, 125 pts), intermittent finasteride therapy during 6 months followed by 6 months free of treatment (B, 125 pts) and the placebo-given controls (C, 125 pts).

<table>
<thead>
<tr>
<th>Groups</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>elevated CgA*</td>
<td>17/125, 13.6%</td>
<td>7/125, 5.6%</td>
<td>8/125, 6.4%</td>
</tr>
<tr>
<td>respective acquired PC</td>
<td>6/17, 35.3%</td>
<td>5/7, 71.4%</td>
<td>5/8, 62.5%</td>
</tr>
<tr>
<td>GS 6</td>
<td>3 pts, 50%</td>
<td>4 pts, 80%</td>
<td>4 pts, 80%</td>
</tr>
<tr>
<td>GS 7</td>
<td>1 pt, 16.7%</td>
<td>1 pt, 20%</td>
<td>1 pts, 20%</td>
</tr>
<tr>
<td>GS 8</td>
<td>2 pts, 33.3%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>respective total GS 6</td>
<td>50%</td>
<td>80%</td>
<td>75%</td>
</tr>
<tr>
<td>respective total GS&gt;6</td>
<td>50%</td>
<td>20%</td>
<td>25%</td>
</tr>
<tr>
<td>PC with normal CgA</td>
<td>3/108, 2.8%</td>
<td>3/118, 2.5%</td>
<td>6/117 pts, 5.1%</td>
</tr>
<tr>
<td>respective GS 6</td>
<td>2/3 pt, 66.7%</td>
<td>2/3 pts, 66.7%</td>
<td>5/6 pts, 83.3%</td>
</tr>
<tr>
<td>respective GS&gt;6</td>
<td>1/3 pt, 33.3%</td>
<td>1/3 pt, 33.3%</td>
<td>1/6 pts, 16.6%</td>
</tr>
<tr>
<td>overall GS 6</td>
<td>5/9, 55.5%</td>
<td>6/8, 75%</td>
<td>9/11, pts 81.8%</td>
</tr>
<tr>
<td>overall GS&gt;6</td>
<td>4/9, 44.5%</td>
<td>2/8, 25%</td>
<td>2/11, pts 18.2%</td>
</tr>
<tr>
<td>Overall PC,***</td>
<td>9/125, 7.2%</td>
<td>8/125, 6.4%</td>
<td>11/125, 8.8%</td>
</tr>
</tbody>
</table>

*Mean elevated CgA values in groups A-C were (±SD) 139±27 ng/mL, 126±20 ng/mL and 111±5 ng/mL and the retained value in all groups was 51±21 ng/mL. **PC group C/A ratio 11/9, 1.22 or 22% diminution of PC in group A versus C. ***PC group C/B ratio 11/8, 1.37 or 37% diminution of PC in group B versus C.
The PC incidence in patients with retained normal CgA level differs insignificantly in groups A and B (3/108, 2.8% and 3/118, 2.5%, respectively) but is much higher in controls (6/112, 5.1%). Identical number of PC GS>6 patients was acquired in all three studied groups (Table I). A slightly lower percent in respective controls came from a larger number of patients entered in this subgroup (Table I). Expectedly, free of NED capacity sporadic PC showed no preferences towards tumor aggressiveness expressed as GS >6. However, the reduced intracapsular DHT level in treated patients with normal CgA level remained the only determinant for downgrading PC incidence compared to the controls (Table I).

Overall, the acquired NED, detected as a raise in CgA, is responsible for the recorded higher GS in finasteride treated patients relative to the controls. In continuously treated patients NED is more advanced than it is in patients referred to a discontinuous treatment and thus in the former PC patients GS>6 are a more abundant category. This same phenomenon might also be responsible for the higher percent of PC GS>6 in PCPT study although it has not been recognized there. However, differences in PC prevalence between untreated and finasteride treated patients arise not from the acquired NED but might be a consequence of finasteride-induced reduction in DHT that downregulates PC promotion. Data in Table I seem to favor such a view since PC incidence in untreated controls with elevated CgA is 1.77-fold higher than in continuously treated subjects and slightly lower (0.87-fold) compared to respective patients referred to intermittent therapy. These results might be additional proofs in favor of discontinuous androgen deprivation in all hormone-therapy protocols including chemoprevention.

Parallel to the work on the link between positive margins after radical prostatectomy (RP) and the recorded NED data (16) other studies have found positive association of time to progression and NED positivity versus Gleason’s score, extracapsular extension, seminal vesicle invasion, surgical margin infiltration and tumor volume in prostate cancer patients following radical prostatectomy. All these data clearly indicate the effects of NED even in very early stages of the natural history of PC activating a dramatic increase in the biological potential of the disease (6, 17, 18). The large body of evidence implies NED not only as a paracrine stimulus for the propagation of local carcinoma cells and their possible dedifferentiation (6, 7) but in later stages represents a keystone of PC progression toward an androgen-independent state (7). There is also a great deal of evidence on neuropeptides conferring antiapoptotic capabilities on adenocarcinoma cells thus influencing their survival and further proliferation (17, 18). Consequently, NED makes inoperative a critical intracellular defence mechanism against a tumorigenic growth (18). All these events may contribute to the aggressive clinical course of PC having neuroendocrine elements (7, 17, 18).

Recently, an ascertainment bias has been proposed to account for an increase in high grade PC found at the end of PCPT finasteride treatment for chemoprevention. The higher sensitivity for PSA of higher GS disease should make more likely the detection of a high-grade disease respecting the true result of such cases (19). This assumption was statistically confirmed by logistic regression due to effects of finasteride on prostatic volume. However, reports neglecting the NED factor (11, 19) can hardly endure the challenge of data indicating NED-provided PC as highly resistant to apoptosis (20), the fact that breaks free an avenue for a PC hormonal refractoriness.

In addition, statistical analysis (19) can hardly explain differences in CgA data in conjunction with GS PC recordings during continuous and intermittent finasteride treatment (Table I) since both treatments put forth identical effects on both prostatic volume and PSA concentration. The NED data offer an ample correlation with high-grade GS recordings that are for real and not only statistical. Indeed, current chemoprevention protocols as well as those for BPH therapy need to be carefully reconsidered prior to choosing between continuous and intermittent finasteride treatment. Other authors express the same attitude (20).

In addition, already ongoing studies (21) examine both type 1 and 2 5alpha reductase inhibitors (finasteride and dutasteride) in several scenarios (general population studies, subjects with elevated PSA and a negative biopsy). It would be interesting to challenge the results of these studies on NED versus GS data.

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References