COMBINATION THERAPY OF ETHINYLESTRADIOL AND SOMATOSTATIN ANALOGUE REINTRODUCES OBJECTIVE CLINICAL RESPONSES AND DECREASES CHROMOGRANIN A IN PATIENTS WITH ANDROGEN ABLATION REFRACTORY PROSTATE CANCER

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ABSTRACT

Purpose: We evaluated whether a combination therapy of ethinylestradiol and somatostatin analogue can reintroduce objective clinical responses in patients with metastatic androgen ablation refractory prostate cancer (PC).

Materials and Methods: Ten patients with stage D3 disease and bone metastases who had progression despite initial responses to combined androgen blockade and in whom antiandrogen withdrawal subsequently failed discontinued combined androgen blockade and received 1 mg ethinylestradiol orally daily and 73.9 mg lanreotide acetate intramuscularly every 4 weeks. Serum prostate specific antigen (PSA), chromogranin A (CgA), Eastern Cooperative Oncology Group performance status and bone pain scores were assessed at regular intervals. Median followup was 18 months (range 10 to 24).

Results: Nine of the 10 cases (90%, 95% CI 55.5 to 99.8) had an objective clinical response, defined as a greater than 50% PSA decrease (median 87.1%, range 50.2% to 94.4%). PSA normalization (less than 4 ng/ml) was achieved in 3 cases. All patients reported significant and durable improvement in bone pain (median duration 17.5 months) and performance status (median duration 18 months) without major treatment related side effects. Two patients with disease progression died secondary to PC at 16 and 10 months, respectively. All other patients were without progression. We observed a statistically significant decrease in serum CgA during administration and at the response to therapy (median 38.4%, range 28.6% to 64.9%, (p <0.0001). Interestingly CgA was not increased at relapse.

Conclusions: This combination therapy seems to reintroduce an objective clinical response and symptomatic improvement in androgen ablation refractory PC cases.

KEY WORDS: prostate, prostatic neoplasms, estrogens, somatostatin, neoplasm metastasis

The progression to androgen ablation refractory stage D3 prostate cancer corresponds to cancer cell escape from androgen withdrawal induced apoptosis.1 Notably salvage chemotherapy cannot extend the median survival of approximately 10 months for patients with stage D3.2, 3 Treatment with estrogens has been used as effective palliation for patients with advanced prostatic cancer with a rate of retarding tumor growth in 70% to 80%.4, 5 In recent years increasing attention has been focused on neuroendocrine (NE) differentiation of prostate adenocarcinoma.6 Chromogranin A (CgA) appears to be the best marker of NE activity in the prostate gland.7 NE cell hyperactivation may be one of the mechanisms by which prostate cancer progresses during hormone therapy in an androgen independent tumor.8 Somatostatin analogues have also been used to treat patients with advanced hormone refractory prostate cancer9 with symptomatic positive responses. In particular Koutsilieris et al reported that the combination of a luteinizing hormone-releasing hormone (LH-RH) analogue with dexamethasone and a somatostatin analogue produced objective clinical responses in 11 stage D3 prostate cancer cases.10

In the current study we followed the study design of Koutsilieris et al.10 As in that series, we evaluated patients with metastatic androgen ablation refractory prostate cancer. However, unlike Koutsilieris et al, we discontinued LH-RH analogue and started combination therapy with ethinylestradiol and lanreotide acetate. The rationale for our combination therapy was to inhibit the protective (anti-apoptotic) effect of NE system on prostate adenocarcinoma cells (somatostatin analogue), use a new mechanism to induce castration (estrogen) and add a direct cytotoxic effect on prostate cells (estrogen). Therefore, in this longitudinal study we evaluated whether the combination of ethinylestradiol and lanreotide acetate would produce a new objective, symptomatic clinical response in patients with metastatic D3 prostate cancer.

PATIENTS AND METHODS

Patients and treatment. Between January 2002 and December 2002, 10 new cases of androgen ablation therapy refractory (stage D3) prostate adenocarcinoma were detected and followed at our department. We prospectively evaluated these 10 consecutive patients with stage D3 disease, who received combination therapy consisting of 1 mg ethinylestradiol orally daily and 73.9 mg lanreotide acetate intramuscularly every 4 weeks. All patients were treated on an outpatient basis following Declaration of Helsinki principles. None of these cases showed the concomitant presence of another advanced stage malignancy or life expectancy less than 3 months. No patients had a history of prostatectomy or radiotherapy and none were excluded from study based on renal or gastrointestinal function, or diabetes. No patients had a history of severe cardiovascular diseases, or other
disorders, therapy or conditions known to interfere with CgA. All patients had diffuse skeletal metastases (greater than 3 metastatic foci), as documented by radionuclide bone scan and computerized tomography. These patients had no evidence of measurable soft tissue metastases except in lymph nodes on computerized tomography. Table 1 lists patient baseline clinical characteristics.

All 10 patients had previously experienced objective clinical responses to combined androgen blockade (CAB) using triptorelin plus antiandrogen (flutamide or bicalutamide), as documented by a prostate specific antigen (PSA) decrease of more than 50% of baseline less than 24 months in duration. At progression all patients were withdrawn from antiandrogens for at least 6 weeks with no response (table 2). The criteria for progression after previous therapies included increasing PSA to more than 50% of the PSA nadir and a minimum PSA increase of 5 ng/ml monthly for 2 months in responders greater than 25% of baseline PSA in nonresponders, and/or detection of new metastatic foci on bone scan. Therefore, all patients discontinued CAB and received ethinylestradiol plus lanreotide combination therapy.

Followup. Patients were evaluated monthly with physical examination and measurements of serum testosterone using a Testo-CT2 (Schering-Plough Corp., Milan, Italy) radioimmunoassay (RIA) diagnostic kit, PSA by RIA (Hybritech, Inc., San Diego, California) complete blood count and liver function tests. Serum CgA was assessed by RIA (CiS Bio International, Cedex, France) at baseline, at a 3-month interval, at the response to therapy at the time of the PSA nadir and after relapse from combination therapy. The detection limit of this kit is 1.5 ng/ml. Inter assay and intra-assay coefficients of variation of the CgA assay are 5.8% and 3.8%, respectively.

Each blood sample was collected in the early morning after an overnight fast. Serum samples were immediately frozen and stored at −20°C until analysis.

Followup bone scans were performed every 6 months. Evaluation of symptomatic improvement and quality of life were performed according to the Eastern Cooperative Oncology Group (ECOG)-WHO performance status score,11 and bone pain and analgesic requirements.10 Any decrease in the ECOG or bone pain score more than 1 month in duration was considered a palliative response. As previously described,11 the criteria used to evaluate the response after at least 2 successive measurements were a complete response—PSA normalization (less than 4 ng/ml), a partial response—at least 50% PSA decrease from baseline and a stable response—less than 50% PSA decrease from baseline.

**RESULTS**

**Objective and symptomatic response.** Nine of the 10 cases (90%, 95% CI = 55.5% to 99.8%) had a complete or partial objective clinical response to combination therapy, corresponding to a statistically significant (vs baseline refractoriness) rate of reintroduction of responsiveness to the combination of lanreotide plus ethinylestradiol were compared in pairwise fashion with baseline values, ie each patient baseline status served as a control for the assessment of the response to therapy without the need for a separate control group or for randomization of patients into a treatment vs a control group. The Wilcoxon nonparametric rank test for paired samples was used to compare baseline ECOG and bone pain scores with their respective values during combination treatment. The rate of reintroduction of responsiveness to combination therapy was compared with the baseline refractoriness of patients to CAB and antiandrogen withdrawal using the McNemar paired chi-square test with the Yates correction. Nonparametric Friedman’s ANOVA for multiple relates samples and the Wilcoxon rank test for paired samples were used to assess potential changes in CgA. These statistical tests use nonparametric and their use is appropriate for analyses involving a small number of patients. Survival analysis was performed with the Kaplan-Meier method.

**Table 1. Patient characteristics at study entry**

<table>
<thead>
<tr>
<th>No. pts</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yrs) ± SD</td>
<td>73.60 ± 4.70 (74.0, 62-80)</td>
</tr>
<tr>
<td>(median, range)</td>
<td></td>
</tr>
<tr>
<td>No. stage D3</td>
<td>10</td>
</tr>
<tr>
<td>No. Gleason score:</td>
<td></td>
</tr>
<tr>
<td>7 (4 + 3)</td>
<td>3</td>
</tr>
<tr>
<td>8 (5 + 3)</td>
<td>6</td>
</tr>
<tr>
<td>9 (5 + 4)</td>
<td>1</td>
</tr>
<tr>
<td>Mean ng/ml PSA ± SD</td>
<td>64.5 ± 27.1 (57.3, 32.5-112.7)</td>
</tr>
<tr>
<td>(median, range)</td>
<td></td>
</tr>
<tr>
<td>Mean ng/ml CgA ± SD</td>
<td>134.0 ± 36.7 (127.5, 90.3-200.7)</td>
</tr>
<tr>
<td>(median, range)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Previous treatments**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No. Pts</th>
<th>Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH-RH analogue + flutamide</td>
<td>4</td>
<td>Pts 1, 2, 8, 9</td>
</tr>
<tr>
<td>LH-RH analogue + bicalutamide</td>
<td>6</td>
<td>Pts 3, 4, 5, 6, 7, 10</td>
</tr>
<tr>
<td>Antiandrogen withdrawal</td>
<td>10</td>
<td>None</td>
</tr>
</tbody>
</table>

**Table 3. Biochemical response to combination therapy**

<table>
<thead>
<tr>
<th>Pt No.—Age</th>
<th>Baseline (ng/ml)</th>
<th>Nadir (ng/ml)</th>
<th>Max % Decrease</th>
<th>Mss to Nadir</th>
<th>PSA Last Followup (ng/ml)</th>
<th>Relapse (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSA CgA</td>
<td>PSA CgA</td>
<td>PSA CgA</td>
<td>PSA CgA</td>
<td>PSA CgA</td>
<td>PSA CgA</td>
</tr>
<tr>
<td>1—72†</td>
<td>32.5 135.0</td>
<td>3.3 83.0</td>
<td>89.9 38.5</td>
<td>12 3</td>
<td>3.6</td>
<td>No No</td>
</tr>
<tr>
<td>2—73</td>
<td>57.3 115.0</td>
<td>7.4 81.3</td>
<td>87.1 29.3</td>
<td>10 3</td>
<td>8.5</td>
<td>No No</td>
</tr>
<tr>
<td>3—62</td>
<td>88.0 200.7</td>
<td>33.5 70.2</td>
<td>62.0 64.9</td>
<td>6 3</td>
<td>40.7</td>
<td>No No</td>
</tr>
<tr>
<td>4—80</td>
<td>32.6 130.7</td>
<td>9.0 86.6</td>
<td>72.4 38.4</td>
<td>3 3</td>
<td>12.5</td>
<td>No No</td>
</tr>
<tr>
<td>5—76</td>
<td>86.7 126.3</td>
<td>43.2 75.5</td>
<td>50.2 40.1</td>
<td>4 6</td>
<td>151.6</td>
<td>95.7 81.3</td>
</tr>
<tr>
<td>6—73†</td>
<td>112.7 195.5</td>
<td>77.5 78.3</td>
<td>31.3 60.0</td>
<td>4 3</td>
<td>190.4</td>
<td>132.5 85.2</td>
</tr>
<tr>
<td>7—75†</td>
<td>49.5 90.3</td>
<td>3.7 64.5</td>
<td>92.5 28.6</td>
<td>5 6</td>
<td>3.8</td>
<td>No No</td>
</tr>
<tr>
<td>8—77</td>
<td>84.6 129.6</td>
<td>10.2 78.3</td>
<td>88.0 35.1</td>
<td>6 3</td>
<td>7.2</td>
<td>No No</td>
</tr>
<tr>
<td>9—74</td>
<td>42.1 97.5</td>
<td>5.6 60.5</td>
<td>86.7 38.0</td>
<td>5 3</td>
<td>7.2</td>
<td>No No</td>
</tr>
<tr>
<td>10—74†</td>
<td>58.6 128.6</td>
<td>3.2 70.6</td>
<td>94.4 45.1</td>
<td>4 6</td>
<td>3.6</td>
<td>No No</td>
</tr>
</tbody>
</table>

† PSA normalization (less than 4.0 ng/ml) after combination therapy. 
‡ Less than 50% PSA decrease from baseline.
apy was 31.3% (table 3). No modification of bone scan results during the complete or partial response to therapy was noted. In all cases PSA responses were accompanied by a concomitant statistically significant decrease in the bone pain score as well as significant improvement in the ECOG performance status score (each \( p < 0.0001 \), tables 3 to 5, fig. 1). During combination therapy 5 patients (50%, 95% CI 12.3 to 87.7) experienced a lack of bone pain without analgesics for a median of 18 months (95% CI 16 to 22, range 18 to 24). Six of the 10 cases achieved normal performance status (ECOG 0) for a median of 17 months (95% CI 14 to 21, range 13 to 24).

**Progression-free survival and overall survival.** Patients 5 and 6 had progression after 12 and 7 months of followup, respectively (table 6). In these 2 cases, PSA at relapse was 95.7 and 132.5 ng/ml, respectively. These 2 men died of disease progression at 16 and 10 months of followup, respectively, as manifested by increasing PSA, new bone lesions on bone scan, deterioration in bone pain and performance status (tables 4 to 6). The remaining 8 patients were without disease progression at a median of 19.5 months (95% CI 17 to 21, range 16 to 24) during combination therapy.

**Serum CgA and side effect profile.** A comparison of serum CgA at baseline, during followup, at maximal response and at relapse from therapy revealed a significant change during the course of combination therapy (Friedman’s nonparametric ANOVA \( p < 0.0001 \)). We observed a significant decrease in serum CgA during the administration of combination therapy (median maximal decrease 38.4% of baseline, 95% CI 33.2 to 50.3, range 28.6% to 64.9%) compared with baseline (mean baseline 134.0 ± 36.7 ng/ml, median 127.4 vs at maximal response or PSA nadir 78.3 ± 7.6, median 76.9, Wilcoxon’s rank sum test \( p < 0.0001 \), fig. 2). Median time to CgA nadir was 3 months (95% CI 3 to 6, range 3 to 6, 95% CI 12 to 19).

Testosterone was suppressed (less than 1.5 nmol/l) at baseline and it remained less than 1.5 nmol/l throughout the study course (mean 0.66 ± 0.17 nmol/l, median 0.60, range 0.40 to 1.0). No major treatment related side effects were reported during combination therapy. In particular no serious cardiovascular, renal or liver-gastrointestinal events were noted during followup except transient mild epigastric discomfort, which was effectively controlled with an antacid regimen. None of our 10 patients discontinued treatment due to side effects related to combination therapy. All patients had gynecomastia and mild breast pain.

### Table 4. Bone pain response

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Baseline Pain</th>
<th>Best Pain</th>
<th>Mos to Best Pain</th>
<th>Mos Response</th>
<th>Mos Return to Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>24</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>18</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>14</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>16</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>10</td>
<td>After 10</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>After 6</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>18</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>17</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>18</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>19</td>
<td>No</td>
</tr>
</tbody>
</table>

Median time required to achieve the best bone pain score response was 3 months (range 2 to 4, 95% CI 2 to 3) and median duration of bone pain response was 17.5 months (range 6 to 24, 95% CI 12 to 19).

### Table 5. ECOG performance status improvement

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Baseline Score</th>
<th>Best Score</th>
<th>Mos to Best Score</th>
<th>Mos Response</th>
<th>Mos Return to Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>24</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>0</td>
<td>5</td>
<td>18</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>0</td>
<td>6</td>
<td>13</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>16</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>10</td>
<td>After 10</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>7</td>
<td>After 7</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>17</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>17</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>18</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>18</td>
<td>No</td>
</tr>
</tbody>
</table>

Median time to best ECOG was 3.5 months (range 3 to 6, 95% CI 3 to 5), median duration of ECOG improvement was 18 months (range 7 to 24, 95% CI 12 to 19) and median duration of normal performance status (0) was 17 months (range 13 to 24, 95% CI 14 to 21).

### Table 6. PFS and disease outcome

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>PFS (mos)</th>
<th>Mos Followup</th>
<th>Disease Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>24</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>20</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>16</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>18</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>16</td>
<td>Dead of Ca</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>10</td>
<td>Dead of Ca</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>20</td>
<td>Alive</td>
</tr>
<tr>
<td>8</td>
<td>17</td>
<td>17</td>
<td>Alive</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>20</td>
<td>Alive</td>
</tr>
<tr>
<td>10</td>
<td>19</td>
<td>19</td>
<td>Alive</td>
</tr>
</tbody>
</table>

Median PFS was 18.5 months (range 7 to 24, 95% CI 14 to 21).
tomy specimens from patients with untreated and CAB
eries et al, although baseline PSA was lower (mean 64.5
median 18 months, range 10 to 24). Baseline characteristics
of our population are also comparable with those of Koutsil-
tostatin analogue monotherapy for advanced prostate cancer.
A novel approach was preceded by previous estrogen or soma-
bination therapy with ethinylestradiol and lanreotide. This
fundamental premise is that estrogen therapy may be superior
to castration in terms of efficacy for advanced prostate cancer.
A second approach that estrogen therapy may be superior to
castration in terms of efficacy for advanced prostate cancer.4 A second approach
during androgen ablation therapy occurs principally because prostate
cancer cells can be rescued from androgen ablation in-
duced apoptosis. It has been shown that Bcl2 protein, which
is an anti-apoptotic factor, is preferentially expressed in the foci of prostate cancer cells in the vicinity of NE
differentiation.14 In hormone refractory (D3) prostate cancer
NE cells may protect prostate adenocarcinoma cells from
anticancer therapies through the neutralization of pro-
apoptotic intracellular pathways. Somatostatin analogues
have been used as antiproliferative agents in patients with
pure NE tumors.15 In a study of primary prostate cancer
reverse transcriptase-polymerase chain reaction analysis
showed somatostatin 1, 2 and 5 receptor mRNA in tumor
tissue specimens.16 It has been suggested that androgen
deprivation leads to up-regulation of estrogen re-
ceptor expression in prostate cancer tissue.17 It has been
supposed that the beneficial effect of estrogens is based not
only on a decreased androgen concentration, but also on a
simultaneous direct cytotoxic effect on prostate cancer
cells.18 These data support our rationale to discontinue
LH-RH analogue, substituting estrogen therapy. An impor-
tant question is whether responses achieved in our study
were most likely indirect evidence of a potential survival
benefit provided by combination therapy rather than a re-
ponse to lanreotide only or ethinylestradiol only.
For advanced hormone refractory prostate cancer, Logothetis
et al administered octreotide monotherapy for 6 weeks and
found new osseous metastases and increased alkaline phospha-
tase.9 They concluded that octreotide alone might stimulate
prostatic tumor growth but it may also sensitize tumor cells
to subsequent cytotoxic therapy. These data support the use
of somatostatin analogues for D3 prostate cancer as com-
bination therapy and not as monotherapy. On the other hand,
median progression-free survival in our study clearly sur-
passed the 10 months of survival historically described for
stage D3 cases even when estrogen therapy or salvage che-
motherapy is administered.3, 19
Combination therapy may neutralize the protective effect
of NE cells on prostate adenocarcinoma and continue to in-
duce apoptosis through castration and through a direct cyto-
xic effect of estrogens. In this way combination therapy
may provide an advantage compared with monotherapy.
However, additional studies are required to elucidate fully
the precise in vivo mechanism of action for the combination of
estrogens with somatostatin analogues.
We analyzed modifications in serum CgA during combina-
tion therapy. In our patients time to CgA nadir was lower than
time to PSA nadir. Therefore, it seems that the CgA
response preceded the PSA response. Baseline CgA was sim-
ilar to that reported in another experience with metastatic
prostate cancer.20 The significant decrease in circulating CgA
documented in this cohort of patients suggests that de-
creased NE activity in prostate cancer cells may be a mech-
anism accounting for at least part of the encouraging re-
sponses observed. Interestingly patient serum CgA was not
significantly increased at relapse, suggesting that NE activity
may not be involved at relapse from this combination
therapy. The modifications in CgA reported in our study were
lower compared with those observed in pathologically con-
firmed NE tumors, such as small cell carcinoma of the lung.
However, NE differentiation of prostate adenocarcinoma con-
stitutes of NE cells with a focal distribution in the common
prostatic adenocarcinoma.3, 19
DISCUSSION
To our knowledge this study represents the first experience
in the literature to address whether the combination of ethi-
nylestradiol and lanreotide can offer objective responses
and/or symptomatic improvements in patients with stage D3
prostate cancer. As in the study of Koutsilieris et al,10 the
design of this pilot trial involved a longitudinal methodology,
as defined by Spilker,12 which is appropriate to study even
small cohorts of patients. The number of cases enrolled in our
longitudinal analysis is similar to that in the series of
Koutsilieris et al10 (11) but longer followup was available
(27.1 vs 170.3 months). In our population the duration of
treatment is considered an advantage because the design of
this pilot trial involved a longitudinal methodology,
as defined by Spilker,12 which is appropriate to study even
small cohorts of patients. The number of cases enrolled in our
longitudinal analysis is similar to that in the series of
Koutsilieris et al10 (11) but longer followup was available
(27.1 vs 170.3 months).

We propose a different therapeutic approach. Our pa-
patients discontinued LH-RH analogue and started a new com-
bination therapy with ethinylestradiol and lanreotide. This
novel approach was preceded by previous estrogen or soma-
tostatin analogue monotherapy for advanced prostate cancer.
Some studies have shown that the number of NE tumor
cells12 and serum CgA increase during hormonal therapy6, 13
for prostate cancer. At the cellular level refractoriness to
androgen ablation therapy occurs principally because pros-
tate cancer cells can be rescued from androgen ablation in-
duced apoptosis. It has been shown that Bcl2 protein, which
is an anti-apoptotic factor, is preferentially expressed in the foci of prostate cancer cells in the vicinity of NE
differentiation.14 In hormone refractory (D3) prostate cancer
NE cells may protect prostate adenocarcinoma cells from
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reverse transcriptase-polymerase chain reaction analysis
showed somatostatin 1, 2 and 5 receptor mRNA in tumor
tissue specimens.16 It has been suggested that androgen
deprivation leads to up-regulation of estrogen re-
ceptor expression in prostate cancer tissue.17 It has been
supposed that the beneficial effect of estrogens is based not
only on a decreased androgen concentration, but also on a
simultaneous direct cytotoxic effect on prostate cancer
cells.18 These data support our rationale to discontinue
LH-RH analogue, substituting estrogen therapy. An impor-
tant question is whether responses achieved in our study
were most likely indirect evidence of a potential survival
benefit provided by combination therapy rather than a re-
ponse to lanreotide only or ethinylestradiol only.
For advanced hormone refractory prostate cancer, Logothetis
et al administered octreotide monotherapy for 6 weeks and
found new osseous metastases and increased acid phospha-
tase.9 They concluded that octreotide alone might stimulate
prostatic tumor growth but it may also sensitize tumor cells
to subsequent cytotoxic therapy. These data support the use
of somatostatin analogues for D3 prostate cancer as com-
bination therapy and not as monotherapy. On the other hand,
median progression-free survival in our study clearly sur-
passed the 10 months of survival historically described for
stage D3 cases even when estrogen therapy or salvage che-
motherapy is administered.3, 19
Combination therapy may neutralize the protective effect
of NE cells on prostate adenocarcinoma and continue to in-
duce apoptosis through castration and through a direct cyto-
xic effect of estrogens. In this way combination therapy
may provide an advantage compared with monotherapy.
However, additional studies are required to elucidate fully
the precise in vivo mechanism of action for the combination of
estrogens with somatostatin analogues.
We analyzed modifications in serum CgA during combina-
tion therapy. In our patients time to CgA nadir was lower than
time to PSA nadir. Therefore, it seems that the CgA
response preceded the PSA response. Baseline CgA was sim-
ilar to that reported in another experience with metastatic
prostate cancer.20 The significant decrease in circulating CgA
documented in this cohort of patients suggests that de-
creased NE activity in prostate cancer cells may be a mech-
anism accounting for at least part of the encouraging re-
sponses observed. Interestingly patient serum CgA was not
significantly increased at relapse, suggesting that NE activity
may not be involved at relapse from this combination
therapy. The modifications in CgA reported in our study were
lower compared with those observed in pathologically con-
firmed NE tumors, such as small cell carcinoma of the lung.
However, NE differentiation of prostate adenocarcinoma con-
stitutes of NE cells with a focal distribution in the common
prostatic adenocarcinoma.3, 19

FIG. 2. Mean serum CgA and PSA at baseline, at response and at relapse from combination therapy. Combination treatment was
associated with significant decrease in mean CgA (p < 0.0001). In contrast, relapse from combination therapy in patients 5 and 6 was
not associated with increased CgA compared with during response to therapy (p = 0.1728).
A limitation of our analysis was the determination of only serum CgA. However, none of our patients presented with history of other disorders known to interfere with CgA. Some groups have reported a significant correlation between CgA serum and tissue expression in prostate cancer.5, 8

In our cases the symptomatic improvement in pain and performance status appeared to be temporally associated with changes in objective response markers. It has been suggested that the main mechanism of action of this combination therapy affects mechanisms regulating the growth and/or survival of metastatic cells rather than a nonspecific anti-inflammatory or analgesic effect.10 The rate of and time to achieve the symptomatic and objective responses that we describe are comparable to those reported of Koutsilieris et al. However, with our combination therapy we achieved a longer duration of objective responses. In particular, the median duration of bone pain response, ECOG response and progression-free survival (PFS) was 17.5 (95% CI 12 to 19), 18 (95% CI 12 to 19) and 18.5 (95% CI 14 to 21) months in our study and 13 (95% CI 12 to 14), 19 (95% CI 13 to 25) and 7 (95% CI 3 to 10) months, respectively, in the study of Koutsilieris et al.

We also emphasize that no major treatment related side effects were reported during our combination therapy. It is true that none of our patients had a history of severe cardiovascular diseases at baseline but 1 mg dose of ethinylestradiol and the duration of followup of no longer than 24 months may also have contributed to differences compared with other experiences with estrogren therapy.5, 19 Transient mild gastrointestinal side effects reported in our experience were probably related to lanreotide administration, as reported in a previous trials.10

CONCLUSIONS

It should be emphasized that any conclusion regarding the usefulness of this combination therapy compared with other proposed treatment strategies for stage D3 prostate cancer can only be made in randomized, controlled clinical trials. The results of our study indicate that such trials are warranted because the combination of ethinylestradiol and lanreotide had a favorable toxicity profile and provided objective and symptomatic responses in patients with limited treatment options who were refractory to conventional hormone therapy strategies. This combination therapy may also represent a novel concept in cancer treatment, in which therapies may target not only cancer cell, but also its microenvironment in combination, which can confer protection from apoptosis.10

REFERENCES


