Combination of Somatostatin Analog, Dexamethasone, and Standard Androgen Ablation Therapy in Stage D3 Prostate Cancer Patients with Bone Metastases

Michael Koutsilieris,[1] Constantine S. Mitsiades,[1,2] John Bogdanos,[1,3] Theodoros Dimopoulos,[4] Dimitrios Karamanolakis,[1,3] Constantine Milathianakis,[1,3] and Athanassios Tsintavis[3]

[1]Department of Experimental Physiology, Medical School, University of Athens, Goudi-Athens, Greece; [2]Department of Medical Oncology, Dana-Farber Cancer Institute and Department of Medicine, Harvard Medical School, Boston Massachusetts; [3]Urology Clinic, "METAXA" Anticancer Hospital, Piraeus, Greece; and [4]Urology Clinic, "PANAGIA" General Hospital, Thessaloniki, Greece

ABSTRACT

Purpose: **Androgen ablation-refractory prostate cancer patients (stage D3) develop painful bone metastases and limited responsiveness to conventional therapies, hence the lack of universally accepted "gold standard" treatment for this poor prognosis clinical setting. We tested the safety and efficacy in stage D3 patients of the combination hormonal therapy, which combines administration of somatostatin analog and dexamethasone with standard androgen ablation monotherapy (luteinizing-hormone releasing-hormone analog or orchiectomy).**

Experimental Design: **Thirty eight patients with stage D3 prostate cancer (mean age 71.8 ± 5.9 years) continued receiving androgen ablation therapy in combination with oral dexamethasone (4 mg daily for the 1st month of treatment, tapered down to 1 mg daily by the 4th month, with 1 mg daily maintenance dose thereafter) and somatostatin analog (20 mg octreotide i.m. injections every 28 days).**

Results: **Twenty-three of 38 patients (60.5%) receiving this combination regimen had partial responses [PR, ≥50% prostate-specific antigen (PSA) decline], 9 (21.1%) had stable disease, and 7 (18.4%) had progressive disease. In 47.7% (18 of 38) of patients, their serum PSA levels decreased with treatment but did not return to their respective baselines until the end of follow-up (or death from non-prostate cancer-related causes). The median time-to-return to baseline PSA was 12 months (95% CI, 7–17 months), median progression-free survival was 7 months (95% CI, 4.5–9.5 months), median overall survival was 14 months (95% CI, 10.7–17.4 months), and median prostate cancer-specific overall survival (defined as time from onset of combination therapy until prostate cancer-related death) was 16.0 months (95% CI, 11.9–20.1 months). All patients reported significant and durable improvement of bone pain and performance status (for a median duration of 14 months; 95% CI, 9–19 months), without major treatment-related side effects. We observed a statistically significant ($P < 0.01$) reduction in serum insulin-like growth factor-1 levels at response to the combination therapy. T levels remained suppressed within castration levels at baseline and throughout therapy, including relapse.**

Conclusion: **The combination therapy of dexamethasone plus somatostatin analog and standard androgen ablation manipulation produces objective clinical responses and symptomatic improvement in androgen ablation-refractory refractory prostate cancer patients.**

INTRODUCTION

Androgen ablation therapy almost always produces objective clinical responses in prostate cancer (PrCa) patients with newly diagnosed metastatic disease. However, PrCa eventually progresses to the stage of refractoriness to androgen ablation therapy (stage D3), which is characterized by a median overall survival of <12 months, even with the administration of wide range of cytotoxic chemotherapy regimens (1). Disease progression to stage D3 frequently occurs only in the bony metastases, although androgen ablation therapy still provides adequate and sustained control of disease at the primary site (2–6). These clinical phenomena are attributed mainly to the fact that soluble growth factors and cytokines (collectively termed "survival factors"), which are released by normal cellular constituents of the bone microenvironment and protect PrCa cells metastasizing to the bones against androgen ablation, as well as other antitumor therapies, such as cytotoxic chemotherapy (7, 8).

A major mediator of metastatic PrCa cell rescue against anticancer drug-induced apoptosis is insulin-like growth factor-1 (IGF-1), which has increased local bioavailability in the microenvironment of bone metastases. For example, metastatic PrCa cells release urokinase-type plasminogen activator, which hydrolyzes IGF-binding protein-3, thereby causing increased local release of free, bioavailable, IGF-1 (7). In an effort to neutralize the protective effect conferred on cancer cells by IGF-1 (or other "survival factors" for cancer cells), we have recently developed a therapeutic concept that aims at suppressing the bioavailability of survival factors, such as IGF-1 and/or the activity of its downstream biological effectors. This specific approach was applied recently in the setting of stage D3 metastatic PrCa and involved administration of somatostatin analog

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Requests for reprints: Michael Koutsilieris, Department of Experimental Physiology, Medical School, University of Athens, 75 Micras Asias, Goudi-Athens 115 27, Greece. Phone: 30210-7462597; Fax: 30210-8145871; E-mail: mkoutsemedscape.com or constantine_mitsiades@dfci.harvard.edu.

(SM-A) [which reduces the growth hormone-dependent IGF-1 production, mainly in liver; Ref. 9] and oral dexamethasone [which suppresses the growth hormone-independent increase of local IGF-1 bioavailability in the microenvironment of PrCa bone metastases; Refs. 10 and 11], in combination with luteinizing hormone-releasing hormone analogs (LHRH-A), providing encouraging preliminary results in case series of stage D3 PrCa patients (12, 13).

Herein we report the results of a Phase II clinical trial of this combination therapy in a new cohort of 38 patients with stage D_3 PrCa. In this trial, combination therapy of SM-A plus dexamethasone and standard androgen ablation therapy produced objective clinical responses (disease stabilization or partial responses) in >80% of these patients [including 60% of patients with >50% prostate-specific antigen (PSA) decrease], with median progression-free survival of 7 months and median overall survival of 14 months. These objective clinical responses were accompanied by a favorable profile of well-manageable side effects, including only mild increases of serum glucose and mild proximal muscle weakness, mostly related to oral dexamethasone administration. These favorable data suggest that this combination therapy merits further testing in randomized controlled clinical trials in comparison with salvage chemotherapy or other second-line hormonal therapies in patients with stage D3 PrCa.

MATERIALS AND METHODS

Patients, Materials, and Methods. Thirty-eight patients with androgen ablation refractory (stage D_3) metastatic PrCa were prospectively evaluated for enrollment in our Phase II clinical trial after providing informed consent to receive the combination therapy. All patients had diffuse bony lesions (>6 foci in bone scan) at the time of original diagnosis of metastatic disease (stage D_2) and had subsequently received androgen ablation therapy, which consisted of either chronic administration of LHRH-A monotherapy or combined androgen blockade (LHRH-A or orchiectomy plus antiandrogen, as follows: 250 mg of flutamide thrice daily or 50 mg of bicalutamide daily). After progression to stage D_3, all patents who were receiving combined androgen blockade therapy underwent antiandrogen withdrawal manipulation, while remaining on basic androgen ablation therapy with LHRH-A. At study entry, and for at least 3 months before onset of antisurvival factor therapy, all patients had steadily increasing PSA values (confirmed by monthly repeat PSA measurements showing >10 ng/ml net increase between successive monthly values) and progressive deterioration of performance status. All patients enrolled in this trial had diffuse bony lesions (>6 foci in bone scan) at the time of study entry.

The combination therapy consisted of (*a*) continuation of the form of androgen ablation therapy that each patient was receiving before enrollment in this trial; (*b*) oral dexamethasone (4 mg daily during the 1st month of treatment, tapered down to 3, 2, and 1 mg daily during the 2nd, 3rd, and 4th month of treatment, respectively, with 1 mg daily maintenance dose thereafter for the entire follow-up period); and (*c*) chronic administration of the SM-A octreotide 20 mg, i.m, every 28 days (Novartis Hellas S.A.). All patients were followed up on an outpatient basis, according to the principles of the Declaration of Helsinki (14) and a protocol reviewed and approved by the local ethics committee for human subjects in research. Concomitant presence of another malignancy and life expectancy <3 months were criteria for exclusion. No patients were excluded from this study on the basis of cardiopulmonary, renal, gastrointestinal dysfunction or diabetes. No patients had evidence of measurable soft tissue metastases (except for lymph nodes), as assessed by computerized tomography scan. All patients were followed-up (clinical and biochemical work-up) at monthly intervals. The bone scans were performed at study entry and every 6–12 months thereafter.

Clinical responses to therapy was defined, according to criteria published previously (13), as either (*a*) progressive disease (PD; progressive increase of PSA by ≥25% from baseline, for at least two consecutive measurements, and/or steady deterioration of pain score and performance status), (*b*) partial response (PR; PSA decline by ≥50% over baseline value, for at least two consecutive assessments, accompanied by significant improvement in pain score and performance status), or (*c*) stable disease (SD; PSA decline by <50% from baseline value, for at least 2 consecutive measurements, and accompanied by significant improvement in pain score and performance status score). The time to best clinical response was defined as the time between onset of therapy and documentation of best clinical response (nadir PSA, lowest pain score values and best performance status). Time to disease progression was defined as the time between onset of combination therapy and steady rise of PSA levels by ≥50% over their nadir values or detection of new metastatic lesions by bone scan and computerized tomography scan and/or documentation of steady deterioration in pain score and performance status score. In the absence of deterioration in clinical symptoms (pain score and performance status), a net increase (in two consecutive measurements) of PSA value by >10 ng/ml over the nadir PSA value was required to document disease progression. Overall survival was calculated as the time between onset of therapy and death or end of follow-up. Prostate cancer-specific overall survival was defined as time from onset of combination therapy until prostate cancer-related death (with patient censoring at end of follow-up or non-prostate cancer-related death). For patients with decreases of PSA levels during combination therapy, time-to-return to baseline PSA was defined as the time between onset of therapy until the return of serum PSA levels to values equal or higher to the respective baseline PSA level.

Evaluation of symptomatic improvement and quality of life was performed with the Eastern Cooperative Oncology Group-WHO performance status score (15) and a bone pain score, which provides, on 6-point scale (from 0 to 5), a composite expression of pain intensity and analgesic requirements (type and quantity of analgesics consumed: *i.e.*, 0 = lack of bone pain without analgesics; 1 = occasional mild pain, not necessitating use of analgesics; 2 = constant moderate pain necessitating use of non-opiate analgesics; 3 = constant pain (severe), necessitating constant consumption of common analgesics; 4 = severe constant pain, requiring use of opiate analgesics; and 5 = severe pain refractory even to opiate analgesics). Reduction of the Eastern Cooperative Oncology Group or bone pain score lasting for >1 month was considered a palliative response.

Tumor markers, indices of bone and mineral metabolism and hormonal serum measurements were performed at monthly intervals using commercially available standard kits for PSA (IMX kit; Abbott Lab), alkaline phosphatase (AP), testosterone (T; Testo-CT2 RIA kit, Schering-Plough Corp. SpA, Milan, Italy), dehydroepiandrosterone sulfate (DHEA-S; Immunotech RIA kit, Miami, FL), IGF-1 (ELISA kit; R&D Systems Europe, Abingdon, United Kingdom), and tartrate-resistant acid phosphatase type 5b (BONE TRAP; ELISA kit; SBA, Oulu, Finland). Tartrate-resistant acid phosphatase type 5b (TRACP-5b), which is derived from osteoclasts, is a novel sensitive marker of bone resorption (analytical sensitivity of 0.06 units/liter with intra-assay variation $<6\%$ and inter-assay variation of $<8\%$), having greater clinical sensitivity than other indices of bone resorption, such as collagen N-telopeptides, collagen C-telopeptides, and bone sialoprotein in patients with breast cancer and overt bone metastases (16).

In view of the effects of SM-A on pancreatic function (17) and of dexamethasone on blood glucose (12, 13), all patients received instructions to appropriately modify their diet in regard to intake of lipids (especially the day before and at the day of SM-A injections, to minimize gastrointestinal discomfort) and carbohydrates. Blood glucose levels were monitored bi-weekly during the first 3 months of therapy and monthly thereafter. For six patients with known prior medical history of diabetes, the dosage of their oral antidiabetic drug was increased, especially during the initial period of combination therapy, when dexamethasone was administered at daily doses of 4, 3, and 2 mg during the 1st, 2nd, and 3rd months of follow-up, respectively. Antacid therapy was preventively offered in seven patients with a known past medical history of chronic gastritis/peptic ulcer or gastroesophageal reflux disease.

Bone-scintigraphy with ^{99m} Technetium (^{99m} Tc) was performed in all patients at study entry and every 6–12 months thereafter. In addition, octreotide-scintigraphy (octreoscan), depicting mainly the expression of somatostatin receptor-2 (SSTR-2; Ref. 18) at a dosage of 185 MBq (5 mCi) using whole body scans 6–8 h after injection, was performed at study entry in a subgroup of 22 patients. This enabled us to analyze (*a*) whether octreoscan findings were consistent with ^{99m} Tc scintigraphy results for skeletal metastases, and (*b*) whether detection of SSTR-2 by octreoscan correlated with clinical responses to combination therapy, in a manner suggestive of a possible direct action of SM-A on metastatic cancer cells via SSTR-2.

To detect differences in biochemical measurements, bone pain and performance status scores among subgroups of patients enrolled in our trial, we performed one-way ANOVA (with Friedman's test and Dunnett's C post hoc tests, where appropriate). Survival analyses for calculation of median progression-free and overall survival, as well as time to return to baseline bone pain, were performed with the Kaplan-Meier method, and the log-rank test was used to detect differences in survival distributions between subgroups of patients. Log-rank tests were used to test the homogeneity of survival functions across strata defined by baseline clinical/biochemical parameters, *e.g.*, PSA, AP, testosterone levels, and so forth. All statistical analyses were performed with the SPSS 11.1 statistical package.

RESULTS

Characteristics of Patients at Study Entry. The clinical characteristics of the 38 androgen ablation refractory patients who received the combination regimen are given in Table 1. Seventeen patients (44.7%) had also previously received salvage chemotherapy, and five other patients had previously received radionuclide therapy with strontium-89 ($n = 3$ patients) or ^{186}rhenium-hydroxethylidene diphosphonate (^{186}Rh-HEDP) ($n = 2$ patients; Table 1).

Objective Clinical Response to Combination Therapy. Analysis of objective clinical response revealed that 23 of 38 patients (60.5%) had PR, 9 patients (21.1%) had SD, and 7 patients (18.4%) had PD.

Time to Best Clinical Response. The median time between onset of treatment and documentation of time to best clinical response in patients with PR or SD (31 patients) was 3 months (range 2–6 months, 95% confidence intervals (95% CI) 2.41–3.59 months). Kaplan-Meier analyses showed no significant difference in time to best clinical response between patients with PR *versus* SD, *i.e.* 3 months (95% CI, 2.07–3.93) *versus* 3 months (95% CI, 2.40–3.60 months), respectively ($P = 0.5642$, log-rank test). These data therefore indicate that the combination therapy produces its best clinical responses within a median time of 3 months. Notably, during the initial phase of response to combination therapy (1–3 months), three patients had significant improvements in pain and performance status scores, which were accompanied by increase of PSA values (albeit $<15\%$ from baseline values). This initial contrast between decreasing pain and improving performance status scores *versus* rising PSA values was subsequently followed by further improvement in the pain and performance status scores and by significant decline of PSA values ($>50\%$) after the 3rd month of treatment.

Progression-Free Survival and Overall Survival. The median progression-free survival of patients in this trial was 7 months (95% CI, 4.5–9.5 months; Fig. 1*A*). The median pro-

Table 1 Clinical characteristics of patients at study entry ($N = 38$)

Age (years)	71.8 ± 5.92 (mean ± SD) (median: 71, range 63–89)
Prior hormonal therapies	
LHRH-A [a] monotherapy	5 patients (13.2%)
CAB (LHRH-A/orchiectomy plus antiandrogen)	33 patients (86.8%)
Antiandrogens	
Flutamide	20 patients (52.6%)
bicalutamide	13 patients (34.2%)
Antiandrogen withdrawal	5 patients with PSA decline for 3 months
Prior chemotherapy	
Estramustine phosphate plus etoposide	10 patients (26.3%)
Mitoxandrone plus prednisone	7 patients (18.4%)
Prior radiation therapy	
Strontium	3 patients (7.9%)
Rhenium	2 patients (5.3%)
Pain score (0–5 scale)	Median = 4 (min = 1; max = 5)

[a] LHRH-A, luteinizing-hormone releasing-hormone analog; CAB, combined androgen blockade.

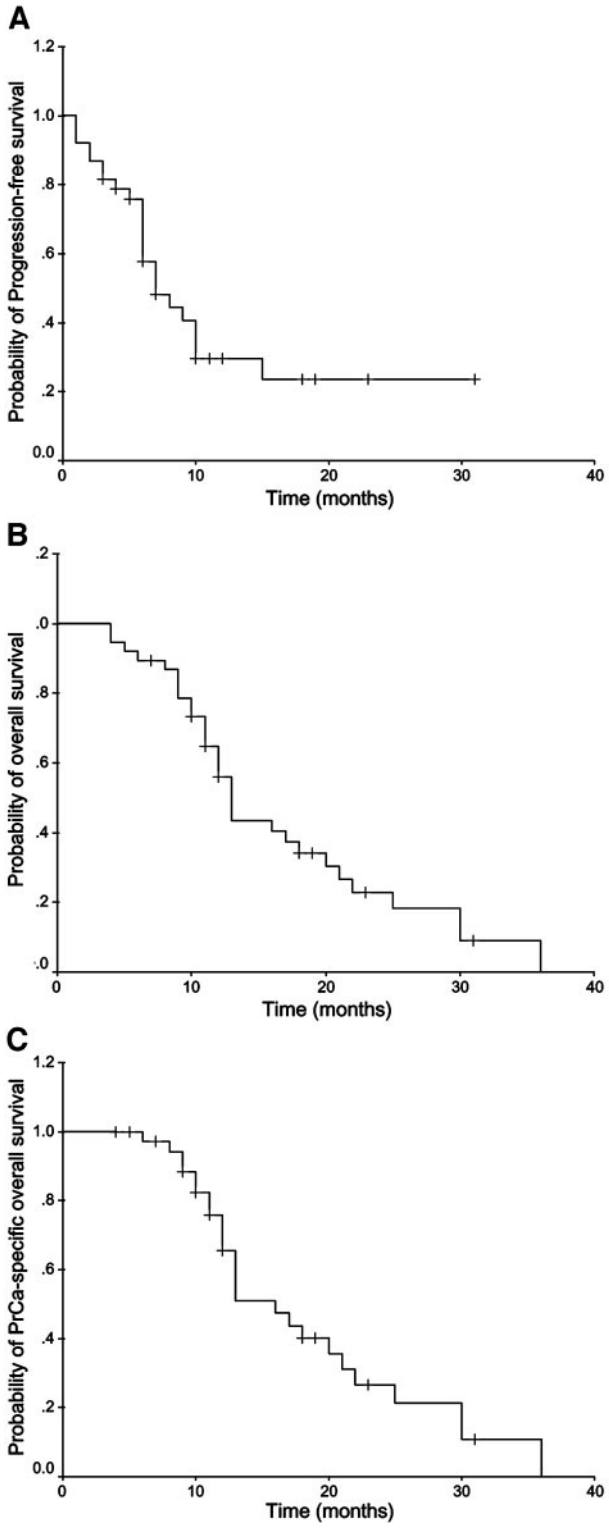

Fig. 1 Survival curves (plotted with the Kaplan-Meier method) of prostate cancer (PrCa) patients receiving our combination regimen for treatment of androgen ablation-refractory (stage D_3) disease. *A,* progression-free survival (median of 7 months, 95% CI, 4.5–9.5 months). *B,* overall survival (median of 14 months, 95% CI, 10.7–17.4 months). *C,* PrCa-specific overall survival (median of 16 months, 95% CI, 11.9–20.1 months).

gression-free survival among patients who had PR, SD, or PD was 10 months (95% CI, 7.6–12.4), 7 months (95% CI, 5.7–8.3), and 2 months (95% CI, 0.8–3.2), respectively (log-rank tests, $P < 0.0001$ for comparison of patients with PR *versus* PD, $P = 0.0002$ for comparison of patients with SD *versus* PD and $P = 0.2277$ for comparison of PR *versus* SD). Furthermore, it is notable that in 47.7% (18 of 38) of patients, serum PSA levels decreased during combination therapy but did not return to their respective baselines until the end of follow-up (or death from prostate cancer-related or non-prostate cancer-related causes). In fact, the median time-to-return to baseline PSA values for all treated patients was 12 months (95% CI, 7–17 months), whereas the median times-to-return to baseline PSA for patients with PR and SD were 7 and 15 months, respectively.

The median overall survival of patients in this trial was 14 months (95% CI, 10.7–17.4 months; Fig. 1*B*). During the follow-up period, 5 patients died from causes unrelated to prostate cancer or the combination regimen, while they were experiencing objective clinical responses to therapy. Therefore, the median prostate cancer-specific overall survival (defined as time from onset of combination therapy until prostate cancer-related death, with patient censoring at end of follow-up or non-prostate cancer-related death) was 16 months (95% CI, 11.9–20.1 months; Fig. 1*C*). To obtain insight into potential clinical/biochemical parameters that might influence the response of prostate cancer patients to this regimen, log-rank tests were used to test the homogeneity of survival functions across strata defined by baseline clinical/biochemical parameters, including age, serum PSA, AP, IGF-1, testosterone, DHEA-S, bone pain score (dichotomized as $<$ or $>$ that of the median baseline value of the respective parameter), prior treatment with cytotoxic chemotherapy, or prior radiation therapy. However, in univariate analyses, none of these parameters had a statistically significant association with progression-free survival ($P > 0.05$ for all comparisons).

Octreoscan, ^{99m} T Bone Scintigraphy and Type of Clinical Response. Twenty two of 38 stage D3 patients underwent octreotide-scintigraphy at study entry, in an effort to analyze (*a*) whether somatostatin receptor expression in bone lesions (mainly SSTR-2) correlated with findings of ^{99m} Tc-scintigraphy in the skeleton of these patients and (*b*) whether positive octreoscan analysis correlated with objective clinical responses to this therapy. Only 4 of 22 patients had positive octreotide-scintigraphy results that were consistent with sites of increased uptake detected by ^{99m} Tc bone scintigraphy. Moreover, only one of these patients had objective clinical response to this therapy. In marked contrast, 15 of 18 patients with negative octreotide-scintigraphy had objective clinical responses to this regimen. These data suggest that expression of SSTR-2 in bony lesions, as detected by octreotide-scintigraphy, correlates with neither ^{99m} Tc bone scan analysis nor clinical response to this combination therapy, which implies that the clinical responses of the somatostatin analog-containing regimen cannot be attributed to direct the effect of the SM-A on SSTRs on metastatic tumor cells.

Pain Score Changes During Therapy. Comparisons of bone pain scores at baseline, at the time of PSA nadir and at progression showed significant differences in bone pain scores across these time-points ($P < 0.001$, non-parametric Friedman

test), with lower bone pain scores at the time of PSA nadir than baseline ($P < 0.01$, Dunnett's C test). Interestingly, even patients who did not respond to this regimen had improved bone pain scores at the time of disease progression *versus* baseline ($P = 0.03$, Dunnett's C test). Importantly, the bone pain scores of treated patients never returned to their respective baselines in 21 of 38 (55.3%) or never became worse than their baseline values in 23 of 38 (60.5%) of patients. In further support of the durability of these palliative responses, the median time-to-return to baseline bone pain score and the median time-to-bone pain score more severe than at baseline were 14 months (95% CI, 9–19 months) and 17 months (95% CI, 14–20 months), respectively. Among patients with PR, SD, or PD, the median time-to-return baseline bone pain scores were 16 months (95% CI, 15–17 months), 9 months (95% CI, 6–12 months), and 8 months (95% CI, 4–12 months), respectively (log-rank tests, $P < 0.0001$ for comparison of patients with PR *versus* PD, $P = 0.0016$ for comparison of patients of patients with PR *versus* SD, and $P = 0.0960$ for comparison of SD *versus* PD).

Performance Status. The performance status scores of patients showed significant differences during combination therapy ($P < 0.001$, non-parametric Friedman test), with improved performance status at the time of PSA nadir than baseline ($P < 0.01$, Dunnett's C test). Interestingly, improvements in performance status of patients were observed even in cases of patients for whom this therapy failed to produce major objective clinical responses.

Correlation of Baseline Biochemical Measurements with Type of Clinical Response. Table 2 summarizes the results of a series of tumor marker and hormonal measurements (PSA, AP, IGF-1, testosterone, DHEA-S, and TRACP-5b) at study entry. Consistent with the prolonged administration of androgen ablation therapy in those stage D_3 patients, T and DHEA-S values were decreased to castration levels at study entry. There were no statistically significant differences among patients with PR *versus* SD *versus* PD, in terms of age, baseline PSA, or AP levels ($P = 0.378$, $P = 0.078$, and $P = 0.758$, respectively, non-parametric Kruskal-Wallis test). Furthermore, there were no statistically significant differences between those groups of patients, in terms of age and pain score or other baseline biochemical or hormonal parameters (one-way ANOVA; P values for IGF-1 = 0.557; T = 0.097; DHEA-S = 0.270; pain score = 0.076; performance status score = 0.27; and TRACP-5b = 0.10), suggesting that these baseline parameters cannot serve to predict the type of objective clinical response of these stage D3 patients to this therapy.

Table 2 Baseline biochemical parameters

	Mean	SD [a]	Median	Range
PSA (ng/ml)	331.7	649.1	117.5	15–2888
AP (units/liter)	560.5	532.2	377	122–2600
IGF-1 (ng/ml)	182.2	44.7	188	122–280
Testosterone (ng/ml)	0.28	0.10	0.28	0.1–0.5
DHEA-S (μg/ml)	0.41	0.13	0.4	0.2–07
TRACP-5b	14.14	10.65	9.6	4.5–33.6

[a] SD, stable disease; PSA, prostate-specific antigen; AP, alkaline phosphatase; IGF-1, ; DHEA-S, dehydroepiandrosterone sulfate; TRACP-5b, tartrate-resistant acid phosphatase type 5b.

Changes of Biochemical Parameters during Combination Therapy. Comparisons of AP, IGF-1, T, DHEA-S, and TRACP-5b values are baseline, at the time of PSA nadir and disease progression (or end of follow-up) showed significant differences throughout the course of treatment with the combination regimen (non-parametric related samples Friedman test, as follows: $P < 0.001$ for AP, $P < 0.002$ for IGF-1, $P < 0.001$ for T, $P = 0.001$ for DHEA-S; Fig. 2). In particular, AP, IGF-1, T, DHEA-S, and TRACP-5b values were decreased at the time of serum PSA nadir compared with their respective baseline values (as shown by Dunnett's C tests, $P < 0.01$ in all cases). Furthermore, we observed no significant differences between IGF-1, T, DHEA-S, and TRACP-5b levels at the time of PSA nadir *versus* at disease progression (Dunnett's C tests, $P > 0.05$ in all cases). In contrast, AP values at disease progression were higher than at PSA nadir (Dunnett's test, $P = 0.001$) and comparable with baseline levels (Dunnett's test, $P = 0.76$), which mirrors the changes in serum PSA levels and is consistent with the notion that the changes in PSA, AP levels and bone pain scores during the combination regimen are reflective of changes in tumor burden of PrCa bone metastases. It is notable that the decreases of T and DHEA-S levels during treatment were statistically significant but very modest, because their baseline values were already significantly lower than the age-specific lower limit of normal levels (consistent with the chronic pharmacological castration of these patients before enrollment to this trial). In marked contrast, administration of the combination regimen was associated with pronounced reduction of serum IGF-1 levels (mean of 181.6 ± 10.3 *versus* 93.9 ± 5.2 ng/ml at baseline *versus* at the time of PSA nadir, respectively). Furthermore, we observed no significant differences between IGF-1, T, and DHEA-S levels at the time of PSA nadir *versus* at disease progression (Dunnett's C tests, $P > 0.05$ in all cases). Taken together these data suggest that a decline in circulating IGF-1 levels may participate in the mechanism of clinical responses to this regimen. However relapse from this therapy or disease progression after initial response to this regimen cannot be directly associated with either persistently high (non-declining) or with rebounding serum IGF-1 levels, respectively. Furthermore, the very modest declines in T and DHEA-S values associated with the antisurvival factor combination regimen are unlikely to be the predominant mechanism contributing to the clinical responses to this treatment. In respect to tartrate-resistant acid phosphatase measurements, their lower levels during treatment (in comparison to baseline tartrate-resistant acid phosphatase levels), indicates that this therapy is associated with decrease in bone resorption. However, disease progression or relapse from this therapy is associated with neither persistently high (non-declining) nor rebounding TRACP-5b levels, which suggests that the development of resistance to combination therapy cannot be attributed to increased bone resorption.

Profile of Side Effects. The mean fasting blood glucose levels of treated patients remained within normal levels (80–120 ng/dl or 3.5–6.3 mM) throughout the study, although 10 patients (26.8%) developed, during the first 2 months of treatment, transient hyperglycemia with maximum fasting blood glucose levels not exceeding 160 ng/dl (8.8 mM). Furthermore, 12 patients (31.58%) developed mild facial Cushingoid features, and 5 patients (13.16%) reported mild to moderate proximal muscle

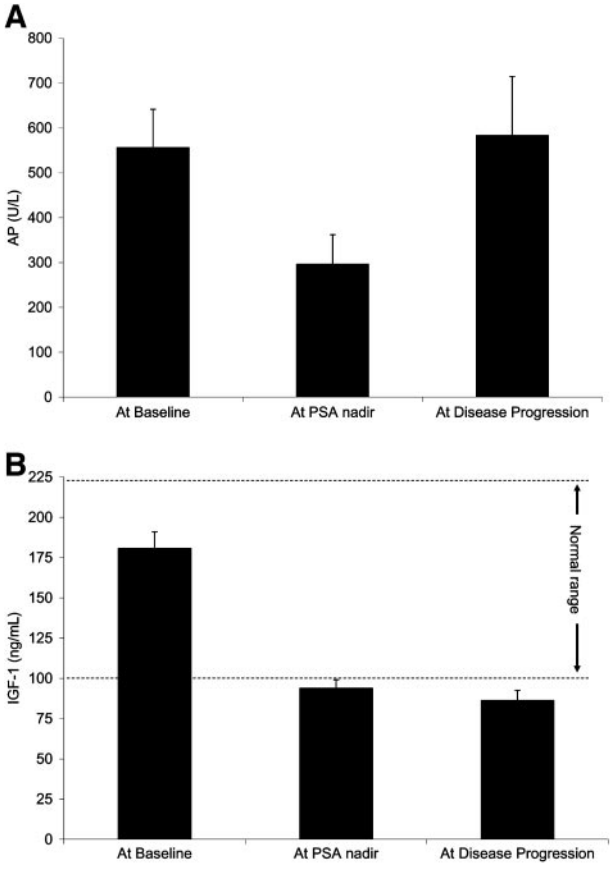

Fig. 2 Mean (±S.E) levels of serum alkaline phosphatase (AP; *panel A*) and insulin-like growth factor 1 (IGF-1; *panel B*) at baseline, at prostate-specific antigen (PSA) nadir response and at relapse from combination regimen with somatostatin analog (SM-A), dexamethasone, and androgen ablation monotherapy. At the time of PSA nadir, the levels of both AP and IGF-1 have statistically significant reductions in comparison to their respective baseline values.

weakness. These side effects subsided after dexamethasone tapering according to the protocol. Behavioral changes consistent with glucocorticoid-related delirium were reported by the family of one patient, but rapidly subsided after dexamethasone tapering from 4 to 1 mg/day). No major cardiovascular, renal, or liver-gastrointestinal toxicities were reported, whereas the mild epigastric-intestinal discomfort (cramps) reported by six patients (15.8%) was effectively controlled with oral administration of antacids and/or supplements of pancreatic enzymes.

DISCUSSION

In this study, we report the results of a Phase II clinical trial of a combination of somatostatin analog and low-dose dexamethasone with LHRH-A or orchiectomy in prostate cancer patients with advanced metastatic disease (hallmarked by diffuse bone metastases) and refractoriness to standard androgen ablation therapy. Of 38 patients who were treated with this combination regimen, 23 had partial responses, 9 had stable disease, and 7 had progressive disease. The median time to return to baseline PSA level was 12 months, median progression-free survival was 7 months, median overall survival was 14 months, and median prostate cancer-specific overall survival was 16 months. Importantly, the regimen was well tolerated, with manageable and transient side effects, and was also associated with durable improvement of bone pain and performance status.

The bone is the most frequent site of distant metastases of PrCa and is almost always the first (and often the only) site where disease progresses to stage D_3 (19). In addition, the number of skeletal metastatic foci is a very powerful independent prognostic factor of limited response of metastatic PrCa patients to hormone ablation therapy (20). The ominous prognosis conferred by skeletal metastases has been directly attributed to the high local levels, at the bone metastatic microenvironment, of antiapoptotic "survival" factors, such as IGF-1 (21–23). An extensive line of investigation has shown that the increased local bioavailability of IGF-1 in PrCa bone metastases not only triggers proliferation of osteoblasts (manifested histologically and radiographically as the osteoblastic reaction hallmarking these lesions; Refs. 19, 21, 22, 24–29), but also activates, in metastatic PrCa cells, a multitude of intracellular proliferative/antiapoptotic pathways [reviewed in Ref. 7], which protect tumor cells from anticancer drug-induced apoptosis, thereby limiting the clinical activity of therapies such as chemotherapy or androgen ablation.

These pieces of evidence indicated that abrogation of the biological activities of IGF-1 and/or its receptor, IGF-1R, could lead to antitumor responses or, at least, to increased activity of other anticancer therapies. To apply this therapeutic concept in stage D3 PrCa patients, we attempted to decrease the bioavailability of IGFs and thus the activation of their receptor IGF-1R. This choice was influenced by the lack of clinically applicable selective small molecule inhibitors of IGF-1R but was also feasible because the activity of IGF-1R is critically dependent after its interaction with IGFs, unlike other receptor systems (*e.g.*, HER2/Neu) where downstream signaling can be activated independently of the presence or absence of the respective ligand(s). Our preclinical studies provided the rationale for administration of a combination of dexamethasone and somatostatin analog to suppress the IGF-1 bioavailability in bone metastatic sites: *i.e.*, dexamethasone decreases osteoblast-derived IGFs (30) and down-regulate urokinase-type plasminogen activator expression by PrCa cells (31, 32), thereby suppressing the urokinase-type plasminogen activator-driven cascade of degradation of IGF-binding protein-3 (thereby preventing the local release of IGF-1, in the metastatic milieu, from its complexes with IGF-binding protein-3 and neutralizing the proapoptotic activity of IGF-binding protein-3; Refs. 21, 22, 28, 31). Somatostatin analogs, on the other hand, significantly suppress the growth hormone-dependent, liver-derived, circulating fraction of IGF-1 bioavailability (9).

The encouraging preliminary experience from clinical applications of this therapeutic concept in case series of stage D3 PrCa patients (12, 13) prompted us to evaluate the safety and efficacy of this combination regimen in a new larger cohort of patients in a Phase II clinical trial setting. Herein we report that the results of this trial, which confirm this regimen in the setting of androgen ablation refractory (stage D3) PrCa. Importantly, the median progression-free survival and overall survival of treated patients were comparable with the best ones reported,

thus far, by other second-line hormone manipulation and/or salvage chemotherapy regimens (33) and were associated with mild and well manageable side effects (primarily related to dexamethasone administration), as well as significant durable improvement in parameters of the quality of life of patients. Therefore, this combination therapy represents a promising second-line hormonal therapy for PrCa patients who have relapsed from androgen ablation therapy.

It is possible that the diverse pharmacological effects of dexamethasone can account for some part of the significant symptomatic improvement (*e.g.*, improvements in bone pain) observed during this therapy. Although some degree of symptomatic improvement was seen even in patients with disease progression (PD), the most pronounced improvements were associated (among patients with PR or SD during combination therapy) with significant changes in objective response markers that reflect tumor burden (PSA) or its effects on bone (AP and TRACP-5b). Conversely, the increases of PSA and AP levels during relapses from combination therapy were generally associated with deterioration of bone pain and performance status. This association between the symptomatic and objective responses to this therapy supports the notion that the main mechanism(s) of action of dexamethasone in this regimen is more likely to involve the modulation of local microenvironmental interaction of tumor cells with osteoblasts and/or osteoclasts and less likely to be secondary to a nonspecific anti-inflammatory or analgesic effects.

Previous studies have used SM-A to treat PrCa in an effort to stimulate the SSTR on the surface of PrCa cells and block the proliferation/survival of these cells. However, these therapies had generally achieved modest, if any, clinical responses (34, 35). In marked difference to those previous clinical applications of SM-A, the current administration of SM-A as part of the antisurvival factor combination was primarily designed to suppress the growth hormone-dependent liver-derived IGF production and did not aim at directly inducing apoptosis of tumor cells by ligation to cell surface SSTRs. This indirect mode action for SM-A in this combination regimen was corroborated by bone octreotide-scintigraphy studies, which documented that only a minority ($<$10%) of stage D3 patients had positive octreoscans, and most of them did not respond to this therapy. Notably, the vast majority of stage D3 patients (68.5%) with negative bone octreotide-scintigraphies responded to our therapy, further supporting the notion that the antitumor activity of SM-A in our regimen was not mediated by direct action of SM-A via SSTR-2 on tumor cells. Nevertheless, it is conceivable that that new cytotoxic SM-A which can target other SSTR subtypes (*e.g.*, SSTR-1,-3,-4,-5) might also have therapeutic applications for the management of metastatic PrCa, by exerting both direct (through binding to SSTRs on tumor cells; Ref. 36) and indirect (through suppression of IGF-1) antitumor actions.

The proposed mechanism for the clinical efficacy of this regimen via abrogation of the protective role of IGF-1 on metastatic PrCa cells is supported not only by preclinical studies on the ability of IGFs to enhance the resistance of tumor cells to proapoptotic stimuli (8, 12, 13) but also by the significant drop in serum IGF-1 levels in patients treated by our combination therapy as well as by the fact that this drop of IGF-1 levels also coincided temporally with the maximal reductions in tumor burden (PSA nadir). It is also conceivable that the anti-IGF-1 effect of this combination therapy is complemented by the ability of dexamethasone to also decrease the local interluekin-6 production, in the bone microenvironment, and interluekin-6 levels in circulation, another cytokine that can trigger PrCa cell drug-resistance (37). Additional studies to accurately quantify the local IGF-1 levels in the sites of bone metastases will be required to fully evaluate the role of the IGF system as a target of this combination therapy (and/or potentially identify other coexisting/adjunct pathways mediating or facilitating the antitumor activity of this regimen). However, currently available approaches to address this question, *e.g.*, repeated computerized tomography-guided biopsies of the sites of bone metastases for measurements of tissue levels of IGFs, have significant limitations, particularly our concern (shared by our local ethics committee) regarding significant discomfort and risk to patients.

Notably, at the time of progression, the circulating levels of IGF-1, DHEA-S, and T did not differ from their respective values at the time of best clinical response to this combination therapy. A possible implication of this finding may be that the relapse from this therapy is not related to rebounding levels of IGF-1 and/or androgens but to the ability of tumor cells to eventually develop compensatory mechanisms to sustain their survival and evade the activity of antisurvival factor therapy. Although additional studies will be required to delineate the precise mechanisms of response to and progression from this combination therapy, it is still important to emphasize that the ability of this regimen to introduce clinical responses to previously androgen ablation-refractory patients is an indication of the biological activity of this therapeutic approach and of the potential to flexibly develop a broad range of combination manipulations with other recently emerging therapeutic strategies for PrCa, with the ultimate goal to prolong the survival of patients and improve the quality of their lives.

It should be strongly emphasized that any definitive assessments regarding the efficacy, precise mechanism of action(s), and the optimal approach for use of this regimen are yet to be drawn and should await completion of randomized controlled clinical trials. However, our study affirms that this combination therapy has activity in the setting of hormone refractory PrCa and, importantly, highlights a novel therapeutic paradigm of an adjuvant treatment strategy which focuses on enhancing the antitumor activity of androgen ablation manipulation by disrupting the protecting effect of the host tissue microenvironment on tumor cells. Importantly, the particular impact of this combination therapy on the IGFs/IGF-1R pathway suggests that this conceptual framework may be applicable to other IGF-1 responsive malignancies, *e.g.*, myeloma, breast cancer, or liver cancer (23).

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