Combination of somatostatin analogues and dexamethasone (antisurvival-factor concept) with luteinizing hormone-releasing hormone in androgen ablation-refractory prostate cancer with bone metastasis

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INTRODUCTION

Androgen ablation therapy (AAT), the first-line therapy for prostate cancer with bone involvement, initially offers an objective clinical response. However, the development of refractoriness to AAT (stage D3) signals a poor median survival for such patients. The best clinical response at this stage was reported for the regimen of docetaxel plus prednisone, which was recently shown to be better than that for mitoxantrone plus prednisone (overall survival 18 vs 16 months, respectively) [1].

The development of bone metastasis involves specific host-tissue recognition of circulating prostate cancer cells. This recognition is followed by tumour cell migration to and invasion of the bone matrix and, finally, by the establishment of local cell–cell interactions with cells residing in the bone matrix, thus leading to osteoblastic metastasis [2,3]. However, the predominantly bone-specific nature of the refractoriness to AAT implies that specifically local environmental cues, and not only genetic factors related to clonal evolution of the tumour, might be responsible for rescuing prostate cancer cells from apoptosis induced by androgen deprivation [4,5]. It might be that host tissues such as bone that are rich in IGF-I, TGF-β1, interleukin-6, parathyroid-related peptide and/or endothelin-1 are sanctuaries for prostate cancer cells, and this possibility might also account for the change by prostate cancer cells from an androgen-dependent to an androgen-independent phenotype while they still have active androgen receptors (ARs) [5,6]. It appears that a baseline level of AR activation can potentially be reinforced by cross-talk with growth factor signalling pathways [5]. Therefore, the presence of appropriate survival factor (SF) stimuli, such as those from IGF-I in bone, can compensate the prostate cancer cells for the lack of androgen support during AAT. It is conceivable that chemotherapy-induced apoptosis is abrogated by the same SF pathways that confer resistance to hormonal therapy in the first place [4–6]. This possibility has led to the concept that inhibition of SF activity in the bone metastasis microenvironment might be clinically important.

Thus we review hormonal manipulation suppressing SFs in the bone metastasis microenvironment (anti-SF [ASF] therapy) in prostate cancer refractory to AAT and resistant to chemotherapy.

At our institution the novel concept of ASF manipulation was tested in combination with AAT in terminally ill patients with prostate cancer who: (i) had progressed to the stage independent of AAT and were receiving combined androgen blockade (LHRH analogue plus flutamide); (ii) had no response to antiandrogen withdrawal manipulation; and (iii) had no response to salvage chemotherapy [6]. The concept of ASF therapy was designed to test whether a regimen of somatostatin analogue (SM-A) and dexamethasone would reintroduce objective clinical responses in patients with stage D3 and who had disease progression while receiving AAT. The ASF therapy included oral dexamethasone (4 mg daily during the first month of treatment, tapered to 3, 2 and 1 mg daily during the second, third and fourth months, respectively, with 1 mg daily maintenance dose thereafter during the entire follow-up period) plus SM-A (Somatuline Autogel®, Ipsen, Slough, UK: lanreotide, 120 mg i.m. every 28 days; or Sandostatin-LAR®, Novartis Int. Basel, Switzerland: octreotide, 30 mg i.m. every 28 days) in combination with hormone ablation therapy (orchidectomy or LHRH agonist: triptorelin, 3.75 mg i.m. every 28 days, or leuprolide, 3.75 mg i.m. every 28 days, or respective 3-month depot injections).

The ASF therapy was initially tested in patients who had prostate cancer refractory to AAT (Table 1) [7]. In all, 44 patients were prospectively evaluated for enrolment in a phase II investigator-driven clinical trial, and 38 of them provided informed consent to receive ASF therapy. The ASF therapy produced objective clinical responses (disease stabilization or partial responses) in >80% of these patients (including 60% of patients whose PSA level decreased by half or more); the median progression-free survival was 7 months, the median overall survival 14 months and the median prostate cancer-specific overall survival 16 months. These objective clinical responses were accompanied by a favourable side-effect profile, which included only slight increases of serum glucose and mild proximal muscle weakness, that were mostly related to oral dexamethasone administration. Notably only three of 19 patients who had octreotide scintigraphy (which detects somatostatin receptor–2) at study entry had a positive scan that was consistent with sites of increased uptake detected by 99mTc bone scintigraphy. Moreover, only one of these patients had an objective clinical response to ASF therapy. Notably, 13 of 16 patients with negative octreotide scintigraphs showed objective
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Clinical responses to ASF therapy. These data confirmed our initial observation that octreotide scintigraphy does not add significantly to the evaluation of patients with stage D3 disease. In addition, these data suggest that expression of somatostatin receptor-2 in bony lesions, as detected by octreotide scintigraphy, correlates with neither $^{99m}$Tc bone scans nor clinical response to ASF therapy. This finding in turn indicates that clinical responses to the SM-A-containing ASF regimen cannot be attributed to a direct effect of the ASF on prostate cancer cells. The median progression-free survival was 7 months and the median overall survival was 18 months. In addition, there was a statistically significant ($P = 0.018$) reduction in serum IGF-I levels at the time of response to the combined therapy (Fig. 1), thereby corroborating the data that led to the concept of the ASF regimen [7].

In view of these results, ASF therapy was then compared with salvage chemotherapy in a randomized phase II clinical study designed to evaluate the efficacy of this combined therapy relative to that of cytotoxic chemotherapy regimens under investigation in advanced prostate cancer at our institution [8]. Overall, 40 patients with prostate cancer refractory to AAT were randomized to each of the treatment arms of the study. Group 1 had chemotherapy (estramustine phosphate, 140 mg three times daily, and etoposide, 100 mg orally for 21 days) and group 2 received the combination of SM-A (lanreotide, 30 mg i.m. every 14 days) and dexamethasone (4 mg tapered to 1 mg) in addition to androgen ablation by orchidectomy or LHRH agonist (triptorelin, 3.75 mg i.m. every 28 days). The clinical and PSA responses, overall survival, time to progression, and toxicity were compared between the groups. Eligible for final evaluation were 20 patients from group 1 and 18 from group 2. There was a PSA response (decrease by half or more) in 45% of group 1, receiving chemotherapy in addition to AAT by orchidectomy or triptorelin, and in 44% of group 2, receiving ASF therapy in addition to AAT by orchidectomy or triptorelin (no significant difference). There was a partial clinical response in 29% of group 1 and 30% of group 2 (also no significant difference). Changes in performance status and pain score during treatment were not significantly different between the groups. However, haematological toxicity was more frequent in group 1 (80% of patients), and mild glucose intolerance was more frequent in group 2 (22%). The overall survival was 18.8 months in group 1 and 18 months in group 2 (difference not statistically significant). The time to progression was 6 months in group 1 and 4 months in group 2 (not statistically significant), and in the PSA response subgroup, the time to progression was 8 months (group 1) or 7.7 months (group 2; not statistically significant). The conclusion was that, for apparently similar efficacy and effectiveness, the regimens used in these two groups have totally different side-effect profiles, which, remarkably, favour ASF therapy [8].

Currently, a randomized phase II trial by the South European Uroncological Group is being carried out in 72 patients with hormone-

![Image](image-url)

**TABLE 1 A summary of results of the study by Koutsilieris et al. [7]**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Partial response</th>
<th>Stable disease</th>
<th>Progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decline in PSA level</td>
<td>≥50%</td>
<td>&lt;50%</td>
<td>–</td>
</tr>
<tr>
<td>Objective clinical response, n (%)</td>
<td>23 (61)</td>
<td>9 (21)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Median (range) months to best clinical response</td>
<td>3 (2–6)</td>
<td>3 (2–6)</td>
<td>–</td>
</tr>
<tr>
<td>Progression-free survival, months</td>
<td>10</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

**FIG. 1.** Mean (SEM) serum IGF-I at baseline, at the nadir of the PSA response, and at the time of relapse after a combined regimen consisting of SM-A, dexamethasone and androgen-oblitative monotherapy. At the time of the PSA nadir, the IGF-I level was statistically significantly less than its baseline value. Adapted with permission from Koutsilieris et al. [7].
refractory prostate cancer and M0 (PSA >20 ng/mL) and M1 disease, to compare triptorelin and dexamethasone treatment, either with (33 men) or without (32 men) SM-A (lanreotide, 120 mg every 4 weeks), with respect to PSA response rate (>50% decrease), time to PSA progression, duration of survival and toxicity [9]. An interim analysis presented at the 2006 American Society of Clinical Oncology showed no difference in PSA response rate between the groups (64% in the SM-A arm vs 66%) [9]. However, these interim data suggest a possible advantage of adding the ASF regimen (SM-A and dexamethasone) to triptorelin in the duration of the PSA response (6.6 vs 3.4 months) and the time to PSA progression (5.8 vs 1.8 months). Both treatment regimens were well tolerated. The median duration of survival has not yet been reached.

CONCLUSION

ASF therapy was not designed to stand alone in the treatment of advanced (stage D3) prostate cancer. Indeed, ASF therapy was developed to enhance the efficacy of existing anticancer therapies, mainly AAT and salvage chemotherapy. Although IGF-I is not the only bone-derived cancer cell SF, it is the main target of ASF therapy. This novel concept indicates that the therapeutic focus should be not only on the effects of cancer cells on host tissue, but also on the effects of host tissues on tumour biology.

CONFLICTS OF INTERESTS

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REFERENCES


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Abbreviations: AAT, androgen ablation therapy; AR, androgen receptor; (A)SF, (anti)-survival factor; SM-A, somatostatin analogue.