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Growth Hormone Inhibitors in Prostate Cancer: A Systematic Analysis

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Key Words
Prostate cancer · Growth hormone inhibitors · Somatostatins

Abstract
Objective: Despite initial therapeutic success through androgen ablation in patients with advanced prostate cancer, the vast majority progress to androgen independence. Somatostatin (SST) analogs are a viable therapeutic modality before resorting to chemotherapy or immunotherapy. Their mechanism of action is related to a reduction in the IGF-1 (survival factor, reaction on neuroendocrine cells) appearing incrementally after long-term androgen deprivation and a possible suppression of GnRH receptors in prostate cancer following exposure to LHRH agonists. ***Methods:*** The computerized databases Medline, NCBI and OMIM were searched for the terms, somatostatin and prostate cancer, in parallel with printed bibliographic references. Forty-two studies were included and 267 patients with androgen-independent prostate cancer (AIPC) who were treated with SST analogs alone or in combination with other medications, e.g. dexamethasone, were analyzed. ***Results:*** In 42 studies with 267 AIPC patients, SST analogs were found to be effective, particularly when combined with estrogens or corticosteroids. The side effects are mild and related to the gastrointestinal tract. ***Conclusions:*** It would be interesting to study SST analogs in randomized trials including patients with well-defined AIPC. Whether SST analogs could be given earlier during sequential hormonal therapy remains to be studied.

Despite initial therapeutic success through androgen ablation in patients with advanced prostate cancer, the vast majority progress to androgen independence. The median overall survival from the primary hormonal treatment is in the range of 23–37 months and depends on multiple tumor-related risk factors like Gleason score and the presence of biochemical markers [1]. One key to the practical management is the classification of prostate cancers into 3 groups based on endocrine sensitivity: hormone-naïve; androgen-independent with preserved hormone sensitivity to castrate levels of testosterone (androgen-independent prostate cancer, AIPC), and androgen-independent with loss of hormone sensitivity (hormone-resistant prostate cancer, HRPC). Failure of the definitive local therapy (e.g. radical prostatectomy, external radiation or low-dose rate brachytherapy), which occurs in almost 15,000 patients/year as documented by the German Tumor Registry in Munich, requires further intervention with salvage androgen deprivation. Multiple therapeutic strategies for inducing castrate levels of serum testosterone are available to date. If a decision can be made to begin hormonal therapy, the strategy must be thoroughly discussed with the patient and adapted to individual needs (including watchful waiting) in balancing the potential benefits versus adverse effects. The optimal timing of hormonal therapy for patients with disease progression remains difficult to establish [2]. Traditionally, gonadal androgen ablation, luteinizing hormone-releasing hormone (LHRH) analogs or castration is the first choice. A non-traditional option is peripheral androgen blockade: non-steroidal anti-androgen combined with a

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5α-reductase inhibitor stops the conversion of testosterone to its active metabolite 5α-dihydrotestosterone and the binding to the androgen receptor (AR) [3]. As it does not interfere with the circulating testosterone levels and avoids the systemic side effects of hormonal intervention, this approach represents a promising investigational therapy for patients with prostate-specific antigen (PSA)-only disease. This clinical outcome is driven by an altered sensitivity of the AR and induced by secondary mutations within the AR gene [4]. At this point, withdrawal of the anti-androgen may result in a short-term clinical response based on augmented receptor sensitivity to very low levels of testosterone.

This endocrine withdrawal syndrome usually lasts not longer than 4–6 months and is accompanied by enhanced apoptosis and tumor shrinkage [5]. Patients develop resistance to androgen withdrawal therapies mainly as a consequence of mutations in the AR gene. As the AR gene is X-linked, only one mutated allele suffices for phenotypic alterations [6]. At this stage, somatic point mutations within the hormone-binding domain provide selective growth advantage to androgen-independent cells which spread under androgen deprivation. However, some mutant receptors might still be responsive, e.g., to progesterone or estrogens. Therefore, secondary or sequential hormonal manipulation may be useful [7].

A surrogate end point for success after each sequence is a 50% or greater PSA decrease within 12 weeks. The rationale to switch from one sequence (or step) to another sequence is a measurable progression of disease despite castrate serum testosterone or progressive disease, as evidenced by at least 1 new lesion on the bone scan or rising PSA (minimum 5 ng/ml with 2 consecutive increases of 50%) [7]. The AIPC, though resistant to castration, is still sensitive to secondary hormonal manipulations among which somatostatins (SSTs) are of interest. SSTs are a family of regulatory peptides which can act as hormones and can exert a paracrine or autocrine regulation or function as a monotransmitter, but mainly they inhibit cell secretion and proliferation [8]. In suppressing growth hormone (GH) secretion, SSTs interfere with the production of insulin-like growth factor-1 (IGF-1), which may stimulate prostate cancer cells. This mitogenic effect is modulated by IGF-binding proteins. As a serine protease PSA is capable of clearing IGF-1 from its binding protein. Thus, IGF-1 can bind to its prostatic receptors [9].

Growth factor stimulation plays an essential role in the upregulation of survival signals. Apparently, GH-dependent and -independent production of the IGF family are involved in the pathological growth of prostate cancer cells [10, 11]. Production decreases when combined with a corticosteroid GH-independent IGF-1, and a direct cytotoxic effect on prostate cancer cells is added when combined with an estrogen [12]. In addition to the efficacy of SST analog administration, this novel concept of anti-survival factor (ASF) therapy – a term coined by Koutsilieris et al. [10] – was reviewed.

Materials and Methods

The computerized databases Medline, NCBI and OMIM were searched for the terms, somatostatin and prostate cancer, in parallel with printed bibliographic references. Forty-two studies were included and 267 patients with AIPC who were treated with SST analogs alone or in combination with other medications, e.g. dexamethasone, were analyzed.

SST Analogs in Prostate Cancer: Background

Many studies suggested that specific mutations leading to androgen independence are already present at initial stages in a subset of primary tumors cells, and later it was found that they were dominant through clonal selection [13]. Further mutations within the AR gene [4] provide a selective growth advantage to this preexisting clone of androgen-independent cells which spread under conditions of androgen deprivation. The frequent occurrence of AR gene amplifications [14] determines the increase in AR sensitivity to very low levels of androgens [4]. Thus, cellular proliferation may be promoted under incomplete androgen blockade of either a surgical or medical type. In addition, androgen withdrawal is also able to trigger secondary AR gene amplification and increases AR sensitivity [6]. Moreover, it induces neuroendocrine differentiation of prostate cells which secrete neuropeptides and IGF-1, two epigenetic mechanisms of tumor resistance [10]. Clinically, the development of neuroendocrine differentiation can be assessed by measuring the chromogranin A level [15]. It was proposed that the local bioavailability of these neuropeptides and growth factors (EGF, IGF-1 and IGF-2) accounts for anti-apoptotic mechanisms representing survival factor-mediated resistance to androgen withdrawal therapy [10]. This is the basis for ASF therapy.

Several studies have investigated the benefit of successive 'on' and 'off' hormonal interventions (intermittent androgen deprivation) aiming at preserving the apoptotic potential of the tumor cells. These hormonal regimes proved capable of overcoming true AIPC, characterized

by a rapidly increasing PSA or even the presence of visceral metastases. At this stage (D3), studies have explored the usefulness of SST analogs. These regulatory peptide products were isolated during the search for a GH [16]. After purifying the major SST-14 peptide, precursor forms of greater molecular weight were subsequently recognized. The SST-28 form, or pro-SST, is a 28 amino acid polypeptide with SST-14 making up the C-terminus. The two bioactive forms act in different ways on five types of SST receptors (SSTRs), are highly unstable, have a very short half-time, and differ significantly in their relative potency [17]. Different functional SSTRs are co-expressed in the brain, pituitary gland, pancreas, kidneys, adrenals, thyroid and prostate. The prostate cancer cell lines, LNCaP, PC-3 and DU 145, have been shown to express SSTR-1, -2 and -3 [17].

Differences between normal and cancerous prostate tissue are of note: the prostate epithelium expresses SSTR-4, stromal cells primarily express SSTR-2, and cells from benign prostatic hyperplasia predominantly express SSTR-3 [18]; the prostate cancer cells and neuroendocrine cells appear to be rich in SSTR-1 and SSTR-4, while SSTR-2 was found in the stroma [19]. This supports the hypothesis in which SSTR-2 expression may control the cancer cell through stromal influence [20]. In normally dividing cells, SST has a clear anti-proliferative action and this effect is likely to be mediated through the receptor subtypes SSTR-1, 4 and 5 involved in cell cycle arrest [21] (fig. 1). On tumor cells, SSTs may act through different mechanisms like the suppression of GH and inhibition of the release of various peptide hormones secreted by the neuroendocrine cells developing in AIPC [22]. These peptides apparently activate anti-apoptotic pathways, coined survival pathways [23]. Long-acting SSTs were developed by Schally [24] resulting in octapeptide super analogs being more potent than native SST. They suppress the IGF-1 production comparable to native efficiency, if administered subcutaneously. Individual doses ranging from 150 to 1,500 μg/day must be adjusted individually.

Octreotide long-acting release is a SST analog designed for monthly injections. Like the endogenous SST, octreotide long-acting release inhibits the secretion of GH as well as various peptide hormones secreted by neuroendocrine cells. The action of octreotide preparations is thought to be meditated through the SSTR-2 receptor pathway.

Lanreotide and its slow-releasing form, lanreotide SR (Somatuline®), are SST analogs with a good affinity to SSTR-2 and 5 [12] (fig. 2). Once prostate cancer becomes hormone-resistant (HRPC), they express SSTR-1 and 4, thus the commercially available octapeptide SST analogs have limitations (fig. 2). A dextran-conjugated derivate, sms-d70, was applied to 10 patients with HRPC. Only stabilization of pain was recorded in a phase-I trial when sms-d70 was injected subcutaneously up to 50 mg/week. If injected intravenously (5–10 mg/week up to 14 months) 3 patients had a >50% PSA decline [25]. Another way to approach HRPC is coupling the SST analogs to cytotoxic agents for tumor targeting. Such an analog of SST, AN-238, consisting of the radical 2-pyrrolinodoxorubicin (AN-201) linked covalently to the SST octapeptide carrier RC-121, was initially used to target xenografts of PC-3 human androgen-independent prostate cancer,

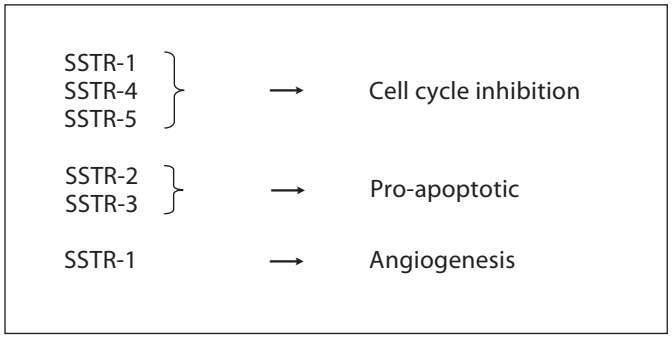

Fig. 1. Somatostatin receptor-activated signal transduction pathways responsible for growth inhibition [12, 21].

SSTR-1	↑	SOM-230
SSTR-2	↑	Lanreotide, Octreotide, Vapreotide, SOM-230
SSTR-3	↑	SOM-230, ⇑ Lanreotide, Octreotide, Vapreotide
SSTR-4	⇑	SOM-230
SSTR-5	↑	Lanreotide, SOM-230, ⇑ Octreotide, Vapreotide

Fig. 2. Somatostatin receptor affinity of somatostatin analogs [21, 39].

which express SSTR-2 and 5 inhibiting tumor growth [26, 27]. Another advance is the development of radiolabeled carriers like the SST analog octreoscan to detect and treat SSTRs expressing tumors [28]. Radioactive treatment targeted to the prostatic tumor was tested using radiolabeled lanreotide [29]. In a recent update, the efficacy of ^{111}In- and ^{90}Y-DOTA-lanreotide was tested in neuroendocrine tumors [30].

Clinical Experiences with SST Analogs in AIPC

Monotherapy

In 1994, Logothetis et al. [31] conducted one of the earliest studies on SST analogs in 22 patients with hormone-refractory carcinoma of the prostate. Doses of 100 mg octreotide in subcutaneous preparations were administered every 8 h for 6 weeks, aiming at evaluation for toxicity and clinical response. While only 2 patients dropped out due to intolerable gastrointestinal side effects, no patient had clear evidence of tumor regression. On the contrary, there was an impression of accelerated tumor growth with the use of octreotide. Among the treated patients, 12 developed new osseous and visceral metastases, 1 suffered disseminated intravascular coagulation and 2 reported neurological complications. However, as 6 patients underwent further chemotherapy and 5 of them achieved tumor regression, it was concluded that octreotide might sensitize tumor cells to subsequent chemotherapy. In another open study, 5 patients with metastatic prostate cancer received octreotide (0.4–1 mg/day s.c.) resulting in a temporary halt in rising PSA for up to 3 months [32]. In treating 24 patients, Vainas et al. [33] reached similar conclusions. In another phase-II trial 14 patients with metastatic prostate cancer were treated with 0.4 mg octreotide in addition to androgen withdrawal. Octreotide was well tolerated and 6 of 14 patients responded (mean survival 18.5 months) [33].

Lanreotide was tested in a dose-escalation trial of 25 patients with metastatic HRPC [34]. Four up to 24 mg/day of lanreotide was administered by continuous intravenous infusion for at least 28 days. Toxicities included grade-I diarrhea, bloating, infection, nausea and flatulence, symptoms which were, however, self-limiting and occurred only during the initial therapy. Continuous infusion of 24 mg/day of lanreotide appeared to be well tolerated, but the clinical activity in HRPC was inadequate [34]. In a phase-I–II study 30 patients with AIPC received weekly 4–24 mg lanreotide s.c. over 12 weeks; 20% responded with a 50% PSA decline lasting for an average of 38 weeks [35]. After SST receptor scintigraphy Acosta and Abrahamsson [36] treated 11 patients with AIPC in an open study. Octreotide 0.3 mg/day was injected subcutaneously over 2 weeks. Then 30 mg/month was injected intramuscularly over 8 months. Nine of 11 patients had a >50% PSA decline and 8 of 11 responded with a >50% reduction in osseous metastases. Side effects were mild with diarrhea and nausea.

Combination Therapy

The ASF therapy introduced by Koutsilieris et al. [37] should enhance the efficacy of SST analog administration in AIPC. For this purpose the SST analogs should not be used alone. Accordingly, 4 patients in a case study were treated with 30 mg lanreotide i.m. every 14 days along with 4 mg dexamethasone daily plus standard hormone ablation. For all 4 patients a good clinical response was reported [37]. Subsequently, 11 patients who had relapsed after LHRH-A plus anti-androgen and its withdrawal received lanreotide 30 mg for 14 days plus 4 mg dexamethasone (tapered down to 1 mg after the 2nd month) plus LHRH-A: 10 of 11 patients responded (8 of 11 had a >50% PSA decline). Remarkably, all 11 had a significant improvement in bone pain with an overall survival of 18 (range 6–22; 95% CI 16–20) months. IGF-1 levels were reduced by 60% [38]. The same group re-examined this therapeutic combination in 38 patients using 20 mg octreotide i.m. every 28 days, 4 mg daily oral dexamethasone for the 1st month and standard LHRH-A therapy. 23 of 38 patients had a partial response (≥50% PSA decline), 8 of 38 had stable and 7 of 38 progressive disease. The median prostate cancer-specific survival was 16 (95% CI 11.9–20.1) months. Again the IGF-1 was significantly suppressed from 181.6 to 93.9 ng/ml at the PSA nadir. It is of note that 17 of 38 patients previously received estramustine phosphate plus etoposide or mitoxantrone. Thirteen patients with relapsing prostate cancer after gonadal androgen deprivation (8 had a LHRH analog, 5 had orchiectomy; a transient ketoconazol induced remission in the orchiectomized patients lasting 10 months) received the SST analog vapreotide (1 mg subcutaneously t.i.d.). Eight of 13 patients had a 71 ± 8% PSA decline; 2 additional men responded with a fall in prostatic acid phosphatase. In accordance with the ECOG criteria, there were 2 complete, 4 partial responses and 2 stable diseases [39]. The combination of estramustine (420 mg/day) plus lanreotide (73.9 mg i.m.) every 4 weeks lead to a long-term survival in 1 patient; his marker of neuroendocrine differentiation, chromogranin A, was 816 ng/ml and came down to 12 ng/ml with a lasting PSA

of 0.1 ng/ml [40]. In a randomized phase-II trial Dimopoulos et al. [41] compared the efficacy of estramustine plus 100 mg etoposide for 21 days versus 30 mg lanreotide i.m. every 14 days, 4 mg tapered down to 1 mg dexamethasone daily and LHRH-A in 40 AIPC or HRPC patients. The results proved equally efficient for both regimens. Di Silverio and Sciarra [42] treated 10 patients with 1 mg oral ethinylestradiol daily to suppress testosterone and 73.9 mg lanreotide intramuscularly every 4 weeks, while LHRH-A was discontinued. The PSA response rate was 90% and the serum chromogranin A declined. Moreover, the performance status along with the bone pain improved in all patients over a median duration of 18 months. The median progression-free survival was 18.5 months. Sciarra et al. [12] summarized data on 20 patients receiving lanreotide plus ethinylestradiol leading to a 95% PSA response, general improvement in the performance status and lessened bone pain. They reemphasized the need to monitor the degree of neuroendocrine cell differentiation with chromogranin A. Chromogranin A is the quantitatively major secretory protein of vesicles inside neuroendocrine prostate cells. The differences in the expression of SSTRs between primary and AIPC are likely to be related to the changes in the neuroendocrine phenotype during androgen deprivation. Circulating chromogranin A is only marginally affected by hormones or chemotherapy but suppressed by SST analogs [8]. Finally, an interesting mechanism is related to the observation that LHRH receptors are expressed in prostate cancer after exposure to an LHRH agonist [43]. It remains to be demonstrated whether lanreotide suppresses GnRH receptors in the prostate.

Conclusion

Due to the high incidence of rising PSA following unsuccessful local therapy with curative intent of prostate cancer, sequential hormonal manipulation plays an increasingly important role [3]. To enhance the longevity of the patients, secondary hormonal manipulations have to be employed. SST analogs are a viable therapeutic modality before resorting to chemotherapy. Their mechanism of action is related to a reduction of the IGF-1 (survival factor, reaction on neuroendocrine cells) appearing incrementally after long-term androgen deprivation and a possible suppression of GnRH receptors in prostate cancer following exposure to LHRH agonists.

In 42 studies with 267 AIPC patients, SST analogs were found to be effective, particularly when combined with estrogens or corticosteroids. The side effects are mild and related to the gastrointestinal tract. However, it would be interesting to study SST analogs in randomized trials including patients with well-defined AIPC. Whether SST analogs could be given earlier during sequential hormonal therapy remains to be studied.

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