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SOMATOSTATIN ANALOGUES IN THE TREATMENT OF BREAST AND PROSTATE CANCER

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Summary—Newly developed somatostatin analogues may be useful agents in the treatment of breast and prostate cancer. Potential mechanisms of antitumor action include suppression of circulating levels of trophic hormones and growth factors as well as direct effects at the tumor level, potentially involving autocrine/paracrine mechanisms. Pilot clinical trials conducted in heavily pretreated women with advanced breast cancer indicate that SMS 201-995 (Sandostatin®) has minimal toxicity and moderately suppresses stimulated growth hormone secretion and basal somatomedin-C level. Somatostatin analogues have also been found to retard the growth of experimental prostate cancer, particularly when used in combination with LHRH analogues. The therapeutic efficacy of these compounds used alone or in combination with other agents in the treatment of breast and prostate cancer remains to be established in larger clinical trials involving less heavily pretreated patients.

INTRODUCTION

Newly developed somatostatin analogues have been found to be highly effective in the management of a variety of functioning endocrine tumors [1]. In contrast to native somatostatin, these compounds have a longer half-life [2] and, thus, their administration does not require constant i.v. infusion. An additional attractive feature of these analogues is the lack of major toxicity encountered as far in their clinical use [1].

It has been proposed that these drugs may also be effective in the treatment of other solid tumors, particularly hormone-responsive neoplasms. We will review here current information on the use of somatostatin analogues in the treatment of breast and prostate cancer.

BREAST CANCER

Somatostatin analogues may influence breast cancer cell proliferation through multiple mechanisms. One of them may involve a direct effect at the tumor level, as supported by the presence of somatostatin receptors in up to $\frac{1}{3}$ of human breast cancer specimens [3] and the ability of the somatostatin analogue, SMS 201-995, to inhibit MCF-7 breast cancer cell proliferation in culture [4]. In addition, somatostatin analogues could also affect growth-factor-mediated breast cancer growth since in the MIA PaCa-2 human pancreatic cancer cell line, they have been found to dephosphorylate the EGF receptor and inhibit EGF-induced proliferation [5]. Suppression of circulating levels of IGF-I [6–8] and EGF [9] could be additional mechanisms of antitumor action since both growth factors have been shown to be potent stimulators of breast cancer growth [10]. Finally, it may not be possible with the combined administration of dopaminergic drugs and somatostatin analogues to inhibit both prolactin and growth hormone (GH) secretion and, thus, completely block lactogenic activity. The potential involvement of lactogenic hormones in tumor growth is supported by the presence of prolactin receptors in up to 50% of human breast cancer specimens [11] and the proliferative action exerted by prolactin *in vitro* in a significant fraction of human breast tumors [12]. The lack of therapeutic efficacy observed with the use of dopaminergic drugs alone in women with metastatic breast cancer [13] may have been due to the inability of this class of compounds to suppress the secretion of GH, which in humans is lactogenic.

We have recently completed a pilot clinical trial to evaluate the endocrine effects and toxicity of the combined administration of the somatostatin analogue, SMS 201-995 (Sandostatin®)

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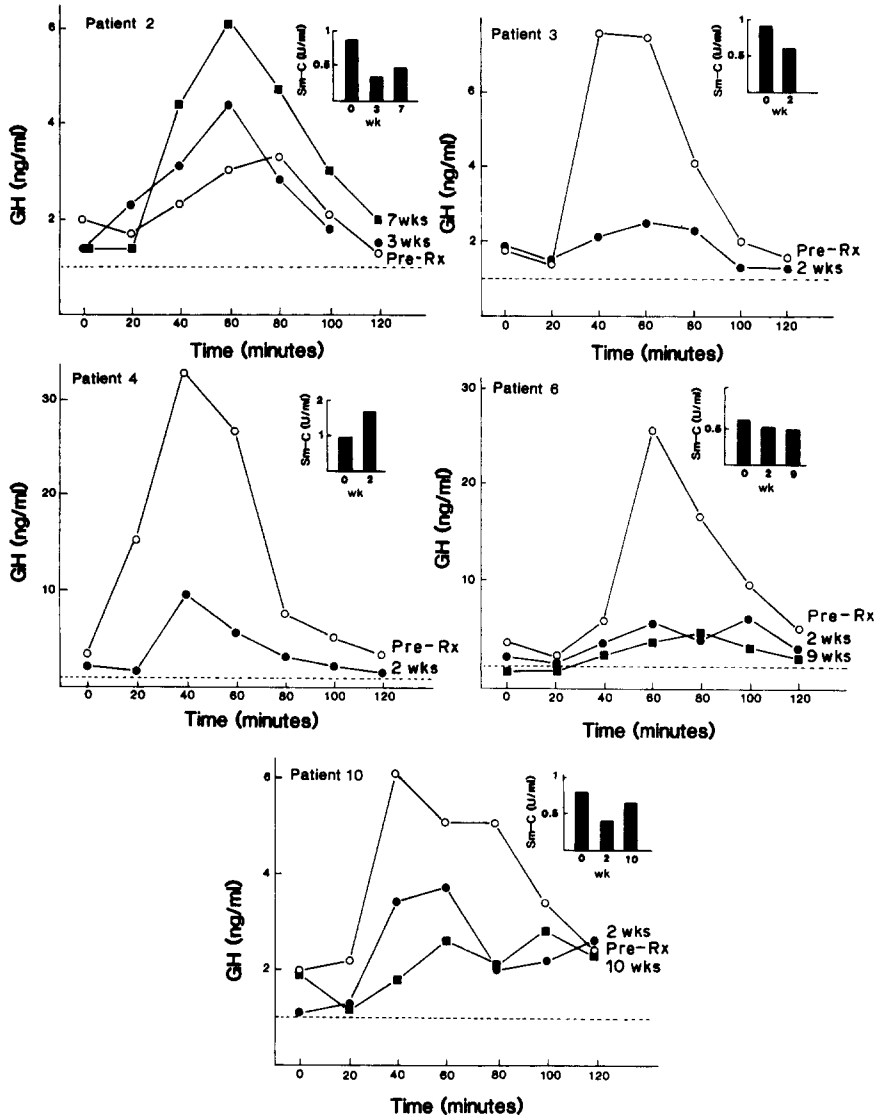

Fig. 1. Stimulated GH levels during insulin-induced hypoglycemia before and during the combined administration of SMS 201-995 and bromocriptine. For each patient, the corresponding changes in Sm-C at the same time intervals are depicted in the insert. A repeat-measures ANOVA with weeks on treatment and minutes of test as within-subject factors was used to assess the overall effect of treatment on stimulated GH levels (F-test P-value = 0.0008). Individual comparisons between weeks on treatment at each of the time points during the ITT revealed that, compared to pretreatment, GH levels were significantly ($P < 0.05$, t-test) lower on week 2 and weeks 7–10 at 40 and 60 min. No significant difference in GH levels was detected between 2 weeks and 7–10 weeks treatment. (Reproduced with permission from Manni *et al.* [6].)

(100–200 μg s.c. in a.m. and h.s.) and bromocriptine (2.5 mg orally twice a day) in a group of 10 heavily pretreated postmenopausal women with advanced breast cancer [6]. We observed, that during treatment, stimulated GH levels following either insulin-induced hypoglycemia (Fig. 1) or L-DOPA (Fig. 2) were suppressed in 7 of 9 patients. It should be noted that in patient 5, who remained on treatment for a more prolonged period of time, the suppression in GH secretion persisted up to 23 weeks without any evidence of escape. Basal somatomedin-C (Sm-C) levels declined in 6 of the 9 women. A concordant decrease in both growth hormone and Sm-C secretion was, however, only observed in 4 patients. The reason for the discordance in the treatment effects on GH and Sm-C secretion in some patients is unclear. It is possible, however, that stimulated GH secretion following provocative testing may not strictly correlate with 24 h GH production, which is more likely to be reflected by circulating Sm-C levels. Overall, Sm-C levels were 1.063 ± 0.123 U/ml (SEM) at baseline, 0.782 ± 0.146 at 2 weeks and 0.771

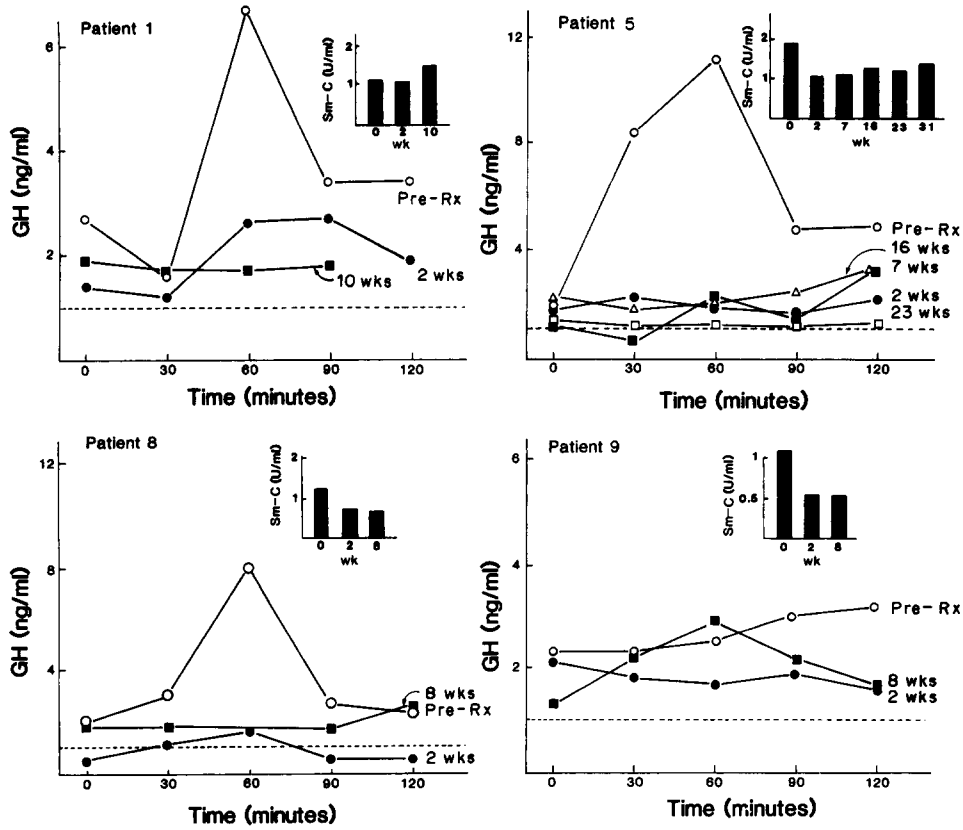

Fig. 2. Stimulated GH levels following L-DOPA administration before and during combined treatment with SMS 201-995 and bromocriptine. For each patient, the corresponding changes in Sm-C at the same time intervals are depicted in the insert. Statistical analysis of the data was performed as described for Fig. 1. Overall analysis revealed that GH levels were significantly lower during treatment than at baseline (F-test P-value = 0.0001). Individual comparisons between weeks on treatment at each of the time points during the L-DOPA test revealed that, compared to pretreatment, GH levels were significantly ($P < 0.05$, t-test) lower on week 2 at 30, 60 and 120 min on weeks 7–10 at 30 and 60 min. No significant difference in GH levels was detected between 2 weeks and 7–10 weeks of treatment. (Reproduced with permission from Manni *et al.* [6].)

$\pm$ 0.146 at 7–10 weeks of treatment. This nearly 30% reduction was not statistically significant by a repeat-measures ANOVA (F-test P-value = 0.1021).

Combined somatostatin analog and bromocriptine therapy effectively suppressed TRH-stimulated prolactin secretion. In contrast, circulating levels of FSH, LH, E_1, E_2, E_1-S, thyroxine and cortisol were not affected, thus suggesting a specific effect of treatment on lactogenic hormone secretion.

Side effects were minimal and consisted only of nausea, which occurred in 3 patients, but was severe enough in only 1 to necessitate discontinuation of therapy. In this group of heavily pretreated women, no objective remissions were observed, although 1 patient experienced disease stabilization lasting 7 months.

Recently, Vennin *et al.* [8] completed a pilot clinical trial using SMS 201-995 alone (100 μg bid, s.c.) in 16 heavily pretreated postmenopausal patients with advanced breast cancer. These investigators reported a median 33% decrease in the circulating IGF-I level (range 26–71%) in 8 patients, while in 3 no significant change in IGF-I secretion was observed. The authors reported disease stabilization in 3 of 14 evaluable patients and only minimal toxicity in 4 patients consisting of transient diarrhea. Significant reductions in basal and arginine-stimulated GH levels and in IGF-I have also been reported recently by Pollack *et al.* [7] in 8 patients with solid non-endocrine tumors treated with a considerably higher dose of SMS 201-995 (400 μg every 8 h). Despite this higher dose, no major toxicity was observed.

Following demonstration of the endocrine effects and feasibility of somatostatin analogue therapy, the therapeutic potential of this form of treatment, either alone or in combination with other modalities, needs to be tested in larger numbers of patients with less advanced disease.

PROSTATE CANCER

Somatostatin analogues are currently being evaluated as potential effective tools in the treatment of prostate cancer. Several of these compounds have been shown to inhibit the growth of transplanted Dunning rat prostate tumors [14, 15]. Of interest, the combined administration of somatostatin and LHRH analogues has been found to induce greater tumor regression than that observed with the individual treatments [15]. In agreement with its superior antiproliferative effect, the combination treatment also resulted in more pronounced histologic changes consisting of regression of the epithelium and proliferation of the connective tissue component [15].

As in the case of breast cancer, somatostatin analogues could act directly at the tissue level since somatostatin receptors have been detected in the Dunning tumor [16]. In addition, this compound could interfere with the action of growth factors such as TGF-α-like peptides, which recently have been shown to have an important growth regulatory role in prostate cancer cells [17]. Finally, somatostatin analogues could affect experimental prostate cancer growth indirectly through suppression of circulating levels of GH and prolactin. Such suppressive effects, however, have not been universally found in rats and may depend upon the specific analogue used. Inhibition of prolactin and GH secretion has been observed with RC-121 and RC-160 [18] but not SMS 201-995 administration [14].

Information on the clinical usefulness of somatostatin analogue therapy in human prostate cancer is still lacking. Conflicting data exist regarding the presence of somatostatin receptors in human prostate cancer specimens which has been observed by some [16] but not all investigators [19].

CONCLUSIONS

In summary, there appears to be reasonable rationale for further testing somatostatin analogue therapy in the treatment of solid tumors such as breast and prostate cancer. Lack of significant toxicity also encourages this line of investigation. Recent evidence indicates that somatostatin analogues differ considerably from one another with regard to their binding affinities to the somatostatin receptor in a given tumor [16]. Furthermore, their relative binding affinities appear to change from tumor to tumor [16]. Consequently, it may be necessary to select the appropriate somatostatin analogue on the basis of binding studies to optimize antitumor efficacy.

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