Potential Role for Somatostatin Analogues in Breast Cancer: Rationale and Description of an Ongoing Trial

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Somatostatin analogues such as octreotide have been shown in experimental systems to exhibit antineoplastic activity. Further laboratory and clinical research is needed to clarify the mechanism of action of somatostatin analogues as antineoplastics, and to determine if the encouraging preclinical results will lead to novel endocrine approaches to the treatment of breast cancer.

THE ROLE OF HORMONES such as estrogen in stimulating the proliferation of endocrine-dependent human breast cancer is well established.[1] Furthermore, endocrine treatments currently used to palliate metastatic breast cancer are among the most useful antineoplastic therapies available. Recent basic research concerning the dependence of neoplasms on peptide hormones and growth factors suggests that it may be possible to develop approaches that will extend the usefulness of this modality of cancer treatment.[2]

An important example of this is the current interest in the role of somatostatin in the regulation of cellular proliferation and the potential for therapeutic intervention using Sandostatin®, a long-acting synthetic analogue of this natural inhibitory peptide.

RATIONALE

Somatostatin analogues have been shown to inhibit the growth of a wide variety of tumors, both in culture and in various animal models.[3-5] However, it is unclear at present by which mode of action somatostatin analogues exert their inhibitory effects.

First, it has been demonstrated that a majority of breast cancer cells are insulin-like growth factor I (IGF-I)–receptor positive and that the growth of these cells may be IGF-I–dependent.[6-10] This is supported by experiments demonstrating that blockade of the IGF-I receptor using a monoclonal antibody inhibits the growth of human breast cancer cell lines.[11] In fact, there is increasing evidence to suggest that IGF-I is one of the most potent breast cancer mitogens, perhaps more potent than estrogens.[6] Data from a preliminary trial indicate that it is possible to lower circulating IGF-I levels by means of Sandostatin® administration.[12] In a manner analogous to treatments that effectively palliate steroid-dependent neoplasms by lowering levels of estrogens and androgens, such an approach may be of therapeutic value for IGF-I–dependent tumors.

There is also evidence for direct antiproliferative effects of somatostatin analogues. In two series of human breast cancer primary trials, greater than 30% of the biopsy samples demonstrated high-affinity somatostatin-binding sites.[13,14] Potential consequences of receptor binding include interference with transmission of intracellular signals that regulate growth, ie, through activation of a dephosphorylation process,[15] inhibition of centrosomal separation,[16] and through the inhibition of synthesis and/or secretion of other autocrine growth factors by tumor cells.[17,18]

Finally, the structurally related lactogenic hormones, growth hormone and prolactin, may influence the growth of breast cancer cells.[19] Recent laboratory work has demonstrated that human prolactin receptors can bind both prolactin and growth hormone, and it has also confirmed that many breast cancer cells bear receptors for both prolactin and growth hormone.[20,21] Initial clinical trials designed to test the value of pharmacologically decreasing prolactin levels in advanced disease were uniformly negative.[22,23] However, a more recent study performed in early-stage disease patients has shown that bromocriptine significantly decreases the labeling index of breast tumors when administered perioperatively.[24] Theoretically, the simultaneous use of an agent to decrease growth hormone levels (such as Sandostatin®) and a dopamine agonist to decrease prolactin levels could result in a "selective medical hypophysectomy" that could interfere with lactogenic hormone stimulation of breast cancer cells.

PATIENTS AND METHODS

Based on these hypotheses, a study was designed to investigate, in open conditions, the antineoplastic activity of the somatostatin analogue, Sandostatin®, administered either as a single agent or coadministered with the dopamine agonist, CV 205-502 (Sandoz Canada, Dorval, Quebec, Canada), in metastatic breast cancer. CV 205-502 is a new, long-acting, nonergot, dopamine D_2-receptor agonist that has been shown to be effective in reducing serum prolactin levels in hyperprolactinemic patients when administered once a day.[25]

Estrogen receptor–positive patients of any menopausal status are eligible for study participation should they present with bidimensionally measurable metastatic breast cancer that has become refractory to antiestrogen treatment. The antiestrogen may have been administered in the adjuvant and/or metastatic disease setting. Patients of unknown estrogen-receptor status are also eligible if they are postmenopausal and have experienced a 2-year, disease-free interval. Patients are not eligible if they have received any other antineoplastic therapy (chemotherapy, hormones, or nonpalliative radiation) for their metastatic disease other than an antiestrogen, or if they have rapidly progressing, life-threatening disease. Prior adjuvant chemotherapy is acceptable. Patients are randomized at entry to receive either 400 μg Sandostatin® every 8 hours by subcutaneous injection or 400 μg Sandostatin® every 8 hours in combination with 0.075 mg CV 205-502 orally once a day. Twenty patients per treatment group are planned.

The end points of the study are as follows: (1) tumor response rates, and (2) endocrine and growth factor evaluations including serum prolactin, IGF-I, epidermal growth factor, estradiol, and urinary growth hormone.

SUMMARY

Despite recent advances, the treatment of breast cancer is still far from optimal. This is particularly true for those patients with advanced disease. Furthermore, with the high incidence of breast cancer,[26] it is obvious that there is a need for improved therapies in the oncologist's armamentarium.

The somatostatin analogue, Sandostatin®, possesses unique and pleiotrophic actions that make it worthy of investigation in the clinical setting. The clinical trial described here has been designed to provide relevant data about both tumor responsiveness and the influence of Sandostatin® alone or in combination with CV 205-502 on endocrine and growth factor endpoints. This open-labeled, phase II study may generate data that will justify further evaluation of Sandostatin® in the adjuvant and/or palliative treatment of breast cancer, either as a single agent or in combination with dopamine agonists or, as recently proposed, with antiestrogens.[27]

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