The Potential Role of Somatostatin Analogues in Breast Cancer Treatment

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Existing treatments for breast cancer are helpful for many patients, but treatment failure remains a common event, and there is a strong clinical need to improve upon current therapies. Somatostatin analogues have been evaluated for antineoplastic activity in model systems over the past decade, and encouraging results have been obtained (reviewed in [1, 2]). This has led to suggestions to test these agents clinically in the treatment of breast cancer patients, and a program of clinical trials has recently been initiated. This review will describe aspects of research in this area.

DIRECT MECHANISM OF ACTION

The so-called "direct" mechanism of action of somatostatin analogues in the context of breast cancer treatment refers to inhibition of proliferation and/or induction of apoptosis, which take place as a consequence of a somatostatin analogue binding to a somatostatin receptor on a breast cancer cell. Recent evidence [3] supports earlier reports [4] that documented the presence of somatostatin receptors on primary human breast cancers. There is now a high degree of confidence that at least half of human breast cancers express somatostatin receptors, and it has been possible to image primary breast cancers and nodal metastases by somatostatin analogue scintigraphy [3]. There is some suggestion that somatostatin receptor abundance is greater on well-differentiated, estrogen-receptor positive tumors than on anaplastic cancers. Work to characterize the abundance of each of the five somatostatin receptor subtypes in normal and neoplastic breast epithelial tissue is ongoing [5].

Evidence that the "direct" mechanism of action has relevance for breast cancer comes from tissue culture studies that show inhibition of proliferation of clonal populations of breast cancer cells grown in tissue culture [6]. In most experimental systems (e.g., [6]), such direct inhibition is maximized in the absence of estrogens, and this has led to the proposal that the effect of somatostatin analogues on breast cancers *in vivo* might be maximized if they were co-administered with agents such as antiestrogens or aromatase inhibitors.

In recent years, there has been important progress in understanding the signal transduction pathways involved in the "direct" mechanism of action of somatostatin analogues [7-9]. For example, there are data suggesting that binding of somatostatin or a somatostatin analogue such as octreotide or RC-160 to the type 2 somatostatin receptor activates a phosphotyrosine phosphatase activity [10]. This is the reciprocal activity of the tyrosine kinase activity associated with many peptide mitogen receptor receptors, such as the epidermal growth factor (EGF)[b] receptor or the insulin-like growth factor I (IGF-I) receptor, so it is

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[b] *Abbreviations:* EGF, epidermal growth factor; IGF-I, inulin-like growth factor I.

not unexpected that growth inhibition is a consequence of ligand binding to the type 2 somatostatin receptor. Recent evidence [11] is consistent with the existence of a link between the type 3 somatostatin receptor and a p53-related apoptotic signal transduction pathway.

INDIRECT MECHANISMS OF ACTION

"Indirect" mechanisms of action are those that do not involve an interaction between somatostatin analogues and neoplastic cells but nevertheless result in inhibition of neoplastic behavior. It must be emphasized that for somatostatin-receptor positive neoplasms, the direct and indirect mechanisms of action of somatostatin analogues are not mutually exclusive, and both may contribute to any antiproliferative effect seen. On the other hand, only the indirect mechanisms can have an impact on somatostatin-receptor-negative breast cancers. One potential indirect mechanism of somatostatin analogues under investigation involves reduction of IGF-I bioactivity. In general, IGF-I is a potent mitogen [12, 13] and inhibitor of apoptosis [14]. There is a large body of data to support the view that IGF-I influences breast cancer behavior. Not only is IGF-I a potent breast cancer mitogen *in vitro* [15, 16], but it has been noted that the growth of breast cancer xenografts can be reduced by a blocking antibody to the IGF-I receptor [17] and that the proliferation of human breast cancer xenografts is reduced in hosts that are deficient in IGF-I as a consequence of the "*lit*" mutation [18].

While it has long been recognized that the abnormally high levels of IGF-I seen in acromegaly can be lowered towards normal by somatostatin analogues, it is also true that somatostatin analogues suppress the functioning of the normal growth-hormone/IGF-I axis [19]. This may influence IGF-I-responsive breast cancers. More recent data show that the antiestrogen tamoxifen has a similar suppressive effect on the growth-hormone/IGF-I axis, characterized by inhibition of pituitary growth hormone output [20, 21], reduction of IGF-I serum levels [22], and reduced expression of IGF-I in target organs for metastasis [23]. It has been proposed that these effects of tamoxifen contribute to its antineoplastic action. Interestingly, in breast cancer tissue, IGF-I receptor levels are positively correlated with estrogen receptor levels [24]. Thus, neoplasms identified on the basis of estrogen receptor levels to be likely to respond to antiestrogens are those that are most likely to be most influenced by reductions of IGF bioactivity. Octreotide [25] and antiestrogens [26, 27] may also reduce IGF bioactivity by separate effects on IGF binding proteins.

It has been proposed [28] that a separate rationale for reducing IGF-I levels in the management of breast cancer can be derived from epidemiological evidence that breast cancer incidence is higher and prognosis worse [29-35] in taller as compared to shorter women, when this information is taken in the context of the knowledge that IGF-I level is a determinant of height [36]. This rationale is somewhat controversial: while the association between height and breast cancer risk and outcome is reported to be statistically significant, it nevertheless is modest in magnitude.

BASIS FOR PROPOSED CLINICAL TRIALS

While preclinical models demonstrate antiproliferative activity of somatostatin analogues in experimental breast cancer, such activity is generally not greater in magnitude than that of endocrine therapies already in clinical use. Therefore, there has been little motivation for randomized clinical trials to compare somatostatin analogues as single agents to other approved endocrine therapies in the first-line treatment of breast cancer. There have been some uncontrolled studies suggesting that octreotide treatment can be

useful in salvage therapy of patients who failed prior therapies [37], but this has not been studied in a formal randomized fashion, and the response rates in this setting are not greater than 20 percent.

However, recent experimental results demonstrate greater antineoplastic activity of tamoxifen combined with octreotide than of single-agent tamoxifen or single-agent octreotide [38]. Laboratory research provides at least two plausible mechanisms underlying this observation. First, it is possible that any direct effect of octreotide on breast cancer is amplified in the presence of antiestrogens, as it has been observed that the antiproliferative effects of octreotide are attenuated in the presence of estradiol. Second, in the context of the data that both tamoxifen [22] and octreotide [19] have actions that would be expected to reduce IGF-I bioactivity, there is laboratory [39] and clinical [40] evidence that such reduction is greater when the two agents are co-administered than when they are given individually. These rationales for co-administration of antiestrogens and octreotide are not mutually exclusive.

In view of the preclinical data [38], there is considerable interest in comparing standard tamoxifen therapy to the combination of tamoxifen and octreotide with respect to efficacy and toxicity. Clinical trials to examine this issue will be practical because of the recent availability of a monthly depot formulation of octreotide. One clinical setting for such a trial is in the treatment of patients with previously untreated macroscopic metastatic disease. Another setting is in the adjuvant treatment of breast cancer. This refers to the treatment of apparently disease-free women who may have micrometastatic disease during the post-surgical period, with the objective of reducing the rate of relapse and prolonging disease-free survival. In both the adjuvant and metastatic settings, tamoxifen is known to have beneficial effects, yet there is substantial room for improvement in the efficacy of therapy. Only carefully controlled clinical trials will establish whether the laboratory clues concerning somatostatin analogues reviewed here will translate into improvements in the treatment of breast cancer.

As of January 1997, two clinical trials in this area have been initiated. An international European-based trial is randomizing patients with measurable metastatic breast cancer that has not been previously treated to therapy with either tamoxifen or the tamoxifen -octreotide combination. Clinical endpoints will involve response rate and response duration. A recently activated Canadian trial is carrying out a similar randomized comparison of 800 breast cancer patients, but this trial will be carried out in the post-operative adjuvant setting for women with stage I or stage II breast cancer, with the major clinical endpoint being relapse-free survival. This trial will also examine outcome in the context of the effects of each treatment arm on IGF physiology and the somatostatin receptor status of the tumors. Finally, a 2000 patient adjuvant study similar to the Canadian study but confined to relatively good prognosis stage I breast cancer patients is being planned in the USA. While prior studies have provided data consistent with a favorable toxicity profile for octreotide, these trials will allow for the first time a detailed survey of potential adverse effects (such as cholelithiasis) in a large non-acromegalic, non-neuroendocrine tumor patient population.

Together, these studies will represent one of the largest clinical research programs ever undertaken with a somatostatin analogue. This research program represents an interesting case-study in rapid translation of preclinical data to a clinical trial program, with less than three years elapsing between the *in vivo* preclinical results [38] and the launching of randomized clinical trials. This can be attributed in part to close collaboration between industry, academic clinician-scientists and clinical trials organizations.

The preclinical data focus particular attention on the adjuvant trials, as laboratory studies imply that antineoplastic activity of octreotide is greatest when the tumor burden is small. These trials will not yield clinical outcome data before 2000, but will be followed

with considerable interest in view of the strong clinical need to improve the efficacy of adjuvant therapy for breast cancer. Given the high incidence of this illness, should these trials document a favorable influence of octreotide on clinical endpoints, use of the compound for this new indication would clearly exceed use for current indications such as acromegaly and carcinoid syndrome. This would motivate other studies not only to refine therapy with somatostatin analogues but also to explore other peptide drug candidates in oncology.

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