Enhancement of the Anti-Neoplastic Effects of Tamoxifen by Somatostatin Analogues

Key Words
Tamoxifen
Anti-oestrogenic agents
Breast cancer
Somatostatin analogues
Octreotide
Combination therapy

Abstract
Tamoxifen is useful in the treatment of breast cancer, but its effects in metastatic disease are rarely long term, and development of resistance to the drug is common. In vitro and in vivo data demonstrate anti-neoplastic (anti-proliferative) effects of somatostatin analogues, which may occur via binding to somatostatin receptors on the neoplastic cells, and/or via reductions in insulin-like growth factor-I bioactivity. Moreover, several lines of evidence from in vitro and in vivo studies indicate that the long-acting somatostatin analogue octreotide enhances the anti-neoplastic effects of anti-oestrogenic agents such as tamoxifen. The anti-oestrogen-somatostatin approach appears to have a favourable long-term toxicity profile. Large-scale clinical trials are currently being planned to investigate the efficacy of combined tamoxifen plus octreotide therapy compared to tamoxifen alone in patients with breast cancer.

Background
Tamoxifen is the most widely used compound in breast cancer treatment. The history of its development and introduction into clinical practice has been reviewed elsewhere [1]. The first application of tamoxifen in breast cancer management was in the palliative treatment of metastatic disease. In this setting, the drug clearly had an extremely favourable risk/benefit profile. Dramatic responses to tamoxifen are not rare, and for many patients, long-term control of metastatic proliferation by tamoxifen leads to major improvements in the quality of life. The benefits documented in the metastatic setting justified initial trials of the drug in post-surgical adjuvant treatment. This clinical research showed that, for patients in several major prognostic groups, improvements in disease-free survival and survival resulted from adjuvant tamoxifen therapy. In general, the risk/benefit profile of the drug remains favourable when it is used as post-surgical adjuvant therapy, particularly for post-menopausal patients. There is a low incidence of uterine toxicity, particularly if the drug is given at a dose higher than 20 mg/day. This risk is outweighed by the reduction in risk of breast cancer recurrence, and perhaps by favourable effects on serum lipid profiles and bone density. Adjuvant therapy accounts for most tamoxifen usage in the 1990s. The possibility that tamoxifen will also be useful for breast cancer prevention in certain women at high risk is being addressed in ongoing clinical trials.

While data from clinical trials do not support the opinion that toxicity is a major problem associated with tamoxifen, there remains a serious limitation to tamoxi-
fen therapy. The problem is the limited nature of its efficacy, even in patients with oestrogen-receptor-positive tumours. Although responses to the drug in metastatic disease are common and clinically useful, such responses are rarely long term. The development of tamoxifen resistance and progression of metastatic disease while patients are receiving the drug is commonplace. Similarly, in the adjuvant setting, while it is clear that the risk of developing clinically obvious metastases is significantly decreased in many groups of patients by postoperative tamoxifen treatment, such therapy by no means guarantees that progression of micrometastases will not occur, and failure of adjuvant tamoxifen therapy to prevent development of macrometastatic disease is frequently seen.

Thus, an important research goal is to develop ways to enhance tamoxifen efficacy or delay the emergence of tamoxifen resistance. In this regard, recent preclinical data suggest that it may be beneficial to combine tamoxifen with somatostatin analogues, and several large-scale trials are now planned to determine the clinical relevance of these preclinical results. There are other promising approaches to enhance anti-oestrogen efficacy, but many of these are not presently ready for clinical testing, because they involve novel compounds for which long-term toxicity information is unavailable. The long-term toxicity information is a particularly important issue with respect to proposed novel adjuvant therapies.

Mechanisms of Anti-Neoplastic Activity of Somatostatin Analogues

Somatostatin was originally isolated as a hypothalamic factor that inhibited release of growth hormone (GH) by the pituitary gland. It is now recognised that somatostatin has many functions apart from the inhibition of GH release and that somatostatin receptors are widely distributed beyond the pituitary. In general, the functions of somatostatin are inhibitory: inhibition of GH release, inhibition of gastric acid secretion, inhibition of proliferation, and so on [for a review, see ref. 2]. Therapeutic use of native somatostatin is impractical because of its short serum half-life (about 1 min). Several analogues such as octreotide (SMS 201-995) and RC-160, which have substantially longer serum half-lives and retain bioactivity, have been synthesised. It is now recognised that there are at least five distinct somatostatin receptor subtypes [3]. The specificity of action of various analogues at each type of receptor is the subject of ongoing investigation. Recent data suggest that the anti-proliferative effects of somatostatin are mediated in large part by the type-2 somatostatin receptor [4]. Both octreotide and RC-160 bind to this receptor.

There is substantial literature demonstrating considerable anti-neoplastic activity of somatostatin analogues in many in vitro and in vivo experimental systems [for reviews, see ref. 5, 6]. Increasing information concerning mechanisms of action has emerged over the past decade. Two mechanisms have been proposed, and it is important to emphasise that they are not mutually exclusive.

Direct Mechanism

The 'direct' mechanism of anti-neoplastic action refers to inhibition of proliferation and/or induction of apoptosis, which arise as a consequence of a somatostatin analogue binding to a somatostatin receptor on the target neoplastic cell. Although somatostatin-receptor-negative cells clearly cannot be influenced by the direct mechanism, recent data show that a large proportion of breast (and other) cancers are in fact somatostatin-receptor positive [7]. Characterisation of the molecular basis of the signal transduction pathways associated with each of the five somatostatin receptor subtypes is ongoing. There is evidence that one important signal transduction pathway involves up-regulation of phosphotyrosine phosphatase activity following binding of somatostatin or a somatostatin analogue to somatostatin receptors [8]. This activity is the opposite of that associated with tyrosine-kinase-type peptide growth factor receptors, and therefore it is not unexpected that inhibition of proliferation would be a consequence of up-regulation of this activity.

Indirect Mechanism

The 'indirect' mechanism of action refers to inhibition of proliferation arising as a consequence of the systemic effects of somatostatin analogues, rather than binding of somatostatin analogues to neoplastic cells. Even somatostatin-receptor-negative neoplasms might be inhibited by indirect mechanisms. Several indirect anti-neoplastic actions of somatostatin analogues have been proposed. The indirect mechanism that has received the most attention to date concerns the effect of somatostatin analogues on systemic insulin-like growth factor I (IGF-1) physiology. IGF-1 is an important mitogen for many neoplastic cell types [9, 10], and also inhibits apoptosis [11] and encourages cell mobility [12]. This indirect mechanism of somatostatin analogue action may also involve suppression of angiogenesis, as there are data to suggest that IGF-1 facilitates endothelial cell proliferation [13]. It is well established that somatostatin analogues lower acrome-
gallic GH and IGF-1 levels towards normal. It has also been shown that these agents can lower normal GH and IGF-1 levels [14]. The dose-response characteristics here differ from the acromegalic situation, as a result of physiological efforts at counter-regulation, for example, by increased GH-releasing hormone secretion. The concept proposed is that a modest GH/IGF-1 deficiency in an adult might be associated with substantial inhibition of IGF-1-responsive neoplasms, with only minor symptoms for the patient. An implicit assumption is that a reduction in serum IGF-1 level correlates with changes in tissue IGF-1 bioactivity. There are in vivo experimental systems in which a somatostatin analogue has been found to inhibit the growth of a somatostatin-receptor-negative, IGF-1-receptor-positive neoplasm [15].

In the case of breast cancer, it has been suggested [16, 17] that a rationale for reducing IGF-1 levels can be derived from the epidemiological evidence that breast cancer incidence is higher [18–23] and prognosis worse [18, 19, 21] in taller women, and that height is related in part to the IGF-1 level, which varies considerably between normal individuals [24]. It has also been shown that human breast cancer xenograft growth is reduced in mice that are genetically IGF-1 deficient relative to controls, despite equal oestrogen supplementation [25]. This line of reasoning is speculative, but does deserve study, particularly in the light of separate supportive data from skeletal morphometry studies [26].

**Rationale for Co-Administration of Anti-Oestrogens and Somatostatin Analogues**

**With Respect to the Proposed Direct Mechanism of Action of Somatostatin Analogues**

It was demonstrated in an early report [27], and since confirmed, that a direct anti-neoplastic effect of octreotide on oestrogen-receptor-positive breast cancer cells can be detected using in vitro tissue culture systems. Interestingly, the anti-proliferative effect of octreotide was clearly maximised in the absence of oestrogens [27]. The molecular basis for the attenuation of the anti-proliferative effect of octreotide by oestrogens is uncharacterised, but this observation provides a rationale for co-administering an anti-oestrogen with octreotide. Perhaps consistent with this result is the observation that the anti-neoplastic action of the somatostatin analogue RC-160 in the MXT breast tumour model is enhanced by co-administration of a luteinising-hormone-releasing-hormone analogue, which lowers oestradiol levels [28].

**With Respect to the Proposed Indirect Mechanism of Action of Somatostatin Analogues**

A recently characterised effect of anti-oestrogen therapy in both clinical [16, 29] and laboratory [30, 31] studies is suppression of IGF-1 gene expression and serum IGF-1 levels. These were somewhat unexpected observations, as inhibition of IGF-1 gene expression was not obviously an ‘anti-oestrogenic’ effect. There are now data that suggest that this inhibitory action is related in part to inhibition of pituitary GH output [32, 33], and in part to direct inhibition of IGF-1 gene expression in various target organs of metastasis [31]. It has been shown, in short-term experiments carried out in rats [34], that combined octreotide and tamoxifen suppresses serum IGF-1 levels and IGF-1 gene expression more potently than either agent alone. This demonstrates a potentially relevant biological interaction, and is compatible with an additive anti-neoplastic effect. Furthermore, recent clinical data demonstrate an enhanced suppression of serum IGF-1 levels in patients receiving combined octreotide and tamoxifen relative to those receiving tamoxifen alone [35]. However, this result cannot be extrapolated to conclusions about efficacy, as the hypothesis that a decline in serum IGF-1 is a surrogate end-point related to efficacy is unproven.

**Preclinical Results of Combined Somatostatin and Anti-Oestrogen Therapy**

Combined octreotide-tamoxifen therapy has been studied using the DMBA-induced rat mammary tumour model [36]. Despite some limitations, this model has proved reliable in predicting clinical activity of hormonal therapies for breast cancer [37]. The model detects the anti-neoplastic activity of tamoxifen, which is greater than that of octreotide. However, the incidence and growth of DMBA-induced tumours is significantly reduced in animals co-treated with both agents relative to either agent alone. Furthermore, we were able to detect enhancement of the inhibitory effect of oophorectomy on growth of DMBA-induced tumours [36]. These neoplasms reproducibly regress following oophorectomy, but later regrow. This phenomenon may have features in common with certain forms of resistance to hormonal therapy seen clinically. When octreotide was administered post-oophorectomy, the incidence of regrowth of tumours resistant to endocrine treatment was greatly reduced.

In all experimental systems, a consistent observation has been that the response to octreotide-containing regimes is greater in smaller than in larger neoplasms. The basis for this is unclear. It is consistent with the proposal
that at least a part of the anti-neoplastic activity is an antiangiogenic one. It is also possible that with neoplastic progression, tumours become less dependent on exogenous IGF-1 and/or lose a somatostatin receptor-positive phenotype, either or both of which would reduce responsivity to somatostatin analogues. This fact suggests that somatostatin analogues would be more effective in the adjuvant setting than in the management of metastatic disease.

**Clinical Results of Combined Somatostatin and Anti-Oestrogen Therapy**

Single-agent activity of somatostatin analogues in advanced, heavily treated breast cancer is very low, despite some isolated reports of disease stabilisation. There are no substantial data regarding the use of any somatostatin analogue as first-line therapy, and such trials are not anticipated, because preclinical data do not suggest that somatostatin analogues as single agents have greater activity than currently used hormonal therapies. Rather, they support the hypothesis that the efficacy of anti-oestrogen therapy may be enhanced by co-administration of somatostatin analogues.

A recent trial at the North Central Oncology Group and the Mayo Clinic attempted to compare the efficacies of octreotide, tamoxifen and their combination as first-line therapy for metastatic breast cancer. The final outcome analysis of this trial is not yet available, as patients remain on protocol treatment at this time. Analysis of blood samples obtained in a subset of trial participants, however, has demonstrated that the treatment-related decline in serum IGF-1 levels was significantly greater in the combination group than in the tamoxifen only group [35].

**Conclusions**

There is a clear clinical need to improve the efficacy of anti-oestrogen therapy. Co-administration of a somatostatin analogue is one of several approaches suggested in this regard. The preclinical evidence of improved efficacy in the DMBA model is clear, and the development of a depot formulation of octreotide, together with the established long-term safety profile of this agent, makes clinical trials feasible. Planned trials will involve randomisation to tamoxifen versus tamoxifen plus octreotide. In addition to the standard clinical end-points, these trials will have an important 'translational' research component, which will generate data regarding, for example, the effect of each treatment arm on IGF-1 physiology, and the relationship of this to outcome.

**References**


