Role of somatostatin analogs in the clinical management of non-neuroendocrine solid tumors

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The somatostatin analogs octreotide, lanreotide and RC-160 (vapreotide) are known to have direct and indirect antitumor effects. Direct effects include the arrest of tumor growth and stimulation of apoptosis, resulting in tumor shrinkage. Indirect antiproliferative effects may occur through antiangiogenesis, immunomodulatory effects and the suppression of tumor-stimulating growth factors. With a safety profile of somatostatin analogs established over 20 years of clinical use in the treatment of neuroendocrine tumors, somatostatin analogs are attractive therapeutic options for patients with non-neuroendocrine tumors. In early clinical trials of somatostatin analogs, however, some cancer patients responded well, while others showed a lack of benefit. This variability in clinical response may reflect the selective binding affinities of octreotide, lanreotide and RC-160, which bind with high affinity to just two of the five different somatostatin receptor subtypes. Treatment response may therefore depend on the specific receptor subtype(s) present in the tumor, the relative proportion of receptor(s) expressed on the tumor cell surface and the absolute quantity of each receptor subtype. Greater understanding of the role of somatostatin receptors, their binding affinities and modes of action has led to increased research into the use of somatostatin analogs, particularly octreotide, in cancer treatment as monotherapies, in combination with hormonal treatments and cytotoxic therapies, and in both adjuvant and neoadjuvant settings. A review of the literature suggests that the antitumor potential of somatostatin analogs should be investigated further and additional studies might determine how these analogs can best be used to improve the treatment of patients with non-neuroendocrine tumors. *Anti-Cancer Drugs* 17:601–608 © 2006 Lippincott Williams & Wilkins.

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Introduction

Somatostatin analogs are commonly used for the symptomatic treatment of gastroenteropancreatic neuroendocrine tumors, such as those of the carcinoid or islet cell types [1]. These tumors are characterized by the hypersecretion of hormone peptides and amines, which may cause diverse symptom complexes ranging from hypoglycemic syndromes (in patients with insulinomas) [2], to extensive watery diarrhea, hypokalemia and achlorhydria [in patients with vasoactive intestinal peptide (VIP)-secreting tumors] [3]. The effectiveness of the somatostatin analog octreotide in controlling these symptoms is well documented [4–13]. Nevertheless, the response in patients with islet cell tumors has frequently been found to be transitory (median duration 2.5 months) and not of substantive benefit [14]. Along with more than 10 years of clinical experience, however, octreotide also has a good safety and tolerability profile for both short-term and long-term treatment of patients with cancer [6,15–17].

While octreotide therapy ameliorates symptoms in up to 70% of patients with neuroendocrine tumors and is also associated with antiproliferative activities that shrink (or, more commonly, stabilize growth in) tumors in up to 50% of patients [13,18], there is, however, no consensus as to whether survival rate improves even if tumor progression is slowed down. In one trial, survival in the cohort of patients receiving octreotide therapy was considered to be substantially longer than that in patients receiving chemotherapy [19]. A review of three prospective clinical trials in which somatostatin analogs were used either alone, or in combination with interferon α, to treat disseminated midgut carcinoid tumors, however, highlights the varying responses found in different clinical settings. The authors conclude that although the antiproliferation rate of somatostatin analogs may be enhanced by combination therapy, only by carrying out large-scale multicenter clinical trials would sufficient data be accumulated to help one assess the impact of this treatment on survival [20].

The antiproliferative effects of octreotide do not, however, appear limited to neuroendocrine tumors. Preliminary clinical studies of non-neuroendocrine tumors demonstrate that octreotide can inhibit the growth

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of a variety of tumors, such as breast, stomach, colon and rectal cancers [9,21–24]. Studies have identified several direct and indirect mechanisms that may contribute to the anticancer activity of somatostatin analogs. Direct antitumor activities are mediated through somatostatin receptors, and include antimitotic and apoptotic effects. Indirect antitumor effects are independent of tumor cell membrane-bound somatostatin receptors, and include abrogation of growth factor-stimulated tumor growth and antiangiogenic actions. A growing body of experimental evidence supports these antiproliferative effects of somatostatin analogs. Evidence is also emerging about how somatostatin analogs may be used to enhance the efficacy of other treatment approaches without significantly worsening toxicity. It also seems that the antiproliferative activity of somatostatin analogs, and particularly symptom relief, can be enhanced, or even induced, by combination with other biological agents, especially interferon-α. The combination of lanreotide with interferon-α has been shown to have a major impact on clinical symptoms in advanced medullary thyroid carcinoma with the added advantage of being much better tolerated than interferon-α monotherapy [25]. This paper will examine whether the results from these experimental studies can be translated into clinically useful information on the antineoplastic activity by reviewing the available clinical data on the antitumor effects of somatostatin analogs.

Somatostatin receptor subtypes in tumor cells

Most actions of somatostatin and the synthetic somatostatin analogs are mediated through five receptor subtypes ($sst_{1–5}$). The two active forms of natural somatostatin, somatostatin-14 and somatostatin-28, have comparable binding affinity for each of the five identified and cloned receptor subtypes. Naturally occurring somatostatin and the synthetic somatostatin analogs, such as octreotide, however, have differing affinities for each receptor subtype. (Table 1) [26,27]. The effects of octreotide are mediated through interaction with sst_2 and sst_5 (and to a lesser extent sst_3; Table 1). By comparison, the novel cyclohexapeptide SOM230 has a wider range of binding affinities than octreotide (Table 1).

Variations in binding affinities appear to translate into differences in biological and clinical activities. For example, octreotide is 45 times more potent for inhibiting growth hormone secretion and 11 times more potent for inhibiting glucagon secretion than natural somatostatin [28]. This is useful for the treatment of conditions such as acromegaly and for the symptoms of neuroendocrine tumors, in which octreotide is widely used. Differences in binding affinities also exists among individual somatostatin analogs, which also translate into differing biological activities between these synthetic agents.

Expression of the receptor subtypes varies depending on the target tissue and, in some instances, on whether the tissue is malignant or benign. The various sst subtypes present in some nonendocrine tumors are summarized in Table 2 [29]. It should be noted that sst-expressing tumors frequently contain two or more sst subtypes. Early studies found that somatostatin receptors were preferentially expressed in well-differentiated tumors compared with less differentiated tumors [30,31]. More recently, it has been found that some advanced tumors lose particular receptor subtypes while retaining others [32].

In recent years, a number of investigators have discovered that sst subtypes might form homo/heterodimers to create novel receptors with different functional characteristics [33]. Such discoveries are further stimulating interest in somatostatin analogs as antitumor agents, expanding the range of tumors an individual analog might affect and potentially increasing the array of actions initiated when analogs bind to the receptors on a tumor cell surface. These studies also suggest that a synthetic somatostatin analog with high affinity across a wider spectrum of somatostatin receptor subtypes (e.g. SOM230, a molecule in development by Novartis Oncology) may provide greater clinical benefit than those with affinity for just one or two subtypes.

Somatostatin analogs as potential antitumor agents: mechanisms of action

Somatostatin analogs exert antiproliferative actions on a variety of normal and malignant cells [34]. Although many of these activities are mediated through somatostatin receptors, somatostatin analogs have been shown to inhibit the growth of Swarm chondrosarcomas, an experimental tumor model that is devoid of these receptors [35,36]. This suggests that somatostatin

Table 1 Receptor binding affinities of 'natural' somatostatin, the synthetic analog octreotide and the novel cyclohexapeptide SOM230

	sst_1	sst_2	sst_3	sst_4	sst_5
Natural somatostatin-14	0.93 ± 0.12	0.15 ± 0.02	0.56 ± 0.17	1.5 ± 0.4	0.29 ± 0.04
Octreotide	280 ± 80	0.38 ± 0.08	7.1 ± 1.4	>1000	6.3 ± 1.0
Lanreotide	180 ± 20	0.54 ± 0.08	14 ± 9	230 ± 40	17 ± 5
SOM230	9.3 ± 0.1	1.0 ± 0.1	1.5 ± 0.3	>1000	0.16 ± 0.01

Results are expressed as mean ± SEM IC_{50} values (nmol/l) (adapted from Bruns *et al.* [26]).
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Table 2 Summary of the various sst subtypes present in some nonendocrine tumors

	sst_1	sst_2	sst_3	sst_4	sst_5
Pancreatic	−/+	−/+	+		+
Colon	−	−/+	−/+	−/+	+
Breast	−/+	+	−/+		
Prostatic	+	−/+	−		+
Ovarian	+	+	+		+
Renal cell		+			+
Small cell lung cancer	+	+			
Thymoma	+	+	+		
Astrocytoma		+			

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analogs exert antitumor effects by both direct (via somatostatin receptors) and indirect mechanisms.

Direct antiproliferative effects

The direct antitumor actions of somatostatin analogs usually arrest tumor growth or stimulate apoptosis (programmed cell death), which effectively halts growth and may reduce the size of the tumor. The exact antitumor mechanism initiated by a somatostatin analog depends on the tumor cell type and the receptor subtype to which it binds.

Growth inhibition is reported to occur through the interaction of somatostatin analogs with sst_2 [37,38] and sst_5 [39], which results in inhibition of mitosis and, thus, arrest of the cell cycle [40]. The loss of sst_2 expression in some human adenocarcinomas [32] also results in the loss of regulation of cell proliferation. Therefore, sst_2 loss may help tumor growth and could explain the lack of therapeutic effect of somatostatin analogs in such tumors.

Evidence suggests that somatostatin analogs can induce apoptosis through two separate mechanisms–interaction with sst_3 [41] and inhibition of the potent antiapoptotic hormone, insulin-like growth factor-1 (IGF-1) [27]. The apoptotic actions of somatostatin analogs appear to translate to the clinical setting, as shown by a clinical study using high-dose somatostatin analog in which half the patients experienced an increase in apoptotic index (AI: percentage of apoptotic cells) in biopsies taken 6 months after starting treatment [42].

Indirect actions

Somatostatin analogs exert indirect antiproliferative effects through several mechanisms, including antiangiogenesis. Angiogenesis, the formation of new blood vessels from the existing capillary network, is essential for tumor growth and for the dissemination of metastases. By limiting the blood supply, tumor growth can be effectively controlled. This has been demonstrated in patients with rectal cancer treated with bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), one of the principal proangiogenic factors [43].

The association between VEGF and angiogenesis is further strengthened by work showing that one of the known VEGF receptor subtypes kdr (VEGFR2) is not present on normal resting human endothelial cells, but is uniquely upregulated during the angiogenic switch (the conversion of resting endothelium to a proliferative phenotype) [44]. In experimental models, octreotide exhibits strong antiangiogenic effects [45–48], possibly through the inhibition of VEGF. Preliminary clinical studies further support the importance of antiangiogenic activities and VEGF inhibition in successful octreotide treatment of patients with hepatocellular carcinoma, which is considered hypervascular [49,50]. In clinical studies, a response to octreotide treatment, resulting in significantly lower levels of VEGF than at baseline, was correlated with survival ($P = 0.01$) [49].

Furthermore, it should be noted that normal endothelial cells are devoid of sst_2 receptors and that sst_2 expression on endothelial cells uniquely appears as they proliferate to form new blood vessels. This provides an opportunity for octreotide, with its high affinity for sst_2 (Table 1), to target and inhibit developing blood vessels, either alone or in combination with cytotoxic or cytostatic therapies. As such, octreotide may inhibit angiogenesis through two mechanisms: (a) directly by binding to sst_2 to block cell division and proliferation of the vascular endothelium, and (b) indirectly by blocking the production of endothelial growth factors.

Another indirect mechanism by which somatostatin analogs might operate is through immunomodulatory effects. Preliminary evidence suggests that somatostatin analogs enhance elements of the immune system that may have antitumor effects. For example, these analogs have been shown to affect natural killer cell activity in man [51]. However, evidence remains scarce that this is clinically significant and that it contributes to the antitumor activity of the somatostatin analogs.

Somatostatin analogs also suppress a number of factors that stimulate tumor growth. For example, somatostatin analog suppression of growth hormone release from the pituitary gland results in the inhibition of hepatic production of IGF-1 [41,52]. As noted previously, a reduction in IGF-1 production induces apoptosis in tumor cells. This mechanism was proven clinically effective when octreotide was used to treat IGF-1-dependent tumors, such as growth hormone-secreting adenomas [53], and, to a lesser extent, breast, lung and prostate tumors [54,55]. This is the suggested mechanism for the improved survival rate and clinical response in stage D3 androgen ablation refractory prostate cancer patients,

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nonresponsive to salvage chemotherapy, achieved by combining lanreotide with a combination of dexamethasone and triptorelin. [56] A phase I trial of a long-acting version of octreotide, in metastatic osteosarcoma, however, showed that despite successfully reduced IGF-1 levels, tumor progression was not similarly stabilized or reduced and in fact often worsened [57].

Receptor saturation and plasma drug levels versus antiproliferative effects

In several studies, the response of a variety of cells to octreotide exposure produces a biphasic dose–response curve [46,47,58]. This implies that overdosing or underdosing of somatostatin analogs may result in suboptimal antitumor activity. In general, the K_d (the concentration of drug required to achieve half maximal receptor saturation) of octreotide and other somatostatin analogs is about 1 nmol/l. Octreotide blood levels after administration of 30 mg/month of octreotide in its sustained release form (long-acting repeatable) produces blood levels of about 5000 pg/ml (0.5 ng/ml), which implies that the negative results of clinical studies assessing tumor response may be due to too little drug being administered to achieve optimal receptor saturation. Conversely, other investigators used doses of octreotide up to 8 mg/day and doses of lanreotide greater than 10 mg/day [59]. These studies also failed to improve the antitumor effect of these analogs. At the doses used in these studies, however, one would expect from the in-vitro studies cited above that these authors had exceeded the narrow therapeutic window of these compounds. To date, no tumor-response study has monitored plasma levels of a somatostatin analog to ensure that optimal therapeutic blood levels of the drug were achieved, but not exceeded. Likewise, the efficacy of somatostatin analogs depend on receptor expression patterns of tumors, but these are rarely assessed, although there is evidence that selective treatment has more beneficial outcome. Slow-release lanreotide resulted in a long-lasting antiproliferative effect on metastatic tumor cells in the liver of a patient who had been selected for treatment with the somatostatin analog after immunohistochemical identification of the expression of the somatostatin receptors subsets, sst_1, sst_2 and sst_5 on the tumor cell surface [60].

Somatostatin analogs in the oncology clinic

Early binding studies indicated that many human tumors express somatostatin receptors. Following the promising results from animal studies, high expectations were placed on clinical trials of somatostatin analogs in cancer patients. The results of clinical studies, however, have been mixed. For example, in a randomized, controlled trial in 58 patients with advanced hepatocellular carcinoma, octreotide-treated patients achieved a significant survival benefit (median survival 13 months compared with 4 months in the control arm; $P = 0.002$, log-rank test) together with an overall improvement in the quality of life [61]. By contrast, other studies with somatostatin analogs were disappointing, demonstrating neither an antitumor effect nor an increase in median survival rate [62]. Many of these clinical trials, however, did not stratify patients into treatment arms on the basis of the histologic presence of sst_2 or the clinical expression (a positive OctreoScan, MallincKrodt Medical, St Louis, Missouri, USA) of sst_2 in the tumors. Furthermore, most of these trials failed to optimize the administered drug dose to ensure that adequate receptor saturation was achieved.

Despite the mixed results of early clinical trials, researchers have persisted in evaluating the antiproliferative potential of somatostatin analogs. The appeal of using somatostatin analogs in cancer therapy includes considerable, if sporadic, antitumor activity and a successful history in the symptomatic management of neuroendocrine tumors. In addition, the well-established safety and tolerability profiles of these analogs suggest that treatment should not add substantially to the toxicity of current chemotherapy regimens. Octreotide, which has been used in clinical practice for approximately 20 years, is generally considered to be well tolerated with a good safety profile for both short-term and long-term treatment [63]. Gastrointestinal complaints are the most common side-effects of long-acting analog therapy, although these are generally mild and transient, and improve with continued treatment in most patients. Other side-effects, such as disturbed glucose metabolism and cholelithiasis, are relatively rare and are not considered to be highly clinically relevant in the face of a widespread tumor. Studies are ongoing to determine the optimal dosing levels of somatostatin analogs and to evaluate the combination of these analogs with existing treatment regimens [64–66]. Monotherapy advanced tumors that are resistant to other therapies.

A number of clinical studies have indicated that long-acting somatostatin analogs improve survival and performance status in patients with inoperable hepatocellular carcinoma. For example, a randomized, controlled study with octreotide resulted in significantly increased survival in patients with advanced hepatocellular carcinoma (compared with no treatment) [67]. The median survival was 31 weeks in the 15 patients receiving octreotide and 16 weeks in the 13 patients who received no treatment ($P = 0.037$). All patients in the study were positive for liver tumor somatostatin receptors (by OctreoScan scintigraphy). Further studies are required to identify specific patient subgroups, such as those with less advanced disease or particular etiologies, who will derive the most benefit from treatment. Studies are also needed to determine whether the addition of somatostatin analogs to established treatment regimens, such as

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surgery and cytotoxic chemotherapy, improves survival and quality of life in patients with hepatocellular carcinoma.

The results of studies in tumor models suggest that octreotide monotherapy may be of value in the treatment of advanced pancreatic cancer [68]. An initial small clinical study showed that low-dose (300 μg/day) octreotide [69] is not effective in patients with advanced pancreatic cancer. Another study in a similar patient population, however, indicated that a high-dose (2000 μg octreotide three times daily) may improve survival and quality of life compared with supportive care [70]. In this study, the median survival in patients receiving high-dose octreotide was 6 months, compared with 3 months in patients receiving low-dose octreotide. Additional studies are required to confirm these findings and to identify the optimal dose levels.

Combination with hormonal therapies

A number of cancers, such as breast and prostate cancer, are known to be regulated by hormones, growth factors and other trophic factors. Somatostatin analogs generally inhibit hormone secretion and reduce the proliferation and survival of cells. They inhibit both endocrine secretion (e.g. growth hormone, insulin, glucagons, prolactin, gastrin, cholecystokinin, VIP and secretin) and exocrine secretion (e.g. gastric acid, intestinal fluid and pancreatic enzymes) [71,72]. Somatostatin analogs are good candidates for clinical trials in breast cancer patients because at least 85–90% of human breast tumors are somatostatin receptor positive [73]. Octreotide has demonstrated antiproliferative effects on human breast cancer cells in experimental studies [73]. A number of authors have shown that octreotide exerts antiproliferative effects against breast cancer cells with the greatest effects in cells that express sst_2 [47,74]. In addition, there is evidence that exposure of sst_2-expressing cells to octreotide may upregulate the cells' estrogen receptor and progesterone receptor content, which increases their sensitivity to hormonal manipulation [75,76]. In an experimental study, the combination of octreotide with either an antiestrogen (tamoxifen) or an oophorectomy enhanced the inhibition of growth in 7,12-dimethylbenz [*a*]anthracene-induced mammary tumors in rats that were sst_2 positive [75]. More importantly, the effects of therapy persisted well beyond the known clearance of octreotide, implying that the drug not only had direct antitumor effects, but that it might have inhibited the angiogenic response, which resulted in the delayed revascularization of the tumor after the end of the octreotide administration.

Somatostatin analogs inhibit the secretion of prolactin, growth hormone and IGF-1, and thus may inhibit the development of breast cancer indirectly. As estrogens are able to counteract the antitumor effects of such treatments, the combination of tamoxifen, a somatostatin analog (octreotide) and an antiprolactin agent (quinagolide) may provide additional clinical benefits compared with antiestrogen monotherapy. In one study, 22 postmenopausal patients with metastatic breast cancer were randomized to receive either tamoxifen 40 mg/day or a combination of tamoxifen 40 mg/day, antiprolactin 75 μg and octreotide 0.2 mg subcutaneously three times a day as first-line therapy [77]. Fifty-five percent of patients receiving the combination therapy achieved an objective response compared with 36% in the tamoxifen-only arm. Combination therapy also increased median time to progression compared with that in patients treated with tamoxifen alone (84 versus 33 weeks, respectively), although there was no difference in overall post-relapse survival between the two treatment arms.

Over the past decade, it has become apparent that primary liver cancers express estrogen hormone receptors and that estrogen plays a role in the pathogenesis of hepatocellular carcinoma [78–80]. It is also known that 41% of primary liver cancers express sst [81]. Consequently, studies are now investigating a combination of antiestrogen and somatostatin analog for the treatment of liver cancer. In one randomized, controlled study in patients with advanced liver cancer, patients who received octreotide (0.6 mg/day intravenously) in combination with tamoxifen for 3 months had significantly increased survival rates at 6 months, 1 year and 2 years ($P < 0.01$ for each time point), prolonged survival time, and fewer side-effects than those who received standard chemotherapy (5-fluorouracil and mitomycin C) [82]. This suggests that antihormonal therapy is an effective regimen for primary liver cancer.

In patients with prostate cancer, one study showed that the addition of octreotide to a complete androgen blockade enhanced the rate, quality, and duration of symptom-free treatment response [83]. Patients receiving combination treatment reported 17-month symptom-free survival, whereas those on complete androgen blockade alone had 12-month symptom-free survival. As with the breast cancer study [77], the total survival was similar in the two groups.

These studies suggest that the addition of somatostatin analogs to hormone therapy produces only modest clinical benefits in breast and prostate cancer. This may be due to the range of somatostatin receptor subtypes expressed by these tumor cells. Breast and prostate tumors express subtypes sst_1, sst_2, sst_3 and sst_5, whereas both octreotide and lanreotide only have high-affinity binding for sst_2 (Table 1). Studies to identify novel analogs with high-affinity binding to a greater range of the receptor subtypes are ongoing with the expectation that they will

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show greater clinical benefit than currently available analogs.

Combinations with surgery, chemotherapy and radiotherapy

Preclinical data suggest that there might be useful interactions between octreotide and other antineoplastic agents [84]. In experimental cancer models, the dose-dependent antiproliferative effects of mitomycin C, doxorubicin and taxol were synergistically enhanced by octreotide. Other studies have shown the combination of octreotide with antimitotic drugs, such as vincristine, methotrexate, fluorouracil and suramin, resulted in slightly additive actions [85]. These studies have led to the suggestion that the actions of octreotide, including its antimitotic activities, could ameliorate the resistance to cytostatic drugs without altering drug sensitivity. Somatostatin analogs have already proven useful for arresting bleeding, preventing rebleeding and reducing mortality in various surgical conditions. Established effects in managing chemotherapy-induced diarrhea [86] may also translate to managing dose-limiting radiotherapy-induced side-effects.

Octreotide has been shown to inhibit the growth of colorectal tumors *in vitro* and *in vivo* [87,88], which could, in part, be related to its antiangiogenic properties. Patients with operable colorectal cancer were given octreotide for 2 weeks before surgery, which led to a significant reduction in the expression of VEGF (a key angiogenic growth factor) [89]. The potential benefits of such antiangiogenic activity include a presurgical reduction in tumor volume, reduction in tumor viability and reduction in tumor vascularization. Thus, during surgery, seeding of tumor cells and bleeding would be minimized.

Many antitumor activities of somatostatin analogs have potential application in combination with chemotherapy. Combining agents with differing modes of action is a recognized therapeutic tool for increasing efficacy and preventing drug resistance. Experimental studies demonstrate that octreotide shows antiangiogenic activity and inhibits tumor growth in human hepatocellular carcinoma xenografts [90]. Clinical studies indicate that octreotide also exerts clinical antiproliferative actions on hepatocellular carcinoma through its antiangiogenic effects [49]. As a result, it has been suggested that somatostatin analog therapy may enhance the efficacy and reduce the hepatotoxicity of cytotoxic chemotherapy in an adjuvant or neoadjuvant setting. Further studies, however, are warranted.

Promising areas for future research

Now that the antitumor activity of somatostatin analogs has been clinically demonstrated in some select non-neuroendocrine tumors, these analogs are being tested in an increasing variety of tumor types. The high incidence of somatostatin receptor subtypes sst_1, sst_2 and sst_3 in human cervical and endometrial cancers [91,92] indicates that these cancers are a likely target for treatment with high-affinity, multiligand binding analogs such as the novel agent SOM230 [26]. The expression of somatostatin receptors (particularly sst_1 and sst_2) is widespread in soft tissue sarcomas [93], indicating that somatostatin analogs may be of therapeutic value in these tumors. A study in patients with lymphoproliferative disorders indicated that octreotide is effective and well tolerated in these disorders [94]. Further studies are necessary in these and other tumor types to optimize therapy and to identify patients who may benefit from an improvement in their quality of life, if only for a short duration, by the addition of somatostatin analogs to their current therapy.

Summary

Current in-vitro and in-vivo evidence suggests a role for somatostatin analogs as adjunctive or combination therapy in the treatment of solid tumors. To date, evidence derives largely from clinical studies of octreotide, some of which have demonstrated significant benefits. Novel agents with high-affinity binding across a range of somatostatin receptor subtypes are under investigation to establish their clinical potential.

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