The clinical role of somatostatin analogues as antineoplastic agents: much ado about nothing?

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Received 20 June 2001; revised 17 November 2001; accepted 19 December 2001

Background: Somatostatin (SST) analogues represent a novel approach for the treatment of certain cancers. The objective of this article is to summarise the current knowledge on SST analogues in the treatment of cancer patients.

Methods: Computerised (Medline) and manual searches were performed to identify publications on clinical trials published in the English-speaking literature between 1966 and 2000. Information abstracted included patients’ pre-treatment status, histology, SST receptor (SSTR) evaluation, type of SST analogue, application schedule and dose, duration of treatment, side-effects, response criteria applied (i.e. WHO response criteria, biochemical criteria or symptomatic investigations) and survival.

Results: Our search disclosed 22 case reports, five phase I and 47 phase II trials, and eight randomised clinical trials using SST analogues (octreotide, lanreotide and vapreotide) as antineoplastic agents. With regard to the phase II trials, conflicting results have been demonstrated in almost all tumour entities investigated. The few randomised studies published so far have shown an impact on survival in patients with hepatocellular cancer, while the effect attributed to treatment in patients with gastrointestinal adenocarcinomas might well have been due to an exceptionally short survival in the control group. There appears to be evidence that SST analogues are able to enhance the therapeutic effects of hormonal intervention in patients with breast cancer, prostate cancer and probably pancreatic cancer. Interpretation of the findings, however, is complicated by the fact that patients were heavily pre-treated in some studies and response criteria have not been uniformly applied. In addition, most studies have not been designed to distinguish between receptor-mediated (direct) and indirect effects of SST analogues in tumour patients.

Conclusions: According to the results obtained so far, there can be no doubt about the wide therapeutic index and the high efficacy of SST analogues in the symptomatic management of neuroendocrine tumours. Apart from these indications, the data do not justify recommendation of SST analogues as antineoplastic agents outside of clinical trials, as the optimal dose and schedule of application for antineoplastic activity has not been defined for currently used agents. Carefully designed clinical trials including investigation of SSTR status before treatment, evaluation of an indirect mechanism of SST analogues, and assessment of optimal combination of hormone therapy and chemotherapy with SST analogues are clearly needed in the near future.

Key words: anticancer therapy, clinical trials, somatostatin analogues

Introduction

Somatostatin (SST) was isolated and characterised in 1973 in the laboratory of Guillemin at the Salk Institute [1] following the observations made by Krulich and co-workers [2] during a search for a growth hormone-releasing factor. Following the identification and purification of SST-14, precursor forms of greater molecular weight were subsequently recognised [3–5], such as SST-28, or prosomatostatin, which is a 28 amino acid polypeptide with SST-14 making up the C-terminus [3], while preprosomatostatins are even larger precursor forms of 120 or more amino acids, with SST-28 located at the C-terminus [4]. While all of these forms exert biological activity, they differ markedly in their relative potency [6].

SST has been identified by a variety of immunocytochemical and radioimmunoassay techniques in multiple sites throughout the nervous system, including the cerebral cortex, cerebellum, hypothalamus, the pituitary infundibular process,
pineal gland and spinal cord [4, 7, 8]. While the greatest amounts of SST have been found in the stomach and pancreas, the peptide has also been demonstrated in the duodenum, the jejunum, the ileum and the colon [3, 4, 7]. More than 90% of SST immunoreactivity in the human gut is located within mucosal endocrine cells, the so-called D cells [4, 8].

Native SST is characterised as an inhibitory peptide with exocrine, endocrine, paracrine and autocrine activity [4]. The general inhibitory function of SST is wide ranging and affects a number of organ systems, and it has thus been characterised as the universal endocrine off-switch [4–6]. It inhibits the release of growth hormone and all known gastrointestinal hormones [3–8], but also gastric acid secretion and gastric motility, intestinal absorption, pancreatic bicarbonate and enzyme secretion, and selectively decreases splanchnic and portal blood flow in dogs and humans, without affecting mucosal blood distribution [3–10].

The effects of SST on various organ systems are thought to be mediated via specific SST receptors (SSTRs). To date, five different subtypes (SSTR1–5) have been identified and cloned in human tissues. While all five subtypes display a similar affinity towards SST-14 and SST-28, there are major differences in binding of currently available SST analogues [11] to various SSTR subtypes. According to the current knowledge, SSTRs irrespective of subtype are thought to decrease intracellular cAMP concentration after activation by a specific ligand [11], but investigations concerning the exact intracellular mechanisms effected by different SSTRs with regards to cellular proliferation and possibly induction of apoptosis are ongoing.

Recently, SSTR subtype expression has been characterised in various neoplastic and physiological tissues. This is largely owing to the pioneering work of Reubi and co-workers (for an overview, see [12]), who have performed extensive investigations using autoradiographic techniques. Accordingly, there appears to be a predominance of only one or two SSTR subtypes in most tumours investigated. A high density of SSTR2 was found in bronchial and gastrointestinal neuroendocrine tumours, neuroblastomas, medulloblastomas, meningiomas, paragangliomas, breast cancers, renal cell carcinomas, lymphomas, hepatocellular carcinomas (HCCs), gastrointestinal tumours and small-cell lung cancers (SCLCs) [12]. There is a clear predominance of SSTR1 expression in sarcomas and prostate cancers, which may also express SSTR5 [12]. Several other tumours, including gastroenteropancreatic tumours, phaeochromocytomas, gastric carcinomas and ependymomas, may also express SSTR1, often alternating with SSTR2 or SSTR5 [12]. SSTR3 are often present in inactive pituitary adenomas [12]. Membrane-bound SSTR4 plays a minor role in the group of tumours tested in the study by Reubi et al. [12].

The highly SSTR2-affine octapeptide SST analogues such as octreotide remain the drugs of choice for application in a majority of SST-expressing tumours, since such tumours most often express predominantly SSTR2 [12]. Other SST derivatives, such as lanreotide or vapreotide, which have a good affinity for SSTR5 in addition to that for SSTR2, may advantageously identify SSTR2/SSTR5-expressing tumours [12]. However, none of the analogues presently available for clinical use appears to be useful for detection of tumours preferentially expressing SSTR1, such as sarcomas and prostate cancers, or SSTR3, such as inactive pituitary adenomas [12].

The clinical usefulness of native SST, however, is limited by its short plasma half-life of 1–3 min in humans, necessitating continuous infusion of the peptide [6]. Therefore, long-acting SST analogues have been developed that differ from native SST-14 in terms of receptor affinity and relative potency. The first such analogue was octreotide acetate, a synthetic octapeptide with a prolonged circulating half-life of ∼41–58 min in humans when administered intravenously [6]. The elimination half-life of octreotide after subcutaneous administration was found to be ∼113 min in healthy volunteers [13–15], and this analogue was found to be three times more potent than native SST in suppressing glucose-stimulated insulin secretion and 19 times more potent in inhibiting growth hormone secretion [14]. In recent years, major strides were made in the synthesis of newer, longer-acting analogues specifically designed for antitumour activity. Schally [16] and Cai et al. [17] synthesised 300 analogues using solid-phase methods resulting in octapeptide ‘super analogues’, which are more potent and have longer durations of action than either native SST or octreotide.

Several clinical trials have demonstrated impressive efficacy of SST analogues in a variety of hypersecretory disorders resistant to standard therapy, including acromegaly [18, 19], pancreatic ascites [20] and pancreatic cholera [21]. They have also proved useful for the management of symptoms caused by gastrointestinal neoplasms of endocrine origin, including Zollinger–Ellison’s syndrome [22–25], insulinoma [26, 27], VIPoma [28–31], glucagonoma [32, 33] and carcinoid tumours [24, 34, 35]. In addition to the successful application of SST analogues in relieving symptoms produced by endocrine tumours, antiproliferative actions of SST have been demonstrated in various tumour models including breast [16, 36–39], prostate [16, 40–43], colon [44–46], pancreatic [6, 16, 47–49] and SCLC [50, 51].

SST analogues have a wide therapeutic index and are apparently free of major side-effects [16, 52]. Most of the reported side-effects are gastrointestinal in nature and include minor nausea, bloating, diarrhoea, constipation and steatorrhoea. Currently, octreotide is approved only for the control of symptoms associated with metastatic carcinoid or VIP-secreting tumours; the use of SST analogues, however, has also been tested for antineoplastic activity. This review will focus specifically on the oncologic applications of SST analogues in the treatment of cancer.
Methods

Using a computerised (Medline) and manual search, we identified a total of 82 trials reporting antineoplastic efficacy of a long-acting SST analogue. Only papers with an English abstract were included, and we did not search for unpublished trials. Information abstracted included histological verification of the diagnosis, SSTR evaluation, treatment regimen (adjuvant or palliative) and dose of the SST analogue, pre-treatment criteria including prior surgery, chemotherapy and radiation and the presence or absence of measurable disease, number of patients, overall survival and response rates according to WHO criteria. Tumour responses were analysed as reported by the authors, but only patients achieving at least a partial remission (PR) qualified as responders, while minor response, mixed response, stable disease (SD) and progressive disease (PD) were not rated as responses in our evaluation.

Single case reports, however, do not provide a reliable assessment of the potential therapeutic efficacy of an intervention, for the simple reason that there is no way to ascertain the total number of patients who might have received such a therapy. Thus, case reports and small phase I/II studies (i.e. studies including <15 patients) are excluded from the text but are listed in Tables 1–11 in order to give a representative overview of the efforts undertaken so far, and to pay tribute to the fact that some neoplasms reported are relatively rare diseases.

Neuroendocrine tumours

The observation that SST inhibits the release of various peptide hormones and therefore reverses many symptoms attributable to neuroendocrine tumours has also stimulated interest in its use as an antiproliferative agent. It is not surprising that the first data on the use of SST analogues as antiproliferative agents were reported in patients suffering from neuroendocrine tumours, who underwent treatment with SST analogues mainly for symptomatic palliation. Comparison of results, however, is sometimes difficult, since response criteria in terms of biochemical response or objective regression of lesions as seen on CT were not uniformly applied in all series.

Two trials using different SST analogues in various schedules were performed [53] to investigate further the antineoplastic efficacy and safety of these agents. Octreotide was escalated in doses ranging from 1500 to 6000 µg daily to 13 patients with carcinoids, and lanreotide was given in doses ranging from 2250 to 9000 µg daily to 13 patients with various neuroendocrine malignancies (six carcinoid and two atypical carcinoid tumours, three patients with pancreatic islet cell cancers and two with SCLC). All patients successfully tolerated dose escalations without significant adverse effects and were evaluable for toxicity. Carcinoid syndrome was better controlled with higher doses of octreotide compared with lower doses of octreotide. Thirteen patients given octreotide were evaluable for antitumour efficacy and a PR was observed in four (31%), SD in two and PD in seven patients. Radio-logical changes showing increased tumour necrosis occurred in five patients, but were not accompanied by an objectively measurable reduction of tumour size. Lanreotide resulted in a PR in four patients (two carcinoids, one gastrinoma and one SCLC) (31%), SD in one atypical carcinoid and PD in eight patients (four carcinoid, one atypical carcinoid, two islet cell and one multidrug-resistant SCLC). Six of the carcinoid patients had radiological changes of increased necrosis.

The aim of a multicentre study published by DiBartolomeo et al. [54] was to determine the safety and efficacy of subcutaneous (s.c.) octreotide in controlling carcinoids and other neuroendocrine tumours. Fifty-eight patients were treated with two sequential doses of the drug. The first 23 patients received 500 µg tds and the remaining 35 patients were given 1000 µg tds, and treatment was continued until progression. The predominant tumour type was carcinoid, although medul-lary thyroid carcinoma, pancreatic islet cell tumours and Merkel cell carcinoma were also included. Carcinoid syndrome was documented in 16 patients and abnormal urinary 5-HIAA excretion in 15 cases. The median treatment duration was 5 months (range 2–31 months). The responses were evaluated according to three criteria: objective tumour regression, symptomatic response and biochemical response. An effect on tumour growth could only be demonstrated in two patients (3%) with carcinoids. Symptomatic control, however, was achieved in 73% of patients and a biochemical response was documented in 77% of patients. In 27 patients, the disease stabilised for at least 6 months (range 6–32+ months). The median survival time for all patients was 22 months (range 1–32+ months).

In an open phase III study by Eriksson et al. [55], octreotide was given as a continuous s.c. infusion to 35 patients with malignant neuroendocrine gastro-intestinal tumours and carcinoid syndrome. The starting dose of 1.5 mg/24 h was increased up to 3 mg/24 h at 3 months in some patients. The carcinoid syndrome disappeared in 20% of patients at 3 months and in 23% at 6 months, with 43% and 45% of patients experiencing an subjective improvement at 3 and 6 months, respectively. The mean Karnovsky index increased by >10% in 40% of patients at 3 and 6 months. 5-HIAA levels at 3 months normalised in one patient, fell in 20% (by >50%, P = 0.0021) and stabilised in 66%. There was also a significant decrease in plasma chromogranin levels at 3 months (P = 0.042), which did not persist at 6 months. Tumour size decreased by >50% in one patient at 6 months, but this patient had undergone chem-oembolisation 1 month prior to the start of the study. Most patients had tumour stabilisation (76% and 68%, respectively) or progression (20% and 24%, respectively) at 3 and 6 months. While treatment was well tolerated, dose escalation from 1.5 to 3 mg did not significantly improve clinical, biochemical or tumour responses.

Nineteen patients with advanced neuroendocrine gastro-intestinal tumours (13 carcinoids and six endocrine pancreatic tumours) were enrolled in a trial with lanreotide initiated, again, by Erikson et al. [56]. Liver metastases were present in
18 patients and 15 were heavily pre-treated with interferon (IFN). Lanreotide was administered in four daily s.c. injections, starting at 750 µg/day, then increasing every week up to 12000 µg/day after 6 weeks, a dose which was maintained, if tolerated, for 12 months or until progression. There was only one PR (5%), whereas 12 patients (70%) had SD for a median of 12 months (range 7–15.5 months). Biochemical markers were significantly reduced at 6 months (5-HIAA and plasma chromogranin) and 12 months (chromogranin), and the overall biochemical response rate was 58% with this high dose of lanreotide.

The efficacy and safety of a prolonged release formulation of lanreotide was investigated in a total of 55 patients suffering from gastrointestinal neuroendocrine cancers, including 48 patients with carcinoid tumours, six with gastrinoma and one with VIPoma [57]. In this study, 30 mg of lanreotide were administered via deep intramuscular injection every 14 days for 6 months. However, only two of 31 assessable patients had radiologically documented regression in tumour size, while 25 patients had SD and the remaining four patients progressed. Symptomatic response nevertheless occurred in 38% of patients with carcinoids, in 67% of patients with gastrinoma and in the patient suffering from VIPoma. In addition, a biochemical response was observed in 21 of 45 patients with initially elevated parameters, and an overall improvement of quality of life according to detailed investigations using a standardised query (EORTC QLQ-C30) was demonstrated for the first time. Side-effects were mild, with eight out of 30 patients developing treatment-induced gallstones.

**Lymphoproliferative disorders**

Sixty-one patients with measurable or assessable lymphoproliferative disorders, including 31 patients with stage III or IV low-grade non-Hodgkin's lymphoma (NHL), 21 with chronic lymphocytic leukemia (CLL) and nine with cutaneous T cell NHL (CTCL), were treated with octreotide 150 µg s.c. every 8 h for 1 month [58]. Patients with SD or responding to treatment received an additional 2 months of therapy; patients with an ongoing response after 3 months were treated for an additional ≥3 months. Sixty patients were assessable for toxicity and 56 for response. While there were no complete responses (CRs), 36% [10 of 28 patients; 95% confidence interval (CI) 19% to 56%] had a PR in the low-grade NHL group, and 44% (four of nine; 95% CI 14% to 79%) of patients with CTCL had a PR, while no patient with CLL achieved a PR. Fifty per cent (14 of 28) in the low-grade NHL group, 22% (two of nine) of patients with CTCL and 79% (15 of 19) of patients with CLL had SD, respectively. Among 45 patients with SD or a PR, the mean time to progression was 10.9 months (median 6.2 months, range 1.6–48.5 months). The drug was well tolerated, the most common side-effects being diarrhoea and hyperglycaemia, which occurred in 43% and 33% of patients, respectively.

**Breast cancer**

Canobbio et al. [59] performed a study using the SST analogue lanreotide in 33 postmenopausal untreated breast cancer patients. Blood samples were obtained before treatment, after 14 days and then monthly, in order to evaluate the behaviour of serum insulin-like growth factor I (IGF-I), growth hormone (GH) and lanreotide levels. The drug combination resulted in a significant and synergic reduction of plasma IGF-I concentration, while no significant changes in serum GH were observed. In total, 12.5% of patients exhibited a CR and 37.5% had a PR for an overall objective response rate of 50% (95% CI 35% to 69%). The high remission rate, the absence of overlapping side-effects between tamoxifen and lanreotide and the synergic activity on IGF-I suppression justify a further evaluation of the drug combination.

Twenty-two post-menopausal patients with metastatic breast cancer were randomised to receive either 40 mg/day of tamoxifen or a combination consisting of 40 mg tamoxifen plus 75 µg of a potent anti-prolactin (CV 205–502) orally, plus 0.2 mg of octreotide tds s.c. as first-line endocrine therapy [60]. An objective response was found in 36% of the patients treated with tamoxifen alone and in 55% of the patients treated with the combination therapy. Median time to progression was 33 weeks for patients treated with tamoxifen and 84 weeks for patients treated with combination therapy, but there was no difference in overall post-relapse survival between the two treatment arms.

O’Byrne et al. [61] have recently evaluated the efficacy and tolerability of high-dose vapreotide (RC-160) for pre-treated metastatic breast cancer. An initial dose of 3 mg/day in week 1 was increased to 4.5 mg/day for weeks 2–4, and subsequently to 6 mg/day until progression, administered by continuous subcutaneous infusion in 14 women with previously treated metastatic breast cancer. The treatment was well tolerated, and no dose reductions were required since no grade 3 or 4 toxicities were seen. Abscess formation developed at the infusion site in eight patients, and erythema and discomfort was seen in three additional patients. A significant reduction in IGF-I levels occurred by day 7 and was maintained throughout the duration of treatment. Of interest is the fact that the lowest dose of vapreotide produced the maximal IGF-I response. Although there was no reduction in prolactin levels in patients whose baseline levels were normal, elevated prolactin levels found in three patients returned to normal within 7 days after commencing treatment. No objective tumour responses were observed, and all patients showed disease progression within 3 months after initiation of treatment. These findings demonstrate that high-dose vapreotide administered as a continuous subcutaneous infusion can reduce serum levels of the breast growth factors IGF-I and prolactin, but is ineffective in the management of metastatic breast cancer.
Prostate cancer

Octreotide was also used to treat patients with advanced hormonal-refractory prostate cancer in a study by Logothetis et al. [62]. Twenty-two of 24 patients treated were evaluable for toxicity and 20 for response. The dose of octreotide applied was 0.1 mg s.c. every 8 h for 6 weeks. While only two patients suffered intolerable gastrointestinal side-effects requiring early cessation of therapy, no patient had objective evidence of tumour regression. According to the clinical impression of accelerated tumour growth with the use of octreotide, 10 patients were closely observed for 2 months before the start of octreotide treatment and for the first 2 months on therapy. In these 10 patients, the serum prostatic acid phosphatase level rose at an accelerated rate after 1–2 months of treatment. Among the 20 patients treated and evaluable for response, new osseous metastases developed in 12 and new visceral metastases in four; one developed disseminated intravascular coagulation and two developed neurological complications with a mean time to objective progression of 5.6 weeks. Six patients underwent salvage chemotherapy after disease progressed on octreotide therapy, five of whom achieved objective tumour regressions. The authors therefore concluded that octreotide might stimulate prostatic tumour growth and may sensitize tumour cells to subsequent chemotherapy.

A total of 30 patients with hormone-refractory prostate cancer were treated with a slow-release formulation of lanreotide by Maulard et al. [63]. Patients were given one injection of lanreotide 30 mg i.m. once a week and were followed for PSA levels until PD, and also for toxicity and survival. Patients were treated for a median duration of 12 weeks (range 2–60 weeks), and toxicity was minor. Performance status and bone pain improved in 40% and 35% of patients, respectively. Overall, 20% of patients had a decrease in PSA levels by at least 50%, and 16% showed SD. The 1-year global survival rate was 72%, with the rate being 89% in the group of patients who were responders according to PSA plasma levels and 64% in patients with PD. The response duration ranged from 16 to 60 weeks.

Figg et al. [64] conducted a dose-escalation trial of 25 patients with metastatic hormone-refractory prostate cancer. Dosages of 4, 7, 10, 13, 18 and 24 mg/day of lanreotide were administered by continuous intravenous infusion for at least 28 days. Plasma levels of IGF-I, but not those of IGF-II, declined modestly during therapy. Toxicities included grade I diarrhoea, bloating, infection, nausea and flatulence. The gastrointestinal side-effects were self-limiting and occurred during the initial treatment cycles. In addition, three patients experienced catheter-related infections. No clinical response was noted by either radiological or tumour marker criteria. The maximum tolerated dose of lanreotide was not determined in this series. While continuous intravenous infusion of 24 mg/day of lanreotide appears to be well tolerated, no clinical activity was noted at this dose in patients with advanced metastatic hormone-refractory prostate cancer.

Small-cell lung cancer

Macaulay et al. [65] treated 20 patients with octreotide 250 µg tds for 1 week before chemotherapy (six patients) or at relapse after chemotherapy (14 patients). Octreotide was well tolerated and serum IGF-I levels were suppressed to 62 ± 7% of pre-treatment levels. However, there was no evidence of antitumour activity measured by bulk or serum levels of neuroenolase. In one patient, metastatic skin nodules were shown to be SSTR-positive before and at the end of 2 weeks of octreotide. Despite this the patient had PD, and tumour cells obtained by fine needle aspirate before and after treatment showed no growth inhibition when cultured with octreotide immediately following establishment as a cell line.

In a phase I study by Cotto et al. [66], 18 patients with chemotherapy refractory SCLC received lanreotide administered over 24 h at a dose of 2 mg/day in five patients, and at a dose of 5 mg/day in four patients, while three patients each were treated with 3 mg/day, 8 mg/day and 10.5 mg/day. No discontinuation of treatment was planned prior to tumour evaluation on day 28 unless a severe side-effect was reported. The results of this trial suggest that high doses of lanreotide are well tolerated by patients with SCLC of very poor prognosis, although the agent failed to show any therapeutic activity in SCLC refractory to chemotherapy at any of the doses examined.

Marschke et al. [67] conducted a phase II study of lanreotide in 18 patients with extensive stage SCLC (four with previous treatment, 14 without previous treatment). Patients received 2000 mg of lanreotide subcutaneously three times daily. No patient responded to treatment, and the median time to progression was 44 days with the median survival being 106 days. According to these data, lanreotide was judged not to be active as a single agent in the treatment of extensive-stage SCLC.

Colorectal carcinoma

In a hallmark trial performed by Cascini et al. [68], a total of 46 patients with advanced colorectal cancer refractory to chemotherapy were randomised to receive octreotide at a dose of 200 µg tds for 5 days a week, or best supportive care only. Twenty-four patients received octreotide, while 22 received best supportive care. Patients treated with octreotide had a significant advantage in duration of survival, with a median time of 24 weeks versus 12 weeks in the control group. No patient achieved an objective response, but 11 patients given octreotide showed SD compared with only three in the control group.

Two-hundred-and-sixty patients suffering from advanced colorectal cancer with an Eastern Cooperative Oncology Group performance status of 0 or 1 and without symptoms
related to colon cancer were randomised to receive 150 µg of octreotide s.c. tds or, initially, no treatment [69]. After 91 patients were entered in the double-blind study, saline placebo injections were used for patients in the control arm. Toxicity was tolerable. The major end points were time to progression and survival. The median time to progression for patients receiving the placebo or no treatment was 3.2 months and for those receiving octreotide treatment it was 3.4 months. The median survival time for the no-treatment/placebo group was 16.8 months and for the octreotide-treated cohort was 17 months, with a two-sided log rank P value of 0.77. Octreotide at a dose of 150 µg given three times a day is ineffective in extending time to progression or survival in this subset of patients with advanced colon carcinoma.

Twenty-five patients with distal colorectal cancer were considered for entry in a pre-surgical study of octreotide at a dose of 1 mg every 8 h [70]. Biopsies were performed pre-treatment, during treatment (14 days) and on the day of surgical resection (2 days off treatment). A control series of 16 patients underwent endoscopic and subsequent surgical biopsy. A kinetic index was created called proliferating cell nuclear antigen maximum proliferative index (PCNA-MPI), and a significant decline in PCNA-MPI was observed in six of the 10 treated patients for whom all three biopsies were available, followed by a significant elevation on withdrawal of treatment. Changes in PCNA-MPI in the control group were less frequent and smaller.

To evaluate the tolerability and biologic activity of different doses of lanreotide in patients with advanced colorectal carcinoma, consecutive groups of three patients were each treated with lanreotide at doses of 1, 2, 3, 4, 5 or 6 mg tds s.c. for 2 months [71]. In the event of grade III side-effects, three additional patients were treated with the same dose before the next dose escalation. Serum samples were obtained on days 0, 15, 30 and 60 for serum GH, IGF-I and lanreotide assessment. Twenty-four patients were enrolled and all were evaluable. At the 3 and 6 mg dose levels, the observation of a grade III side-effect required treatment of three additional patients. The overall incidence of side-effects included changes in bowel habits (83%), abdominal cramps (79%), diarrhoea (17%), vomiting (17%), nausea (21%), steatorrhea (78%), hyperglycaemia (35%), hypothyroidism (39%), gallstones (13%) and weight loss (17%). No evidence of an increase in the incidence, intensity or duration of side-effects was observed with dose escalation. Serum IGF-I levels were as follows: day 15: 63, 60 and 67% of the baseline values for the low (1–2 mg), intermediate (3–4 mg) and high (5–6 mg) dose groups, respectively; day 30: 63, 59 and 51%, respectively; and day 60: 73, 63 and 47%, respectively. The highest doses seemed to maintain reduced serum IGF-1 levels; while a ‘rebound’ in serum IGF-1 levels was observed during treatment with the lowest doses. Serum lanreotide levels declined during treatment in all of the dose groups (90 ng/ml on day 15 and 35 ng/ml on day 60 for the 5–6 mg group; 10 ng/ml on day 15 and 1.5 ng/ml on day 60 for the 1–2 mg group). No anti-tumour activity or tumour marker reduction was observed. No increase in toxicity was observed when lanreotide doses were escalated to 6 mg tds s.c. for 2 months.

Seventy-five patients with colorectal cancer were randomised to receive octreotide (200 µg od s.c.) in the 2 weeks before surgery or no treatment [72]. The authors concluded that octreotide reduced the proliferative activity of tumour cells as measured by both [3H]thymidine labelling index and flow cytometry, and also serum IGF-I levels in patients with colorectal cancer.

### Gastric cancer

In a trial carried out by Cascini et al. [68], a total of 29 patients with advanced gastric cancer refractory to chemotherapy were randomised to receive octreotide at a dose of 200 µg tds for 5 days a week, or best supportive care only. Fifteen patients were given octreotide, while 14 received best supportive care. Patients treated with octreotide had a significant advantage in duration of survival, with a median time of 16 weeks compared with 8 weeks in the control group. No patient achieved an objective response. Seven patients given octreotide showed SD compared with only three in the control group.

### Pancreatic cancer

Friess et al. [73] analysed the efficacy of octreotide treatment in 22 patients with histologically verified ductal pancreatic cancer at advanced stages (stage III, 13 patients; stage IV, nine patients). Octreotide was given by self-administered subcutaneous injection (100 µg tds). Upon evidence of tumour progression, the dose of octreotide was increased to 200 µg tds. A monthly follow-up, including clinical status, computed tomography (CT) scan or ultrasonography, and determination of tumour markers carcinoembryonic antigen (CEA) and CA 19-9 was performed. No PR or CR was seen, and 19 patients showed tumour progression with a median survival time of 17 weeks (range 3–42 weeks). In three patients a ‘no change’ evaluation with a survival time ranging from 40 to 68 weeks was registered. In these patients the serum tumour markers CA 19-9 and CEA did not show an increase to more than twice the baseline value during therapy. The results of the analysis indicate that low-dose octreotide treatment is not effective in patients suffering from advanced tumour stages of pancreatic cancer.

Thirty-two patients with advanced pancreatic cancer refractory to chemotherapy were randomised to receive octreotide at a dose of 200 µg tds for 5 days a week, or best supportive care only, with 16 patients each being randomised to the respective treatment modality [68]. Patients treated with octreotide had a significant advantage in duration of survival with a median time of 15 weeks compared with 8 weeks in the control group. No patient achieved an objective response.
Seven patients given octreotide showed SD versus only two in the control group.

**Hepatocellular carcinoma**

Fifty-eight patients with advanced HCC were randomised to receive either octreotide 250 μg bd s.c. or no treatment [74]. Groups were comparable with respect to age, sex, Okuda classification, presence of cirrhosis, and liver biochemistry and virology. Treated patients had an increased median survival (13 compared with 4 months) and an increased cumulative survival rate at 6 and 12 months (75% versus 37%, and 56% versus 13%, respectively). Octreotide administration significantly reduced α-fetoprotein levels at 6 months.

**Conclusions**

Judging from the data obtained so far, there can be no doubt that SST analogues are highly effective in the symptomatic management of patients with neuroendocrine tumours [25–34]. In addition, a high rate of responses in terms of reducing biochemical abnormalities has consistently been reported with these agents, along with a wide therapeutic index in almost all series published so far. The antiproliferative effects of SST analogues as judged by objective tumour regression, however, are not likely to engender much enthusiasm, and the optimal dose and schedule for currently applied SST analogues has not been defined so far. While activity has initially been claimed in almost all tumour entities investigated so far, our review clearly shows that most series have been performed with a non-randomised approach in patients with highly disseminated disease, who had also been pre-treated in the majority of studies, and the results reported are not consistent. There is a well known bias that favours publication of positive results, and the results of anecdotal data are likely to be unrepresentative in a summary of the clinical evidence of benefit. Only eight randomised studies were disclosed by our search, including patients with gastrointestinal adenocarcinomas and HCC, where randomization was performed against an untreated control group [68, 72, 74]. In addition, studies of patients with breast and prostate cancer have randomised patients between application of hormonal intervention as sole modality versus combination with an SST analogue [60, 75], as has also been performed in pancreatic cancer [76, 77]. Several lines of evidence from in vitro and in vivo studies indicate that octreotide enhances the anti-neoplastic effects of anti-oestrogenic agents such as tamoxifen [78]. Large-scale clinical trials are currently being planned to investigate the efficacy of combined tamoxifen plus octreotide therapy as compared with tamoxifen alone in patients with breast cancer.

Despite statistically significant advantages in some studies, their findings should sometimes be interpreted with caution due to a very short survival time in the control group [72] and are counterbalanced by predominantly negative results in the majority of phase II studies.

Interpretation of the findings obtained so far is further complicated by the fact that only limited efforts to elucidate the SSTR status of patients enrolled in the studies before initiation of therapy have been performed. Thus, it is difficult to judge whether the activity seen in some series is due to a receptor–ligand interaction, indirect effects such as decreasing various growth-factors (e.g. IGF-I) by the SST analogue or simply reflects an improvement in patients' well-being due to suppression of paraneoplastic symptoms such as electrolyte loss or severe diarrhoea. In terms of pancreatic cancer, where controversial results have been published, in vitro and in vivo investigations have clearly demonstrated absence of functional SSTRs, except SSTR3 [79, 80], making direct receptor-mediated effects highly unlikely in such patients, since SST analogues used for treatment of this disease target SSTR2 and -5.

While the data reported so far do not justify the routine use of SST analogues outside of clinical trials in non-endocrine tumours, several important conclusions for future studies can be drawn from the data obtained to date. In order to differentiate between receptor-mediated activity and indirect effects, efforts should be made to investigate the SSTR status of patients enrolled in such trials. In a few studies performed to date, radiolabelled SST analogues such as octreotide [79, 80] or lanreotide [81] have been applied for scintigraphic evaluation of SST binding. These agents, however, have a distinct receptor affinity and usually do not bind to all five currently characterised SSTRs with comparable affinity. Further efforts to generate peptides with a broader receptor affinity are therefore warranted. While a negative scan result seems to effectively rule out expression of relevant amounts of SSTR subtypes with high affinity for the tracer applied, a positive result does not automatically indicate expression of respective SSTRs on tumour cells. According to the literature, activated lymphocytes have also been reported to possess high amounts of SSTR, and radiolabelled octreotide has been used to image granulomatous inflammatory sites [82] or inflammation associated with autoimmune disease such as Graves' disease [82]. However, the advent of specific antibodies against various SSTR subtypes suitable for use on paraffin-embedded biopsy samples or surgical specimens [83, 84] should facilitate pretherapeutic evaluation of SSTR status. However, a note of caution should be added insofar as only expression of SSTR2 has consistently been demonstrated to correlate with clinical response [11, 79, 82], while the exact mechanism of action has either not been fully elucidated or only been shown in vitro [11]. In addition, nothing is known about the influence of chemotherapeutic agents on SSTR expression in pre-treated patients or the interaction between chemotherapy and concurrently administered SST analogues, but preliminary data obtained at our institution suggest a down-regulation of SSTR in tumour cells pre-incubated with cytotoxic agents (our unpublished data). Should these data be verified in vivo, they...
Table 1. Neuroendocrine tumour—predominant SSTR expression: SSTR2a

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage and application</th>
<th>Duration of treatment</th>
<th>Number of patients</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide</td>
<td>50 µg bd s.c.</td>
<td>14 months</td>
<td>1 VIPoma</td>
<td>Shrinkage of hepatic metastasis</td>
<td>Kraenzlin [30]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>50 µg od s.c.</td>
<td>9 months</td>
<td>1 VIPoma</td>
<td>Shrinkage of hepatic metastasis</td>
<td>Clements [31]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Not stated, s.c.</td>
<td>1 year</td>
<td>1 gastrinoma</td>
<td>Initial shrinkage of tumour</td>
<td>Shepherd [88]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>50 µg bd s.c.</td>
<td>8 months</td>
<td>1 glucagonoma</td>
<td>No effect</td>
<td>Boden [32]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>50 µg bd s.c.</td>
<td>8 months</td>
<td>1 glucagonoma</td>
<td>No effect</td>
<td>Altimari [33]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>150 µg tds s.c.</td>
<td>18 months</td>
<td>13 carcinoids</td>
<td>Apparent shrinkage of hepatic metastasis in 3 patients</td>
<td>Kvols [35]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>50 µg bd s.c.</td>
<td>18–36 months</td>
<td>4 VIPomas, 4 gastrinomas and/or glucagonomas, 1 carcinoid</td>
<td>Tumour progression</td>
<td>Williams [15]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>100 µg bd s.c.</td>
<td>8 months</td>
<td>2 gastrinoma, 1 carcinoid</td>
<td>Tumour progression</td>
<td>Souquet [24]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>50 µg bd s.c.</td>
<td>2 years</td>
<td>1 VIPoma</td>
<td>Tumour size stable during treatment period</td>
<td>Juby [29]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>100 µg bd s.c.</td>
<td>7 months</td>
<td>1 carcinoid</td>
<td>Shrinkage of hepatic metastasis</td>
<td>Wiedenmann [89]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>50 µg tds s.c. increasing to 250 µg qds according to response</td>
<td>2–16 months</td>
<td>8 carcinoids</td>
<td>Mean daily frequency of diarrhoea, flushing reduced in 8 of 8 patients. A decrease in HIAA noted, suggestive of a reduction in serotonin release</td>
<td>Coupe [90]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>200 µg bd s.c.</td>
<td>Not stated</td>
<td>1 carcinoid</td>
<td>Within 2 months, considerable decrease in abdominal pain; reduction in flushing and diarrhoea</td>
<td>Jackson [91]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Not stated</td>
<td>2 months</td>
<td>1 carcinoid</td>
<td>Symptoms completely disappeared within a few weeks. Regression of liver metastases</td>
<td>Overkamp [92]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Not stated</td>
<td>4 weeks</td>
<td>3 carcinoids</td>
<td>Marked improvement in pain within 10 days</td>
<td>Smith [93]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>300–600 µg/day s.c.</td>
<td>Not stated</td>
<td>1 carcinoid</td>
<td>Rapid resolution of hypercalcemic symptoms</td>
<td>Jaspers [94]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>100–150 µg tds s.c.</td>
<td>10 months</td>
<td>1 carcinoid</td>
<td>Symptoms disappeared after 72 h and this was accompanied by a reduction in tumour mass, urinary excretion of HIAA and normalization of bilirubin, SGOT and alkaline phosphatase levels</td>
<td>Gutierrez [95]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>100 µg tds s.c.</td>
<td>6 months</td>
<td>5 carcinoids, 1 VIPoma</td>
<td>Treatment reduced flushing</td>
<td>Vinik [96]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>450–600 µg/day</td>
<td>Not stated</td>
<td>1 carcinoid</td>
<td>Treatment reduced pain but tumour mass was unchanged</td>
<td>Ranft [97]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>200–500 µg tds s.c.</td>
<td>Not stated</td>
<td>18 carcinoids</td>
<td>13 patients (54%) experienced symptomatic improvement</td>
<td>Moore [98]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>100 µg bd s.c.</td>
<td>Not stated</td>
<td>1 pheochromocytoma</td>
<td>Patient became normocalcaemic for first time in 18 months. Serum calcium rose again after 6 weeks but patient was asymptomatic</td>
<td>Harrison [99]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>1.5–6 mg od s.c.</td>
<td>Not stated</td>
<td>14 carcinoids</td>
<td>PR in 4, SD in 2 patients</td>
<td>Anthony [53]</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>2.25–9 mg od s.c.</td>
<td>Not stated</td>
<td>8 carcinoids, 3 pancreatic islet cell</td>
<td>PR in 3 (carcinoids) patients, SD in 1 carcinoid patient</td>
<td>Anthony [53]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Group 1: 23 patients, 500 µg tds s.c. Group 2: 35 patients, 1000 µg tds s.c.</td>
<td>Median 5 months (range 2–31 months)</td>
<td>58 (predominantly carcinoids, medullary thyroid carcinoma, pancreatic islet cell tumours)</td>
<td>Disease stabilization in 27 patients for at least 6 months (range 6–36 months)</td>
<td>DiBartolomeo [54]</td>
</tr>
</tbody>
</table>
would have widespread consequences for further planning of therapeutic trials to rule out a negative (schedule-dependent) interaction between chemotherapy and SST analogues.

As well as application of ‘cold’ SST analogues for therapy, the concept of receptor-mediated radiotherapy with compounds labelled with isotopes suitable for therapy is also
Table 4. Breast cancer—predominant SSTR expression: SSTR2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage and application</th>
<th>Duration of treatment</th>
<th>Number of patients</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide plus bromocriptine</td>
<td>100–200 µg bd s.c.</td>
<td>7–10 weeks</td>
<td>10</td>
<td>Octreotide plus bromocriptine therapy frequently suppresses GH and PRL secretion</td>
<td>Manni [108]</td>
</tr>
<tr>
<td>Octreotide plus bromocriptine</td>
<td>200 or 400 µg daily as continuous s.c. infusion</td>
<td>Until progression 6</td>
<td>2 patients showed disease stabilization</td>
<td>Anderson [109]</td>
<td></td>
</tr>
<tr>
<td>Octreotide plus bromocriptine</td>
<td>150 µg s.c. bd</td>
<td>8 weeks</td>
<td>8</td>
<td>Prolactin below detectable limits after 2 weeks. GH not completely abolished. Suppression of prolactin and growth hormone levels in all patients. Complete remission of local recurrence in one patient</td>
<td>Holtkamp [110]</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>30 mg fortnightly i.m.</td>
<td>Not stated</td>
<td>10</td>
<td>No effect</td>
<td>DiLei [111]</td>
</tr>
<tr>
<td>Lanreotide plus tamoxifen</td>
<td>Not stated</td>
<td>Not stated</td>
<td>33</td>
<td>Overall objective response rate of 50%</td>
<td>Canobbio [59]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>150 µg bd s.c.</td>
<td>Not stated</td>
<td>10</td>
<td>No effect</td>
<td>Ingle [112]</td>
</tr>
<tr>
<td>Octreotide plus tamoxifen plus anti-prolactin versus tamoxifen alone</td>
<td>200 µg tds s.c.</td>
<td>Not stated</td>
<td>22</td>
<td>Objective response in combination therapy was 55% versus 36% in the tamoxifen group. Median time to progression was 84 weeks versus 33 weeks</td>
<td>Bontenbal [60]</td>
</tr>
<tr>
<td>Octreotide plus tamoxifen</td>
<td>200 µg bd s.c.</td>
<td>Not stated</td>
<td>1</td>
<td>May give effective palliation</td>
<td>Rischke [113]</td>
</tr>
<tr>
<td>RC-160 (octastatin/vapreotide)</td>
<td>3–6 mg</td>
<td>Not stated</td>
<td>14</td>
<td>No objective tumour responses were observed, all patients showing disease progression within 3 months of commencing treatment</td>
<td>O’Byrne [61]</td>
</tr>
</tbody>
</table>

aAccording to Reubi et al. [12].
bBy first author [ref. no.].

Table 5. Prostate cancer—predominant SSTR expression: SSTR1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage and application</th>
<th>Duration of treatment</th>
<th>Number of patients</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide</td>
<td>100 µg tds s.c.</td>
<td>Not stated</td>
<td>7</td>
<td>Pain reduction in patients not previously receiving any treatment and in 2 of 3 patients who had already received other treatment</td>
<td>Carteni [114]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>600–1350 µg/day by continuous s.c. infusion</td>
<td>75 days</td>
<td>10</td>
<td>Reduced serum prolactin, IGF, insulin and glucagon levels. Disease progression occurred after 21 days</td>
<td>Dupont [115]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>400–1000 µg/day s.c. continuous infusion</td>
<td>2–6 months</td>
<td>5</td>
<td>During treatment 3 patients showed only a temporary halt in rising PSA levels for 1–3 months</td>
<td>Verhelst [75]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>100 mg qds s.c.</td>
<td>6 weeks</td>
<td>22</td>
<td>Octreotide stimulates prostatic tumour growth and may sensitise tumour cells to subsequent chemotherapy</td>
<td>Logothetis [62]</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>30 mg once a week i.m.</td>
<td>Until progression</td>
<td>30</td>
<td>The performance status and bone pain were improved in 40% and 35% of patients, respectively. In all, 20% of the patients had a decrease of 50% in PSA levels and 16% showed a disease stabilization</td>
<td>Maulard [63]</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>4–24 µg/day as continuous s.c. infusion</td>
<td>4 weeks</td>
<td>25</td>
<td>No activity</td>
<td>Figg [64]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Not stated</td>
<td>Not stated</td>
<td>14</td>
<td>Octreotide in small doses, in addition to complete androgen blockade, enhance number, quality and duration of symptom-free responses</td>
<td>Vainas [116]</td>
</tr>
</tbody>
</table>

aAccording to Reubi et al. [12].
bBy first author [ref. no.].
intriguing in patients with SSTR-positive malignancies. In fact, preliminary results in patients with neuroendocrine tumours using high dose $^{111}$In-octreotide [82] or $^{90}$Y-DOTA-lanreotide [85] have been promising and further studies are under way to investigate this concept.

Furthermore, SST analogues appear to be cytostatic rather than cytotoxic, and probably require prolonged application for optimal effect in some neoplasms. Accordingly, patients with highly advanced disease and a high tumour burden would not appear to be optimal candidates for therapeutic trials, while

---

**Table 6. Small cell lung cancer—predominant SSTR expression: SSTR2**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage and application</th>
<th>Duration of treatment</th>
<th>Number of patients</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide</td>
<td>250 µg tds s.c.</td>
<td>1 week</td>
<td>20</td>
<td>No evidence of antitumour activity</td>
<td>Macauley [65]</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>2.25–9 mg daily s.c.</td>
<td>Not stated</td>
<td>2</td>
<td>PR in 1 patient</td>
<td>Anthony [53]</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>2–10.5 mg/day as a 24 h continuous infusion</td>
<td>28 days</td>
<td>18</td>
<td>No evidence of antitumour activity</td>
<td>Cotto [66]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>200 µg tds s.c.</td>
<td>1 week</td>
<td>13</td>
<td>Octreotide is effective in reducing neuroenolase levels</td>
<td>Soresi [117]</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>2 mg tds s.c.</td>
<td>Until progression</td>
<td>18</td>
<td>No patient responded to treatment</td>
<td>Marschke [67]</td>
</tr>
</tbody>
</table>

*According to Reubi et al. [12].
*By first author [ref. no.].

**Table 7. Colorectal carcinoma—predominant SSTR expression: SSTR1, SSTR2**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage and application</th>
<th>Duration of treatment</th>
<th>Number of patients</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide</td>
<td>Not stated</td>
<td>Not stated</td>
<td>4</td>
<td>No effect</td>
<td>Savage [118]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>100–200 µg tds s.c.</td>
<td>Until progression</td>
<td>16</td>
<td>Four patients had SD, most patients experienced temporary subjective improvement with a decrease in pain</td>
<td>Klijn [119]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Not stated</td>
<td>2 weeks</td>
<td>12</td>
<td>In four patients a significant decrease in Ki67 immunoreactivity was seen</td>
<td>Iftikhar [120]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>200 µg tds s.c. or best supportive care</td>
<td>Not stated</td>
<td>46</td>
<td>Patients treated with octreotide had a significant advantage in duration of survival with a median time of 24 weeks versus 12 weeks in the control group. 11 patients showed stable disease versus only 3 in the control group</td>
<td>Cascinu [68]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>150 µg tds s.c. or placebo</td>
<td>Not stated</td>
<td>260</td>
<td>No effect</td>
<td>Goldberg [69]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>1 mg four times daily s.c.</td>
<td>2 weeks</td>
<td>25</td>
<td>Reduction in PCNA-MPI</td>
<td>Stewart [70]</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>1–6 mg tds s.c.</td>
<td>2 months</td>
<td>24</td>
<td>No antitumour activity or tumour marker reduction was observed</td>
<td>DiLeo [71]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>200 µg od s.c. before surgery</td>
<td>Not stated</td>
<td>75</td>
<td>Octreotide reduces the proliferative activity of tumour cells and the serum IGF-I levels</td>
<td>Cascinu [72]</td>
</tr>
</tbody>
</table>

*According to Reubi et al. [12].
*By first author [ref. no.].

**Table 8. Gastric cancer—predominant SSTR expression: SSTR1, SSTR2, SSTR5**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage and application</th>
<th>Duration of treatment</th>
<th>Number of patients</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide</td>
<td>Not stated</td>
<td>Not stated</td>
<td>2</td>
<td>No effect</td>
<td>Savage [118]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>100–200 µg tds s.c.</td>
<td>Until progression</td>
<td>4</td>
<td>Three patients had stable disease, most patients experienced temporary subjective improvement with a decrease in pain</td>
<td>Klijn [119]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>200 µg tds s.c. or best supportive care</td>
<td>Not stated</td>
<td>29</td>
<td>Patients treated with octreotide had a significant advantage in duration of survival with a median time of 16 weeks versus 8 weeks in the control group. 7 patients showed stable disease versus only 3 in the control group</td>
<td>Cascinu [68]</td>
</tr>
</tbody>
</table>

*According to Reubi et al. [12].
*By first author [ref. no.].
### Table 9. Pancreatic cancer—predominant SSTR expression: no clear pattern

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage and application</th>
<th>Duration of treatment</th>
<th>Number of patients</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide</td>
<td>Not stated</td>
<td>Not stated</td>
<td>4</td>
<td>No effect</td>
<td>Savage [118]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Continuous s.c. Infusion at 3.5 µg/kg/h</td>
<td>2 weeks</td>
<td>1</td>
<td>Decrease in serum lipase, PR of skin lesions and pain relief after 2 weeks</td>
<td>Feliu [121]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>100–200 µg tds s.c.</td>
<td>Until progression</td>
<td>14</td>
<td>Three patients had SD, the median survival was 2 months. Most patients experienced temporary subjective improvement with a decrease in pain</td>
<td>Klijn [119]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>100–200 µg tds s.c.</td>
<td>Until progression</td>
<td>22</td>
<td>Low-dose octreotide is not effective</td>
<td>Friess [73]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>0.1–2 mg/daily s.c.</td>
<td>Until progression</td>
<td>10</td>
<td>Median survival of 6 months and SD in 4 of 10 patients</td>
<td>Ebert [122]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Palliative surgery ± 1 mg/day s.c.</td>
<td>1 year</td>
<td>10</td>
<td>The treatment with octreotide permitted a better quality of life and a prolonged median survival (15.3 versus 5.3 months)</td>
<td>Mittempergher [123]</td>
</tr>
<tr>
<td>Octreotide</td>
<td>200 µg tds s.c. or best supportive care</td>
<td>Not stated</td>
<td>32</td>
<td>Patients treated with octreotide had a significant advantage in duration of survival with a median time of 15 weeks versus 8 weeks in the control group. 7 patients showed stable disease versus only 2 in the control group</td>
<td>Cascinu [68]</td>
</tr>
<tr>
<td>Octreotide plus tamoxifen</td>
<td>100 µg tds s.c.</td>
<td>Until progression</td>
<td>12</td>
<td>Apparently increased survival compared with historic cohort</td>
<td>Rosenberg [76]</td>
</tr>
<tr>
<td>Octreotide plus goserelin</td>
<td>50–500 µg tds s.c.</td>
<td>7 months (range 1–27 months)</td>
<td>14</td>
<td>One patient with PR for 7 months, nine patients with SD up to 27 months</td>
<td>Fazeny [77]</td>
</tr>
<tr>
<td>Octreotide plus tamoxifen versus best supportive care</td>
<td>100 µg tds s.c.</td>
<td>Until progression</td>
<td>28</td>
<td>Compared with the control group (n = 14) the median survival times for the octreotide–tamoxifen group were 7 and 3.5 months, respectively</td>
<td>Wenger [124]</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>30 mg i.m. every 14 days</td>
<td>Until progression</td>
<td>14</td>
<td>Four patients had SD. The median survival was 4 months (range 1.8–7 months)</td>
<td>Raderer [81]</td>
</tr>
</tbody>
</table>

*aAccording to Reubi et al. [12].

*bBy first author [ref. no.].

### Table 10. Hepatocellular carcinoma—predominant SSTR expression: SSTR2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage and application</th>
<th>Duration of treatment</th>
<th>Number of patients</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide</td>
<td>250 µg bd s.c. or no treatment</td>
<td>Until progression</td>
<td>58</td>
<td>Treated patients had an increased medial survival (13 versus 4 months) and an increased cumulative survival rate at 6 and 12 months (75% versus 37%, and 56% versus 13%)</td>
<td>Kouroumalis [74]</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>30 mg i.m. every 14 days</td>
<td>Until progression</td>
<td>21</td>
<td>One patient showed a PR, 8 patients had SD. The median survival was 4.2 months (range 1.2–13+ months)</td>
<td>Raderer [80]</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>30 mg i.m. every 14 days</td>
<td>Until progression</td>
<td>1</td>
<td>Disease stabilization for 8.5 months</td>
<td>Raderer [81]</td>
</tr>
</tbody>
</table>

*aAccording to Reubi et al. [12].

*bBy first author [ref. no.].

### Table 11. Bile duct carcinoma—predominant SSTR expression: not evaluated

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage and application</th>
<th>Duration of treatment</th>
<th>Number of patients</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide</td>
<td>High-dose s.c.</td>
<td>6 months</td>
<td>1</td>
<td>CR</td>
<td>Sulkowski [125]</td>
</tr>
</tbody>
</table>

*aBy first author [ref. no.].
patients in the adjuvant setting might probably be more suitable candidates for clinical studies. This is further underscored by recent investigations that have disclosed a potential role of SST analogues as anti-angiogenic factors [86, 87], which also deserve further investigation.

Taken together, the data generated so far are not sufficient to wholeheartedly approve or dismiss the clinical potential of currently available SST analogues as antineoplastic agents. Carefully planned clinical trials are still needed to further evaluate the role of SST analogues either as radiolabelled or unlabelled agents alone or in combination with hormone therapy or chemotherapy.

Acknowledgements

M.S. would like to thank Neil Young in particular for continuous inspiration!

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