J Cancer Res Clin Oncol (1997) 123:45–52

ORIGINAL PAPER

B. Fazeny · M. Baur · M. Prohaska · M. Hudec
M. Kremnitzer · S. Meryn · H. Huber · T. Grunt
A. Tuchmann · C. Dittrich

Octreotide combined with goserelin in the therapy of advanced pancreatic cancer – results of a pilot study and review of the literature

Received: 30 April 1996 / Accepted: 28 June 1996

Abstract The two hormone analogues octreotide and goserelin have been shown to decelerate growth of human pancreatic cancer in vitro and in vivo. The objective of this pilot study was to investigate the efficacy and toxicity of the combination of these two agents in patients with advanced pancreatic cancer. Octreotide was injected subcutaneously in dosages increasing weekly, starting with 50 μg twice daily, until the level of maintenance therapy of 500 μg three times a day was reached. In addition, 3.8 mg goserelin acetate was administered subcutaneously at monthly intervals. A median of 7 cycles (range 1–27 cycles) were applied; 13 out of 14 patients entered into the study were evaluable for response and all 14 were evaluated for toxicity. In one patient with initially non-resectable pancreatic cancer, systemic therapy yielded a partial remission lasting 9 months. The degree of tumour regression then allowed a consecutive macroscopic radical tumour resection followed by an additional 6 months of no evidence of disease while the same drug combination was continued. In an additional 9 patients, no change of disease was observed, in some cases for a remarkably long time (up to 27 months). Nevertheless, the objective response rate of 7% (95% confidence interval $0 \pm 21\%$) was low. In 5 patients a clear improvement in their performance status was seen soon after the start of therapy; 3 patients showed progression of the disease at first evaluation or earlier and 1 patient was not evaluable at the time of study assessment. According to the product-limit method of Kaplan and Meier, the time to progression was 3.0 ± 1.8 months [median ± asymptotic standard error (ASE)] and overall survival was 6.0 ± 1.5 months (median ± ASE). Toxicity was rare and only of mild to moderate degree. Overall, the regimen under investigation did not meet the criteria for sufficient antitumoural effectiveness. Nevertheless, this study reinforces the concept that pancreatic cancer is principally responsive to endocrine therapy and therefore the further investigation of hormonal manipulation seems worth while in the future.

Key words Octreotide · Goserelin · Pancreatic cancer

Abbreviation *ASE* asymptotic standard error

B. Fazeny (✉) · T. Grunt · H. Huber
Department of Internal Medicine I. Division of Oncology, University of Vienna, Währinger Gürtel 18–20, A-1090 Vienna, Austria.
Fax: + 43/1/40400/5465

M. Baur · C. Dittrich
Ludwig Boltzmann-Institute for Applied Cancer Research, 3rd Medical Department with Oncology, Kaiser Franz Josef-Hospital, Vienna, Austria

M. Prohaska · M. Kremnitzer · A. Tuchmann
Surgical Department, General Hospital Floridsdorf, Vienna, Austria

M. Hudec
Institute for Statistics and Computer Sciences, University of Vienna, Austria

S. Meryn
Evangelisches Krankenhaus Wien, Vienna, Austria

Introduction

The incidence of pancreatic cancer has been steadily increasing world-wide during the last few decades for unknown reasons. Because of late and unspecific symptoms a radical surgical resection [R0 resection according to the WHO 1990 (World Health Organization 1990)], the only therapy resulting in cure at present, can be performed in only 10%–20% of all patients (Büchler et al. 1989). The prognosis of locally advanced pancreatic cancer is poor with a median survival of 3–5 months. Palliative therapeutic procedures, i.e. chemotherapy even including the new topoisomerase 1 inhibitor CPT-11 (Wagener et al. 1995), radiotherapy or

immunotherapy, have so far failed to improve substantially the prognosis of patients with this disease. Only multimodality treatment (chemotherapy combined with irradiation) seems to achieve superior results with regard to median survival (Wagener et al. 1994). However, this strategy, which was restricted to a selected group of patients with locally advanced disease, was associated with considerable toxicity and prolonged hospitalization.

Since the demonstration of the presence of various hormone receptors in adenocarcinomas of the pancreas, such as progesterone, androgen and oestrogen receptors, by Greenway et al. (1981) and Corbishley et al. (1984, 1986), the primary requirement for investigating hormone therapy in this tumour entity has also been fulfilled.

A clear growth inhibition of acinar and ductal pancreatic cancer by luteinizing-hormone-releasing hormone (LHRH) analogues in rat and hamster models was demonstrated by Redding and Schally in 1984. LHRH receptors were identified in vitro in the human pancreatic carcinoma cell line Mia Pa Ca2 by Serrano et al. in 1988. This suggested that LHRH agonists exert direct inhibitory effects on hormone-responsive pancreatic tumour cells in addition to their effects in conditions of sex hormone deprivation. Subsequently Szende et al. (1991) have identified low-affinity and high-affinity LHRH receptors on pancreatic tumour cells, whereas Fekete et al. (1989a, b) could not detect such binding sites in normal human pancreatic tissue.

The presence of somatostatin receptors has been demonstrated on the cell surface of both non-human adenocarcinomas (Klijn et al. 1987) and the undifferentiated human pancreatic carcinoma cell line Mia Pa Ca2 (Hierowski et al. 1985), whereas Reubi et al. (1988) did not succeed in detecting somatostatin receptors in human exocrine pancreatic adenocarcinoma.

In addition, Schally (1988) and Zalatnai and Schally (1989) reported an advantageous effect of combining a somatostatin analogue with a LHRH analogue in an animal model system. Based on these and additional preclinical results, several studies have focused on the hormonal treatment. Among these, Wong et al. (1993) reported on the treatment of patients with advanced pancreatic cancer by anti-oestrogen therapy and, in a second non-randomised study, anti-oestrogens were combined with octreotide by Rosenberg et al. (1995), both groups claiming a prolongation of survival of the patients treated.

So far, the outcome of the various therapeutic trials on human exocrine pancreatic cancer treated with somatostatin analogues and/or LHRH analogues has been therapeutically unsatisfactory or inconclusive. The aim of this pilot study was to assess the antitumoral effectiveness and the toxicity profile of the combination of octreotide with the LHRH analogue goserelin as palliative therapy in patients with advanced exocrine pancreatic cancer.

Patients and methods

Study eligibility criteria

Protocol entry criteria in this phase II study included patients with histologically verified cancer of the exocrine pancreas, patients with locally advanced non-operable/non-resectable disease and/or with metastasized disease, patients with a relapse after initial R0 resection as well as those in whom only palliative resection could be performed with macroscopic remaining tumour masses (R2 resection), patients previously treated with chemotherapy and/or irradiation who had finished therapy at least 1 month before entering into this study protocol, patients with at least one measurable tumour lesion, patients with Karnofsky's rating between 100% and 50% and patients with a life expectancy of at least 2 months. All functions of vitally important organs had to be preserved or in a well-compensated condition; in addition, informed consent was mandatory.

Drug regimen

Therapy was performed exclusively on an outpatient base. Octreotide (Sandostatin, Sandoz, Vienna), a synthetic somatostatin analogue that has a much longer plasma half-life than natural somatostatin (Bauer et al. 1982; Del Pozo et al. 1986), was given in dosages increasing weekly until the level of maintenance therapy was reached. The drug was applied as self-administered subcutaneous injections into the thigh or the abdominal wall on days 1–7 at 50 μg twice daily, on days 8–14 at 150 μg twice daily, on days 15–21 at 300 μg twice daily, on days 22–28 at 450 μg twice daily and from day 29 until there was evidence of progressive disease at 500 μg three times a day. In addition, 3.8 mg goserelin acetate (Zoladex Depot; Zeneca Vienna) was administered subcutaneously at monthly intervals.

Pretreatment and follow-up evaluation

T and N stages were assessed pathologically, whereas M stage was assessed clinically and/or pathologically. Patients were monitored before start of therapy and before each goserelin acetate administration by physical examination, assessment of performance status and laboratory tests including blood cell count, creatinine, bilirubin, alkaline phosphatase, γ-glutamyltransferase, alanine aminotransferase, aspartate aminotransferase, lipase and amylase, lactate dehydrogenase, electrolytes, total protein, albumin, blood glucose and the tumour marker CA 19-9. The first formal treatment evaluation was done after 2 months of therapy and every 2 months thereafter, including reassessment of tumour extension by means of sonography, computed tomography, chest X-ray and additional diagnostic tools, if clinically indicated.

Response and toxicity evaluation

Clinical response and toxicity were assessed in accordance with the WHO guidelines (Miller et al. 1981). After a minimum of 2 months of therapy, patients were evaluable for response. Time to progression was calculated from the first day of treatment until documented disease progression. After at least 1 month of therapy, patients were accepted for toxicity reporting. Karnofsky ratings were assessed before the start of therapy and at monthly intervals during therapy of all patients.

Statistical methods

The time to progression was right-censored for patients still on treatment at the time of analysis and without any evidence of progressive disease. Deaths clearly designated as being due to malignant disease and deaths of unknown cause were considered progression of disease. Time to progression and survival estimates were performed according to the Kaplan–Meier product-limit method utilizing the statistical software package BMDP.

Results

Patients' characteristics

A total of 14 consecutive patients, 8 male and 6 female, with a median age of 64 years (range 49–76 years) were entered into study (Table 1). At the beginning of therapy, 13 had tumour at an advanced stage (UICC International Union against Cancer 1987) including 1 patient (no. 9) with a local tumour relapse after primary R0 resection of a stage III tumour; in the only patient (no. 11) with stage I disease only an R2 resection of the tumour could be performed with a macroscopically remaining tumour mass; 1 patient presented with tumour stage II but had a macroscopically residual tumour; 5 patients showed tumour stage III and 6 stage IV; in 1 patient (no. 8) the pathological tumour stage could not be defined because the diagnosis was done with fine-needle aspiration only. In 5 patients the tumour could not be radically resected at surgery (R2 resection, n = 5); in 8 patients the tumours were inoperable and therefore a choledochojejunostomy was performed in 3 patients and an exploratory laparotomy in 4, whereas the procedure was restricted to needle aspiration in a single patient in order to obtain a histological specimen.

A single patient (no. 5) was pretreated with interferon α2 and tamoxifen until metastases to the lung developed.

Clinical response and toxicities

All 14 patients entered were evaluable for toxicity and only 13 for response. At the time of evaluation, a median of seven cycles of therapy (range 1–27 cycles) had been applied, yielding an objective response rate of 7% (95% confidence interval 0 ± 21%). In a single patient (no. 4), a partial remission and, in 9 additional patients, no change of disease for up to 27 months were observed. Three patients showed progressive disease within 2 months or less from the onset of therapy; 1 patient was not evaluable for response at time of assessement.

In the 1 patient with partial remission a significant increase in the performance status was observed. In 3 out of 9 patients with no change of disease, Karnofsky's rating tended to increase and in an additional 3 patients it was stable. The clinical course of the patient with the partial remission (no. 4) was remarkable: a choledochojejunostomy in conjunction with a Braun's anastomosis had to be performed as primary surgery because the primary tumour was situated in the head of the pancreas and surrounded by a peritoneal carcinomatosis. After 11 months of therapy, the patient showed tumour regression, which was assessed by sonography as well as computed tomography and accompanied by a decrease of the CA19-9 value from an initial 640 kU/l to 65 kU/l minimum. A second-look operation revealed the former peritoneal carcinomatosis, documented at laparotomy, to have disappeared and therefore Whipple's operation was carried out, resulting in a secondary R0 resection. Pathohistologically, a carcinoma of the head of the pancreas and one infrapancreatic lymph node metastasis were identified, equivalent to a pathohistological tumour stage pT2N1M0 after preoperative systemic therapy. Under further systemic therapy, the patient remained with no evidence of disease for 6 months until progression of disease supervened. The time to progression in this patient was 17 months; the overall survival was 19 months.

In addition, the disease in 2 out of the 9 patients showing no change took a remarkable course. Patient 11 with a R2 resection and residual primary tumour, remained without change for 27 months. Thereafter, progression of the residual primary lesion developed and the actual survival lasted 34+ months. In patient 10, the tumour was clearly shrinking, but the disease had to be classified as no change lasting 8 months because tumour regression did not reach the standard level. A report of a case of octreotide-induced thrombocytopenia (Hanna and Maull 1990) allowed us to modify the treatment of the pre-existing thrombocytopenia from WHO grade 2 – not further evaluated because of the patient's refusal of bone marrow biopsy – so that this patient received only 50% of the scheduled dose of octreotide during the entire treatment period with platelets remaining stable.

The time to progression of the 13 evaluable patients was 3.0 ± 1.8 months (median ± ASE) with a maximum of 27 months (Fig. 1A). Survival of all 14 patients was 6.0 ± 1.5 months (median ± ASE) with 1 still alive more than 34 months from onset of therapy (patient 11) (Fig. 1B).

With regard to toxicity, therapy was accompanied with side-effects; they were not serious and did not reduce markedly the patients' quality of life. Nausea/vomiting WHO grade 3 was observed in a single patient who received only three cycles of therapy because of progression of disease. In one further patient, gastrointestinal side-effects of WHO grade 2, and WHO grade 1 in 2 more patients, were documented. Three patients had diarrhoea of WHO grade 1 and only 1 had WHO grade 2, which was related to the application of therapy. Two patients

Table 1 Patients' characteristics and therapy results. *Pt.* patients, *m* male, *f* female, *Expl.* exploratory, *op.* operation, *met.* metastases, *PD* progressive disease, *NC* no change of disease, *PR* partial remission, *NE* not evaluable, *TTP* time to progression, + still alive

Pt. no.	Age/ sex	Site of primary tumour	Type of operation	Tumour/metastases at start of therapy	TNM	Stage	Grade of differentiation	Karnofsky index		Response	TTP (months)	Survival (months)
								At start (%)	Best[a] (%)			
1	65/m	Tail	Expl. laparotomy	Primary tumour peritoneal met.	T3NXM1	IV	Poor	80	70	NC	3	3 +
2	60/m	Head	Whipple's op.	Residual primary tumour	T3N0M0	II	Poor	90	80	NC	5	6
3	64/m	Head	Whipple's op.	Residual primary tumour	T3N1M0	III	Poor	90	90	NC	2	7,5
4	64/f	Head	Choledocho-jejunostomy	Primary tumour Peritoneal met.	TXNXM1	IV	High	60	90	PR	17	19
5	59/f	Head	Expl. laparotomy	Pulmonary met.	TXNXM1	IV	Moderate	90	90	NC	9	15
6	66/m	Head	Expl. laparotomy	Primary tumour	T3N1M0	III	Moderate	80	80	NC	2	5
7	67/f	Head	Expl. laparotomy	Liver met.	TXNXM1	IV	Poor	90	70	PD	2	3
8	65/f	Head	Needle aspiration	Primary tumour	TXNXMX	NE	Poor	60	50	PD	< 2	2
9	76/m	Head	Whipple's op.	Local relapse	T3N1M0	III	Moderate	60	50	PD	2	3
10	63/f	Head	Whipple's op.	Residual primary tumour	T3N1M0	III	Moderate	80	100	NC	8	30, 5
11	67/f	Corpus	Whipple's op.	Residual primary tumour	T2N0M0	I	High	50	80	NC	27	34 +
12	49/m	Head	Choledocho-jejunostomy	Primary tumour Peritoneal met.	T3N1M1	IV	High	80	90	NC	8	10 +
13	56/m	Head	Choledocho-jejunostomy	Primary tumour	T3N1M0	III	Poor	50	40	NC	3	6
14	74/m	Head	Whipple's op.	Residual primary tumour Peritoneal met.	T3N1M1	IV	Moderate	80	100	NE	NE	2 +

[a] At response evaluation

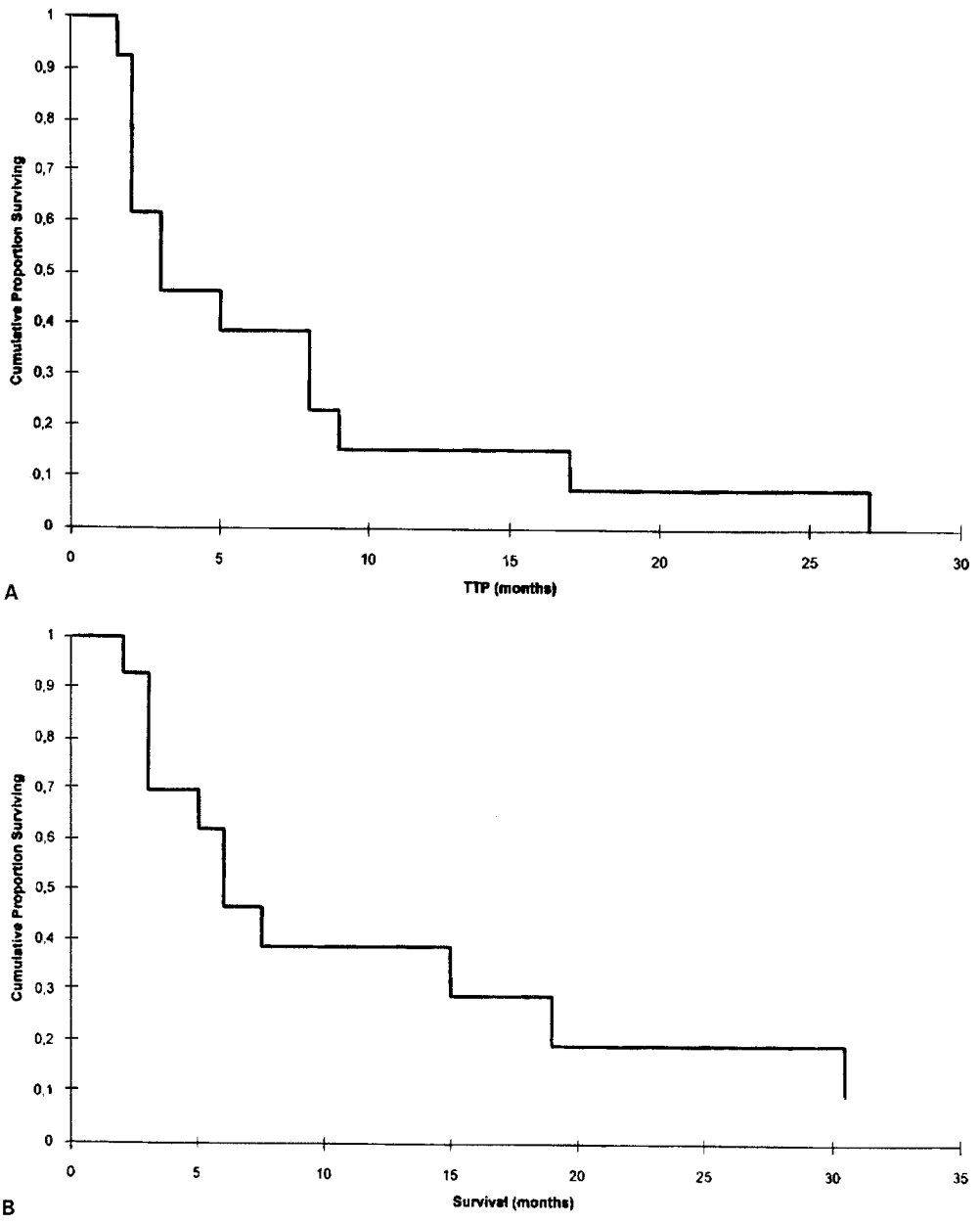

Fig. 1A, B Time to progression (*TTP*) (**A**) and overall survival (**B**) of patients with advanced pancreatic cancer under therapy with octreotide (Sandostatin) combined with goserelin (Zoladex Depot)

complained about mild pain in the abdomen and 1 about pain in both legs after injection of somatostatin. Three patients showed signs of inflammation at the sites of the subcutaneous injections and 1 of them even developed multiple tiny cutaneous necroses (Fig. 2A, B). The sensation of burning at the site of injection could be mitigated by allowing the medication to reach room temperature before its application.

Discussion

Objective responses of advanced pancreatic cancer under single-agent therapy with either a somatostatin analogue (Canobbio et al. 1992) or a LHRH analogue (Gonzales-Barcena et al. 1989) as well as positive reports on the growth-inhibiting effects of *N*-nitrosobis(2-oxopropyl)amine(BOP)-induced pancreatic cancer in a Syrian golden hamster model (Schally 1988; Zalatnai and Schally 1989) under a combination of both analogues encouraged us to test this drug combination in a pilot study of patients with advanced exocrine pancreatic cancer.

So far, clinical reports on studies using either one or a combination of the two hormones are rare (Table 2). The first clinical study on somatostatin analogue treatment was published by Klijn et al. (1990). Two studies of Frieß et al. (1993a, b), using the somatostatin analogue octreotide at a low dose level

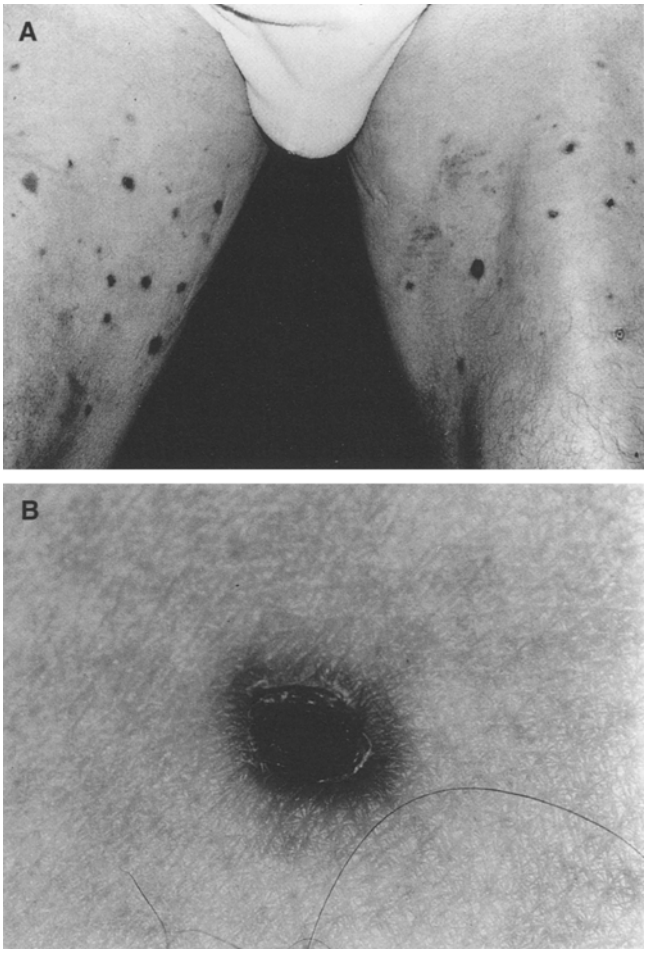

Fig. 2A, B Multiple tiny cutaneous necroses at the sites of the subcutaneous application of octreotide (500 µg/application)

[3 × (100–200 µg/day)] and a high dose level (3 × 2000 µg/day) led to an assumption of dose dependence for octreotide that confirms the reported dose/effect relationship in breast cancer cell lines exposed to somatostatin analogues (Scambia et al. 1988). In Frieß' high-dose study, the median survival increased from 4 to 6 months with symptomatic and clinical improvement. A positive impact on the course of disease could be confirmed by a very recent randomised – octreotide treatment versus best supportive care – by Cascinu et al. (1995) based on a low-dose therapy given 5 days/week. In this trial a significant advantage in duration of survival and in percentage of stable disease was observed for the treated patients although no objective response was reached. The only objective response was observed by Canobbio et al. (1992), who administered the somatostatin analogue BIM 23014 in dosages between 250 µg/day and 1000 µg/day to 18 evaluable patients, resulting in one partial response at the highest dose level. In comparison to the 40% of patients reaching no change in disease, reported in the high-dose octreotide study of Frieß et al. (1993b), where a four times higher dosage of octreotide was used than in our study, our results of 1 partial response and 70% no change, on the basis of 500 µg octreotide three times per day in combination with a LHRH analogue, suggest that combining octreotide with a LHRH analogue might be of therapeutic influence compensating for the putative advantageous effect of a higher octreotide dose.

The literature on the clinical use of LHRH analogues in the treatment of advanced pancreatic cancer is also scarce and is very much based on experimental work carried out by Fekete et al. (1989a, b). Gonzales-Barcena et al. (1989), administering [D-Trp^6] LHRH, were the first who reported one partial remission and an improvement in the patients' quality of life. In the prospective randomized trial of Sperti et al. (1992) – 3.6 mg goserelin s.c. every 4 weeks (group A) compared to no therapy (group B) – median survival increased almost twice in favour of the treated patients. All other investigators, however, like Andren-Sandberg (1989) and Allegretti et al. (1993), administering 3.6 mg goserelin in a monthly schedule, or Frieß et al. (1992), applying 1.2 mg buserelin/day, were unable to show any alteration of quality of life or an objective response or an impact on survival.

Therefore, a logical step for further evaluating the putative role of hormonal therapy in pancreatic cancer was to concentrate on combination therapy with somatostatin and LHRH analogues based on the encouraging preclinical investigation with BOP-induced pancreatic cancer in Syrian golden hamsters (Schally 1988; Zalatnai and Schally 1989). In this study, the group of animals treated with a combination of the two peptides [D-Trp^6] LHRH and the somatostatin analogue RC-160 showed the best results. This impressive preclinical study however, could not be confirmed in the clinical setting by Suri et al. (1991) nor by a prospective randomized trial by Huguier et al. (1992). One can only speculate whether this was due to the low octreotide doses chosen for these clinical trials.

The description by Yamada et al. (1993) of the cloning of five human somatostatin receptor subtypes (hSSTR1-hSSTR5), each possibly mediating the activation of a different effector system as well as different binding affinities of various somatostatin analogues (mechanisms that are also relevant for LHRH analogues), illuminates and accentuates the principal problem of comparing clinical studies using different somatostatin and/or LHRH analogues with regard to their response rates and survival respectively.

Although the indication for the use of somatostatin analogues in the treatment of pancreatic cancer is actually considered unestablished (Lamberts et al. 1996), Schally's hamster model and the results of several clinical trials, ours among them, reinforce the concept that pancreatic cancer is principally responsive to endocrine

Table 2 Synopsis of the clinical trials in patients with advanced pancreatic cancer testing octreotide and luteinizing-hormone-releasing hormone (LHRH). *CR* complete response, *PR* partial remission, *NC* no change of disease, *GNRH* gonadotropin-releasing hormone, *NE* not evaluable

Agent	Treatment design	No. patients evaluable for response	No. responses			Median survival (months)	Author
			CR	PR	NC		
Somatostatin analogues	3 × 200 µg/day octreotide	16	–	–	3	2	Klijn et al. (1990)
	3 × 100 µg/day octreotide (at evidence of progression: 3 × 200 µg/day)	22	–	–	3	4	Frieß et al. (1993a)
	3 × 2000 µg/day octreotide	10	–	–	4	6	Frieß et al. (1993b)
	250–1000 µg/day BIM 23014	18	–	1	6	3	Canobbio et al. (1992)
	3 × 200 µg/day octreotide for 5 days/week	16	–	–	7	5	Cascinu et al. (1995)
	Control group: best supportive care	16	–	–	2	2.7	
LHRH analogues	3.6 mg goserelin every 4 weeks	10	–	–	8	7.5	Andren-Sandberg (1989)
	[D-Trp^6]LHRH Days 1–7 1 mg Day 8–PD 100 µg	17	–	1	12	7.2	Gonzales-Barcena et al. (1989)
	Group A: 3.6 mg goserelin every 4 weeks	15	–	–	3	7.4	Sperti et al. (1992)
	Group B: no therapy	18	–	–	3	4.4	
	1.2 mg/day buserelin	36	–	–	10	5	Frieß et al. (1992)
	3.6 mg goserelin every 4 weeks	7	–	–	NE	NE	Allegretti et al. (1993)
LHRH (GNRH) analogues + somatostatin analogues	100 µg octreotide 3 times/day + 1 mg/day leuprolide s.c.	21	–	–	5	4	Suri et al. (1991)
	3 × 250 µg/day BIM 23014 + 3.75 mg Decapeptyl R every 4 weeks	38	–	–	NE	6	Huguier et al. (1992)
	Control group	43	–	–	NE	4.3	
	2 × 50 µg/day up to 3 × 500 µg/day octreotide + 3.6 mg goserelin every 4 weeks	13	–	1	9	6	This paper

therapy. In addition, the attractive features of this therapeutic concept are the absence of severe side-effects, the frequently observed improvement of patients' performance status and the advantage of treatment administered completely outside the hospital during the entire period of therapy. Furthermore, the definitive identification of different receptor subtype(s) mediating the antiproliferative effects, the expression of these receptor subtype(s) in this tumour entity and the development of subtype-specific analogues should lead to controlled trials of hormonal manipulation with an untreated control group in this malignancy, which is virtually untouched by any systemic therapy at present. Along with these investigations it should be evaluated whether the response of this tumour entity to endocrine therapy correlates with the expression of the corresponding hormone receptors and subtypes on the target tissue.

References

Allegretti A, Lionetto R, Saccomanno S, Paganuzzi M, Onetto M, Martinoli C, Rollandi G, Marugo M, Fazzuoli L, Pugliese V et il gruoppo Ligure per lo studio del pancreas (1993) LH-RH analogue treatment of adenocarcinoma of the pancreas: a phase II study. Oncology 50:77–80

Andren-Sandberg A (1989) Androgen influence on exocrine pancreatic cancer. Int J Pancreatol 4:363–369

Bauer W, Briner U, Doepfner W (1982) SMS 201–995: a very potent and selective octapeptide analogue of somatostatin with prolonged action. Life Sci 31:1133–1140

Büchler M, Kübel R, Klapdor R (1989) Immunotherapy of pancreatic cancer with monoclonal antibody BW494: results from a multicentric phase I-II trial. In: Beger HG, Büchler M, Reisfeld RA, Schulz G (eds) Cancer therapy. Springer, Berlin Heidelberg New York, pp 32–47

Canobbio L, Boccardo F, Cannata D, Gallotti P, Epis R (1992) Treatment of advanced pancreatic cancer with the somatostatin analogue BIM 23014. Cancer 69:648–650

Cascinu S, Del Ferro E, Catalano G (1995) A randomised trial of octreotide vs best supportive care only in advanced cancer patients refractory to chemotherapy. Br J Cancer 71:97–101

Corbishley TP, Iqbal MJ, Johnson PJ, Williams R (1984) Progesterone receptors in malignant and foetal pancreatic tissue. IRCS Med Sci 12:575–576

Corbishley TP, Iqbal MJ, Wilkinson ML, Williams R (1986) Androgen receptor in human and malignant pancreatic tissue and cell lines. Cancer 57:1992–1995

Del Pozo E, Neufeld K, Schlütter F (1986) Endocrine profile of a long-acting somatostatin derivate SMS 201-995. Study in normal volunteers following subcutaneous administration. Acta Endocrinol 111:433–499

Fekete M, Zalatnai A, Comaru-Schally AM, Schally AV (1989a) Membrane receptors for peptides in experimental and human pancreatic cancers. Pancreas 4:521–528

Fekete M, Zalatnai A, Schally AV (1989b) Presence of membrane binding sites for (D-TRP6)-luteinizing hormone-releasing hormone in experimental pancreatic cancer. Cancer Lett 45:87–91

Frieß H, Büchler M, Krüger M, Beger HG (1992) Treatment of duct carcinoma of the pancreas with the LH-RH analogue buserelin. Pancreas 7:516–521

Frieß H, Büchler M, Beglinger Ch, Weber A, Kunz J, Fritsch K, Beger HG (1993a) Low dose octreotide treatment is not effective in patients with advanced pancreatic cancer. Pancreas 8:540–545

Frieß H, Büchler M, Ebert M, Malfertheiner P, Dennler HJ, Beger HG (1993b) Treatment of advanced pancreatic cancer with high dose octreotide. Int J Pancreatol 14:290–291

Gonzalez-Barcena D, Ibarra-Olmos MA, Garcia-Carrasco F, Gutierrez-Samperso C, Comaru-Schally AM, Schally AV (1989) Influence of D-Trp-6-LH-RH on the survival time in patients with advanced pancreatic cancer. Biomed Pharmacother 43:313–317

Greenway B, Iqubal MJ, Johnson PJ & Williams R (1981) Oestrogen receptor proteins in malignant and fetal pancreas. Br Med J 283:751–753

Hanna WT and Maull KI (1990) Sandostatin-induced thrombocytopenia. South Med J 83:77

Hierowski MT, Liebow C, Dusapin K, Schally AV (1985) Stimulation by somatostatin of dephosphorylation of membrane proteins in pancreatic cancer MIAPa CA2 cell lines. FEBS Lett 179:252–256

Huguier M, Samama G, Testart J, Mauban S, Fingerhut A, Nassar J, Houry S, Jaeck D, De Mestier P, Favre JP, Michot F, Vidrequin A, Mantion G, Veyrieres M, Fourtanier G, Lointier P, Gignoux M (1992) Treatment of adenocarcinoma of the pancreas with somatostatin and gonadoliberin (luteinizing hormone-releasing hormone). Am J Surg 146:348–353

Klijn JGM, Setyono-Han B, Bakker GH, Henkelman MS, Portengen H, Foekens JA (1987) Effects of somatostatin analog (Sandostatin) treatment in experimental and human cancer. In: Klijn JGM, Paridaens R, Foekens JA (eds) Hormonal manipulation of cancer: peptides, growth factors and new (anti) steroidal agents. (EORTC monograph series, vol 18) Raven, New York, pp 459–468

Klijn JGM, Hoff AM, Planting ASTh, Verweij J, Kok T, Lamberts SWJ, Portengen H, Foekens JA (1990) Treatment of patients with metastatic pancreatic and gastrointestinal tumors with the somatostatin analogue Sandostatin: a phase II study including endocrine effects. Br J Cancer 62:627–630

Lamberts SWJ, Van der Lely AJ, De Herder WW, Hofland LJ (1996) Octreotide. N Engl J Med 334:246–254

Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47:207–214

Redding TW, Schally AV (1984) Inhibition of growth of pancreatic carcinomas in animal models by analogs of hypothalamic hormones. Proc Natl Acad Sci USA 81:248–252

Reubi JC, Horisberger U, Essed CE, Jeekel J, Klijn JGH, Lamberts SWJ (1988) Absence of somatostatin receptors in human exocrine pancreatic adenocarcinomas. Gastroenterology 95:760–763

Rosenberg L, Barkun AN, Denis MH, Pollak M (1995) Low dose octreotide and tamoxifen in the treatment of adenocarcinoma of the pancreas. Cancer 75:23–28

Scambia G, Benedetti BP, Baiocchi G, Perrone L, Iacobelli S, Mancuso S (1988) Antiproliferative effects of somatostatin analog SMS 201–995 on three human breast cancer cell lines. J Cancer Res Clin Oncol 144:106–108

Schally AV (1988) Oncological applications of somatostatin analogues. Cancer Res 48:6977–6985

Serrano MJ, Liebow C, Reilly C, Shally AV (1988) LH-RH analogue causes direct inhibition of growth of pancreatic cancer cells in culture. Pancreas 3:617

Sperti C, Fasquali C, Catalini S, Alfano D'Andrea A, Militello C, Piccoli A, Pedrazzoli S (1992) Hormonal treatment of advanced pancreatic cancer with LH-RH analogue. European J Surg Oncol 18:267–271

Suri P, Lipton A, Harvey HA, Wyszynski E, Dixon R, Hamilton RW (1991) Hormonal treatment of pancreatic carcinoma with GNRH and somatostatin analogs. Proc Am Soc Clin Oncol 10:302

Szende B, Srkalovic G, Timar J, Mulchahey JJ, Neill JD, Lapis K, Csikos A, Szenpeshazi K, Schally A (1991) Localization of receptors for luteinizing hormone-releasing hormone in pancreatic and mammary cancer cells. Proc Natl Acad Sci USA 88:4153–4156

UICC International Union against Cancer (1987) TNM Klassifikation maligner Tumoren, vol 4. Springer, Berlin Heidelberg New York

Wagener DJTh, Mulder PHM de, Wils JA (1994) Multimodality treatment of locally advanced pancreatic cancer. Annal Oncol 5 [Suppl 3]: 81–86

Wagener DJTh, Verdonk HER, Dirix LY, Catimel G, Siegenthaler P, Buitenhuis M, Methieu-Boué, Verweij J (1995) Phase II trial of CPT-11 in patients with advanced pancreatic cancer, an EORTC early clinical trials group study. Ann Oncol 6:129–132

Wong A and Chan A (1993) Survival benefit of tamoxifen therapy in adenocarcinoma of pancreas. Cancer 71:2200–2203

World Health Organization (WHO) (1990) International classification of disease for oncology, 2nd edn WHO, Geneva

Yamada Y, Kagimoto S, Kubota A, Yasuda K, Masuda K, Someya A, Ihara Y, Li Q, Imura H, Seino S, Seino Y (1993) Cloning, functional expression and pharmacological characterization of a fourth (hSSTR4) and a fifth (hSSTR5) human somatostatin receptor subtype. Biochem Biophys Res Commun 2:844–852

Zalatnai A, Schally AV (1989) Treatment of *N*-nitrosobis(2-oxopropyl)amine-induced pancreatic cancer in Syrian golden hamsters with D-Trp-6-LH-RH and somatostatin analogue RC-160 microcapsules. Cancer Res 49:1810–1815