Neuroendocrine tumors of the pancreas.
Natural history and therapeutic options

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CONCLUSION

Pancreatic neuroendocrine tumors (NET) characteristically grow slowly. Approximately half of all patients never develop hypersecretion/hormone-related symptoms and syndromes [1]. NET producing excessive amounts of hormones and biogenic amines are also called functional or hormone-active tumors whereas non-“hypersecretory” tumors are correspondingly referred to as non-functional or hormone-inactive NET. In the latter case, as a consequence of this indolent clinical course, most patients have widespread disease at first diagnosis. While the overall incidence of gastroenteropancreatic (GEP) NET in postmortem examinations is 2/100,000, the clinical incidence of GEP NET is only 0.3-0.7/100,000 [2, 3]. Accordingly, pancreatic NET have even a 2-fold lower incidence, i.e. 0.2-0.03/100,000. Neuroendocrine pancreatic tumors derive from the so-called foregut. Their natural course is considerably worse as compared to midgut tumors [4]. Pancreatic NET are characterized by a local spread infiltrating adjacent nerve fibers, vessels, and lymph nodes. In addition, metastases are primarily observed in the liver and at later stages in the bone, orbita, mediastinum, and lungs.

Disease presentation and prognosis

Incidental discovery of small, asymptomatic NET of the pancreas is rare. In contrast to intestinal NET (30%-40%) and hereditary (i.e. multiple endocrine neoplasia type I [MEN I]-associated) pancreatic NET, multicentricity in sporadic pancreatic NET is rarely found [5]. Frequent recurrences after apparently curative surgery are evidence of hidden, undiagnosed micro-metastases. Life expectancy of these patients is far better as compared to patients diagnosed with unresectable abdominal and hepatic metastases. Survival in the latter group is only 30% at 5 years follow-up [5].

Clearly, survival rate depends on both tumor volume (including metastatic tumor burden) and the location of the primary tumor [6].
A small size of the primary is a favorable prognostic parameter. However, in contrast to appendiceal NET, where tumors smaller than 1 cm scarcely ever metastasize, pancreatic NET should be considered surgically as aggressive carcinomas [1].

Additional factors have prognostic importance:
- tumor differentiation: prognosis is poor (median survival less than 6 months) in patients with undifferentiated, anaplastic, neuroendocrine tumors of the gastrointestinal tract [7];
- associated neoplasms: secondary malignancies develop in up to almost 30% of patients with pancreatic NET (28% of 209 and 16.6% of 2,125 patients in two different series [8]).

Treatment options

Therapy has therefore to deal either surgically with localized treatment or after failure of this modality with systemic medical therapy.

Biotherapy or systemic chemotherapy are used to reduce symptoms, induce stable disease and prolong survival. Biotherapy can be performed with either somatostatin analogs (SSA), with interferon-α (IFN-α) or in some cases a combination of both. Chemotherapy uses mainly streptozocin in combination with 5-fluorouracil or doxorubicin in differentiated tumors, or cisplatin and vepeside in anaplastic tumors. For the control of hypersecretion-related symptoms and syndrome(s), reduction of tumor burden using rather experimental forms of cytoreductive therapy such as aggressive, surgical tumor debulking, (chemo-) or even (radio-) embolization or thermal ablation of liver metastasis are available and are used either alone or in combination with systemic treatment. A new rather promising treatment strategy appears to be receptor-targeted radiolabeled therapy using radiolabeled somatostatin analogs. Liver transplantation has been used in selected patients with no apparent extrahaepatic tumor manifestation.

Surgery

Surgery represents the treatment of choice. Clear indications for surgery are: 1) curative intent e.g. in limited, localized disease (cave MEN-1), 2) local obstruction, and 3) lower or upper GI bleeding [1].

With the exception of insulinomas (90% benign), curative surgery is rarely observed in pancreatic NET patients. In metastatic disease, surgery may be at least in some cases, the first therapeutic option. However, cure is rarely observed in this tumor subgroup (9%) [9]. Limited indications for surgery include the concept of tumor “debulking” (including intraoperative local ablation measures) in both functional and non-functional tumors as well as orthotopic liver transplantation [10].

Whereas a retrospective study by McEntee et al. [11] in neuroendocrine tumors of the small intestine suggested possible prolonged survival following cytoreductive surgery, no comparable data have been published so far for pancreatic NET. However as pointed out previously, due to a faster progression of neuroendocrine pancreatic tumors as compared to intestinal NET, cytoreductive approaches in this tumor subgroup have to be considered with care.

Systemic therapy

Systemic therapy has to consider two treatment aspects, i.e. the control of symptoms as well as the control of proliferation. The first is of relevance in about half of the patients presenting with hypersecretion of gastrin, insulin, VIP, and rarely also glucagon or somatostatin. Correspondingly, classical symptoms and syndromes can be according to the hypersecretion of each hormone delineated to specific syndromes and symptoms, e.g. impaired conscience combined with hypoglycemia and insulin/ hypoglycemia-, gastrin-/Zollinger-Ellison- or VIP-hypersecretion/ Verner-Morrison-syndrome.

Biotherapy

Control of symptoms can be achieved either with somatostatin analogs (SSA, e.g. octreotide and lanreotide) or interferon-alpha. Both SSA as well as IFN-α are available in subcutaneous as well as depot formulation, whereby subcutaneous application is performed three times a day and the depot formulation applied in two to four week intervals. Symptomatic control can be achieved with the SSA octreotide by subcutaneous application in more than two thirds of cases in midgut tumors whereas the control of symptoms in pancreatic NET due to a lower incidence of octreotide receptors (i.e. somatostatin receptor subtype 2 and 5) is ineffective in nonmetastatic insulinomas and also only partly effective in gastrinomas. By contrast VIPomas respond to octreotide therapy extremely well. So far only caseistic data are available for glucagonomas and somatostatinomas. Control of symptoms is only marginally achieved by the use of interferon-α either applied alone or in combination with a somatostatin analogue [1].

Somatostatin analogs

Similar to native somatostatin SSA also inhibit vesicular release of hormones and peptides in many organs, including the gastrointestinal organs. SSA with prolonged half-life are attractive drugs for use in GEP hypersecretion syndromes. Stimulation of somatostatin receptors (sstr) activates intracellular pathways that ultimately inhibit cell growth [12-16]. In vitro, high doses of somatostatin analogs induce apoptosis in tumor cells, and this could also translate into inhibition of tumor growth [17]. Sstr encompass a gene family of at least 5 receptor subtypes. The clinically used SSA bind preferentially to the sstr 2 and sstr 5 subtypes [18, 19]. NET have a higher density of these two subtypes than normal tissue [20]. This allows for a certain degree of specificity in the tumor-targeted effects and may also explain the relatively low degree of side effects. Three different SSA are at present in clinical use: octreotide, lanreotide, and vapreotide. All have a prolonged serum half-life (90 minutes or more) compared with only two minutes for native somatostatin. In addition, depot preparations are now available, which allow for only one intramuscular injection every two or four weeks (lanreotide SR [slow release] and octreotide LAR [long-acting-repeatable] respectively). Therapy usually starts with a low dose, which is then adjusted according to clinical and biochemical response.

The antiserotonergic effect of SSA in VIPoma/Verner-Morrison syndrome is excellent. SSA appear to control also to some extent hypersecretion of insulin in metastatic insulinoma. However, due to low or even lacking expression of sstr 2 and 5, little therapeutic efficacy is observed in benign insulinomas, gastrinomas, glucagonomas and somatostatinomas [1].

Tumor regression due to the antiproliferative effect of SSA has been disappointing especially in pancreatic NET and occurs in less than 10% of patients [21]. However, stabilization of tumor growth (documented by imaging procedures such as CT or MRI) can be observed in up to one third of patients [21, 22]. In a highly selected group of patients with progressive metastatic gastroentero-pancreatic tumors, almost half of the patients demonstrated at least stable disease when treated with an ultra-
high dose of lanreotide (3 x 5 mg/d) [22]. In patients with neuroendocrine tumors of the small intestine ultra-high dose treatment may be slightly more effective than conventional dosage.

Side effects with SSA therapy are minor. At the start of treatment, abdominal discomfort, bloating and steatorrhea may occur, but are mostly mild and usually subside spontaneously within a few weeks. Persistent steatorrhea can be treated with oral substitution of pancreatic enzymes. Somatostatin causes production of lithogenic bile, inhibits cholecystokinin secretion and reduces gallbladder motility. Cholestasis is a consequence and cholecystolithiasis develops in up to 60% of the patients [23-25].

**INTERFERON**

The anti-tumor effect of IFN is thought to be due to several complementary mechanisms. Interferons react with specific cell surface receptors to activate a cytoplasmatic signal transduction cascade, which, ultimately, induces the transcription of multiple interferon inducible genes (ISG) leading ultimately to inhibition of tumor growth, including angiogenesis [26, 27].

IFN therapy is not associated with a clear dose-response relationship. Therefore, the dose which is tolerated for long-term therapy has to be adjusted individually (3 to 5 millions IU per day for 3 days per week).

IFN therapy is accompanied by well known side effects such as “flu-like” symptoms limited to the first five days of treatment in almost all patients. Other side effects are referred to in reference [17]. In contrast to SSA, IFN-α appears to be less effective in controlling symptoms in pancreatic NET.

Published data on antiproliferative effects of IFN are hampered by: 1) the various primary tumor locations included in the studies, 2) the large variation of previous treatment modalities included in the studies (IFN-α as either primary or secondary therapy following surgery or embolization with or without systemic chemotherapy), 3) the IFN dose regimen, type of IFN (rIFN-α, rIFN-α2b, human leukocyte IFN) and treatment time differing considerably between the studies; 4) the variable tumor stages were also only partly considered. Finally, based on the slow growth, tumor progression may have become observable only after prolonged treatment [28].

**COMBINATION THERAPY: SOMATOSTATIN ANALOGS PLUS INTERFERON-α**

The combination of SSA and IFN-α is used in order to: 1) enhance the antiproliferative effect of interferon therapy, 2) add the effect of SSA on hypersecretory syndromes and 3) reduce the dose of IFN-α and thus the degree of IFN-related side effects. Although no additional antiproliferative effect was seen in an early study when SSA and IFN-α were combined [29], other reports demonstrated an increase of stable disease for tumor volume and/or remission or stable biochemical parameters [30, 31]. Interestingly, combination therapy could rescue therapeutic escape as determined by biochemical response and reduction of side effects in patients with IFN monotherapy. However, in contrast to these reports in heavily pretreated patients, a recent prospective, randomized, multicentric study in therapy-naive patients showed no additional therapeutic effect for combination therapy [32].

**Systemic chemotherapy**

Systemic chemotherapy clearly represents a therapeutic option in metastatic pancreatic NET. Streptozotocin (STZ), fluorouracil (5-FU), doxorubicin and cisplatin are currently most often used. STZ is an alkylating nitrosurea compound and has been widely used in combination regiments [33]. STZ is either combined with 5-fluorouracil (5-FU) or doxorubicin. In general, systemic chemotherapy is indicated in patients with metastatic disease, when previous therapy with SSA or interferon has failed. The potency of systemic chemotherapy is clearly higher in pancreatic NET as compared to intestinal NET.

Overall, response rates of up to 66% are obtained especially for combination therapy. Remission times tend to last for up to 27 months [5, 34].

More aggressive treatment schemes, such as etoposide and cisplatin, were ineffective in patients with well differentiated neuroendocrine tumors of the gut. In contrast, in 18 patients with undifferentiated, anaplastic, neuroendocrine tumors (5 tumors were of midgut/hindgut origin) objective responses were obtained [7]. However, the median duration of remission was less than eight months.

It is difficult, however, to draw generalized conclusions from these data. Most studies comprise only a small number of patients, the groups are often heterogeneous as to tumor localization, total tumor burden and pretreatment schemes. Although this review endeavors to report only results from patients with metastasizing pancreatic neuroendocrine tumors these restrictions must be kept in mind.

Side effects are more frequent in systemic chemotherapy than biotherapy. In patients treated with STZ, nausea and vomiting occur in up to 90%, beginning 1 to 4 hrs after administration. In approximately 10% they require cessation of therapy. However, odanacarot or other 5-hydroxy-tryptophan receptor antagonists alleviate these symptoms in most patients. STZ can cause kidney damage in some of the patients. Nephrotoxicity increases with the cumulative dosage of drug administration and is due to both, glomerular and tubular dysfunction [35]. Since bone marrow toxicity is low (leukocytopenia or thrombocytopenia in 9% of the patients), combination of STZ with 5-FU or doxorubicin is usually well tolerated. The half-life of doxorubicin is prolonged when given in combination with STZ and its toxicity is increased.

**Methods of cytoreduction and combination with systemic therapy**

In some patients, surgical excision – or local destruction by other methods – of metastatic, potentially functioning tumor tissue may provide palliation and improve long-term survival. In addition, reduced tumor mass may improve the tumor response to systemic therapy. Cytoreduction, i.e. reduction of the tumor burden, has been obtained by surgical excision, or to some extent also by occlusion of the hepatic artery using surgical ligature or embolization with different particles (e.g. gelfoam powder or alcohol particles) alone or in combination with local chemotherapy (i.e. chemoembolization). Cryoablation has been used in only a few specialized centers. Recently, embolization with radioactive particles (radio-embolization) and receptor-targeted radiotherapy for somatostatin-receptor-positive tumors have been introduced. Finally, in selected patients, liver transplantation has been used to radically reduce metastatic tumor burden and/or to attempt surgical cure.

**Receptor targeted radiotherapy**

Somatostatin receptor-targeted radiotherapy is another, still experimental, approach for localized radiotherapy. The density of ssr is higher in the hepatic metastases of neuroendocrine
tumors than in normal liver parenchyma. Internalisation of sstr2 sub-types occurs after ligand binding in vitro in a permanent tumor cell line expressing sstr2 sub-types [36]. The radiolabeled peptide will therefore accumulate in the metastases and radiation is then delivered preferentially to the malignant cells. Initially only the diagnostic substance \(^{111}\text{In-DPTA0}\)-octreotide was available and has been used in a group of twenty end-stage patients with mainly neuroendocrine tumors [38]. However, \(^{111}\text{In}\) is a relatively low energy \(\beta\)-emitter. \(^{90}\text{Yttrium}\), which delivers a higher energy radiation has therefore been used to synthesize \(^{90}\text{Y-[DOTA0-D-Phe1-Tyr3]-octreotide}\), which binds with high affinity specifically to sstr2 sub-types [38]. \(^{90}\text{Y-[DOTA0-D-Phe1-Tyr3]-octreotide}\) was used in patients with sstr-positive neuroendocrine tumors. Significant tumor volume reduction was seen in two patients, and partial remission or stable disease in another two patients each after multiple dose treatment. Four patients received only single treatment. Of these, two had stable disease, while in the remaining two patients \(^{18}\text{F-fluorodeoxyglucose positron emission tomography}\) showed a substantial reduction in glucose uptake [39], indicating reduced metabolism of tumor tissue.

**Liver transplantation**

Organ transplantation has been suggested for patients in whom metastases from endocrine primaries of the pancreas are confined to the liver. Experience with liver transplantation is limited and only a few cases have been reported, mostly as part of larger series that included other neuroendocrine GEP tumors. Despite a few favorable cases, overall results were not encouraging.

In a recent meta-analysis of published worldwide experience, 30 cases of liver transplantation for neuroendocrine tumors of different histological types were evaluated [10]. Fifteen primaries were localized in the pancreas. The median follow-up of these patients was 9 months. The actuarial survival calculated according to Kaplan-Meier was 52% after one year, with 6 patients alive and at risk at 2 years and 3 patients alive and at risk at three years. Twelve patients died within the first year, six due to the transplantation procedure and the other six patients (17% of all patients) due to tumor recurrence (possibly in part due to the obligatory immune-suppressive treatment). Thus, at the present time liver transplantation for patients with metastatic neuroendocrine tumors cannot be considered as a standard treatment option and should be considered only in selected cases. Improved methods for the detection of extrahepatic metastases are necessary before liver transplantation can be used more frequently for patients with a large bilobar hepatic tumor burden.

**Conclusion**

First treatment choice for patients with pancreatic neuroendocrine tumors is surgical resection. Biotherapy, especially SSA, appears to improve survival time. Based also on the low incidence of side effects, SSA are the first treatment option for systemic therapy. Chemotherapy including STZ and 5-FU is a second choice, which may also achieve symptomatic relief, a high rate of stable disease and considerable prolongation of survival time. Systemic chemotherapy either alone or – as a third treatment option – in combination with (repeated) embolization of hepatic metastases could be considered in selected cases. Streptozotocin in combination with 5-fluorouracil is as effective as streptozotocin and doxorubicin, but has lower toxicity. Receptor-targeted radiotherapy represents a promising new therapeutic tool. However, at the present time its final place in the therapeutic armamentarium remains to be determined.

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