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EDITORIAL

Liver-specific therapies for metastases of neuroendocrine pancreatic tumors

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Abstract

The presence or development of liver metastases in patients with neuroendocrine pancreatic tumors is the most important prognostic factor. Liver resection, transplantation and many different therapeutic approaches are discussed in this special review.

Key words: Liver metastasis; Neuroendocrine pancreatic tumor; Liver resection; Liver transplantation; Chemotherapy; Biotherapy

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INTRODUCTION

Pancreatic endocrine tumors (PETs) represent an important subset of pancreatic neoplasms (Table 1). These tumors account for 2%-4% of all clinically detected pancreatic tumors. They consist of single or multiple benign or malignant neoplasms, and are associated with multiple endocrine neoplasia type 1 (MEN1) in 10%-20%[1]. PETs are rare but fascinating tumors. PETs present as either functional tumors, causing specific hormonal syndromes, like Zollinger-Ellison-Syndrome (ZES) or organic hyperinsulinism, or as non-functional PETs (NFPETs) with symptoms similar to pancreatic adenocarcinomas[1,2]. The total incidence of all PETs is approximately 1 in 100 000 people/year[1,2].

NATURAL HISTORY AND PROGNOSIS

The natural history of PETs is highly variable (Table 1)[3]. Small, benign neoplasms, such as 90% of all sporadic insulinomas, are readily curable by surgical resection. The incidence of insulinomas that are malignant is about 10%. Insulinomas greater than 2 cm in diameter without signs of angioinvasion or metastases are considered benign. Surgery cures all patients with benign insulinomas. Danforth and co-authors reviewed 62 cases of metastatic insulinoma[4]. All tumors had metastases, most commonly to the liver and/or lymph nodes. The recurrence rate was 63%, with the median interval to recurrence of 2.8 years. The median survival for patients with recurrent tumors was 19 mo. Palliative resection was associated with a median survival of 4 years, and in those who had a biopsy only it was 11 mo[4]. Although most gastrinomas grow slowly, 60%-90% are malignant (Figure 1). Patients with metastatic gastrinoma have 5-year survival rates of only 20%-38%. Several studies have provided information on the biological behavior of pancreatic and duodenal gastrinomas. It has been shown that both locations are equally malignant, with 40%-70% of patients presenting with metastases. The postoperative disease-free survival rates for both

Table 1 Neuroendocrine tumors of the pancreas

Tumor type (syndrome)	Incidence of PETs (%)	Clinical presentation	Malignancy (%)
Insulinoma	70-80	Weakness, sweating, tachycardia, anxiety, fatigue, headache, dizziness, disorientation, seizures and unconsciousness	< 10
Gastrinoma	20-25	Intractable or recurrent peptic ulcer disease (hemorrhage, perforation), complications of peptic ulcer, diarrhea	50-60
Non-functional tumors	30-50	Obstructive jaundice, pancreatitis, epigastric pain, duodenal obstruction, weight loss, fatigue	60-90
VIPoma	4	Profuse watery diarrhea, hypotension, abdominal pain	80
Glucagonoma	4	Migratory, necrolytic skin rash, glossitis, stomatitis, angular cheilitis, diabetes, severe weight loss, diarrhea	80
Somatostatinoma	< 5	Weight loss, cholelithiasis, diarrhea, neurofibromatosis	50
Carcinoid	< 1	Flushing, sweating, diarrhea, edema, wheezing	90
ACTHoma	< 1	Cushing's syndrome	> 90
GRFoma	< 1	Acromegaly	30
PTH-like-oma	< 1	Hypercalcemia, bone pain	> 90
Neurotensinoma	< 1	Hypotension, tachycardia, malabsorption	> 80

PETs: pancreatic endocrine tumors.

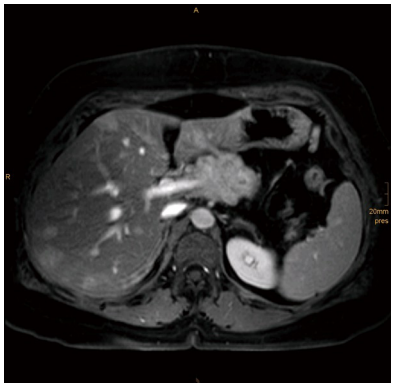

Figure 1 Pancreatic gastrinoma with multiple liver metastases.

tumor types are similar, that is, between 30%-50% after 10 years for sporadic gastrinoma and < 10% for MEN1-related gastrinoma[1,5,6]. Duodenal tumors, however, are smaller, less likely to metastasize to the liver, and have a better prognosis than pancreatic gastrinomas[5]. Most other functional, and all malignant NFPETs, also have a less favourable prognosis. Approximately 50%-80% of these neoplasms recur or metastasize, and up to one-third of patients already have metastases at initial presentation[3]. Historic controls with untreated liver metastases have a 5-year survival rate of only 20%-30%[7]. The natural history of pancreatic tumors in MEN1 patients is difficult to define. Approximately 50% of MEN1-associated pancreatic neoplasms are NFPETs[8]. NFPETs rarely become symptomatic in patients and are commonly detected during regular screening, using CT or MRI. PETs in MEN1 patients usually occur in multiples and NFPETs often coexist beside a clinically dominant functioning lesion. The prevalence of PETs in MEN1 patients is 80%-100%. It is the most common disease-related cause of death, and one should assume that all PETs have the biological ability to develop distant metastases[9]. Patients with PETs generally have a much better prognosis than those with pancreatic adenocarcinoma. Recent studies have reported improved survival after resection; in one study, the median overall survival in resected patients was 58-97 mo, compared with 15-21 mo in patients not undergoing surgery, although the number of patients with information regarding the surgery was small[10]. It is noteworthy that in almost every study, the presence or development of liver metastases, but not lymph-node metastases, is the most important prognostic factor[1,3].

Repeated resections for resectable recurrences or metastases are thought to be indicated in order to improve survival[11]. If an aggressive approach is used, potentially curative resections are possible in up to 62% of patients, and overall, 5-year survival rates of 65% can be achieved[8,11,12]. Debulking resections may also be appropriate. In a study of 170 patients with liver metastases from neuroendocrine tumors, major hepatectomy was performed in 91 patients (54%). The postoperative complication rate was 14%, and two patients died (1.2%). Surgery controlled symptoms in 104 out of 108 patients, but the recurrence rate at 5 years was 59%. Overall survival was 61% and 35% at 5 and 10 years respectively. The authors concluded that debulking extends survival, although recurrence is expected[13]. Removal of the primary tumor in non-metastatic patients may significantly improve survival, compared with that of patients who have not undergone successful primary tumor resection[14]. Solorzano *et al*[15] reported survival data for 163 patients with NFPETs. As expected, patients with localized, non-metastatic disease at the time of diagnosis had a significantly superior median survival compared to those with metastatic disease (7.1 *vs* 2.2 years, $P < 0.0001$). Among those with localized disease, an additional survival advantage was demonstrated for patients who underwent complete resection of the primary tumor, compared to those with locally advanced unresectable tumors (7.1 *vs* 5.2 years)[15].

LIVER RESECTION

An increasing number of studies on surgical treatment of neuroendocrine tumors with liver metastases have been published[15-21] (Figure 2). Although none of these stud-

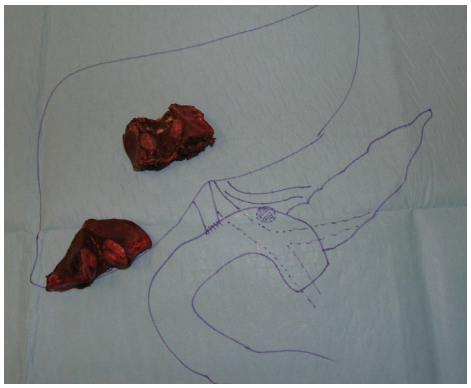

Figure 2 Operative specimen of liver metastases of a non-functional pancreatic endocrine tumor.

ies was a randomized clinical trial, and most of them had a varied proportion of patients with PETs and patients with midgut carcinoid tumors, nevertheless important conclusions can be drawn. In these studies, a total of 118 patients with hepatic metastases from PETs were treated, mostly by surgical resection. There was an average operative mortality of 3% and a 5-year survival rate of 64%[15-21]. In a study by Touzios *et al*[16] the median and 5-year survival were only 20 mo and 25% for patients with their liver metastases treated in a non-aggressive way compared with over 96 mo and 72% for those who had undergone hepatic resection and/or radiofrequency ablation of their liver metastases. In a study by Fendrich *et al*[11], 27 patients with metastases from PETs were treated surgically and 5 and 10-year survival rates of 81% and 72% was achieved. These data are very encouraging, compared with historic controls, where patients with metastatic PETs remained untreated and had a 5-year survival rate of only 30%-40%[22,23]. Que *et al* reviewed the data for 212 patients with partial hepatectomy for metastatic neuroendocrine tumors. The overall morbidity rate was 14%, while the operative mortality rate after partial hepatectomy for metastatic carcinoid disease was 2.3%[24]. However, the favourable outcome observed could be biased, because most of the non-resectable patients with advanced disease were included in the non-surgical group. Therefore, while studies indicate that surgery could benefit some patients with limited liver disease, the best management approach remains inconclusive.

LIVER TRANSPLANTATION

Approximately 120-130 cases of orthotopic liver transplantation for PETs have been published, but long-term follow-up data have been limited, and the individual series were small[25]. Taken together, the data confirm that cure by transplantation is rare. The largest single-center analysis was recently published by Rosenau *et al*[26], reporting on 19 patients who received orthotopic liver transplantation for metastatic NET. The authors reported 1-, 5- and 10-year survival rates of 89, 80 and 50%, respectively. All deaths during long-term follow-up were tumor-associated. Recurrence was diagnosed in 12 patients between 2 wk and 48 mo after the procedure. Orthotopic liver transplantation should therefore only be considered in selected young patients with metastases limited to the liver, and those with a previously resected primary PET who require relief from hormonal or tumor symptoms.

MEDICAL THERAPY

If surgical resection or interventional embolization of the hepatic tumor burden is not feasible, or if the metastases are not confined to the liver, systemic treatment remains the only option. Among systemic therapies, two main approaches have to be considered: biotherapy using somatostatin analoga, interferon or novel multi-targeting agents, and conventional cytoreductive chemotherapy. The choice of therapeutic option depends on the biological behavior of the tumor according to clinical or histopathological parameters, such as grading and proliferation index (Ki67). Furthermore, the localization of the primary tumor (foregut, midgut and hindgut) has to be taken into account, with midgut tumors generally responding less well to systemic chemotherapy, compared to foregut tumors. By definition, none of the systemic therapies is liver-specific, but act on all metastatic sites. In the following section, the main biotherapies and chemotherapeutic regimens will be described.

BIOTHERAPY

Somatostatin analoga are the primary treatment for patients with hormonal symptoms of neuroendocrine tumors of the midgut presenting with carcinoid syndrome. The antisecretory effect of somatostatin analogues results in symptomatic improvement in 40%-80% of the patients[27,28]. In the PROMID study, Rinke *et al*[29] recently provided evidence that a long-acting somatostatin analoga, octreotide LAR, not only provides symptomatic relief, but also mediates anti-proliferative effects by significantly lengthening the time to tumor progression compared with placebo in patients with functionally active and inactive metastatic midgut NETs.

In addition, somatostatin analoga are able to improve symptoms caused by foregut NETs, such as VIPoma and glucagonoma, by overcoming diarrhea and skin rash[28]. In insulinomas, somatostatin analoga have to be used with great caution, since hypoglycemia can deteriorate due to the concomitant suppression of growth hormone and glucagon[28].

Usually, short-acting analoga, such as octreotide, are initially given to test the individual's tolerance, and side effects such as diarrhea and abdominal discomfort. If tolerated well, depot formulations such as octreotide-LAR i.m. or lanreotide autogel s.c. are applied every 4 wk, with the efficacy of lanreotide and octreotide being comparable[28,30,31]. Major side effects of somatostatin analoga may include gallstone formation and, sometimes, but rarely, persistent steatorrhea[28].

Besides somatostatin analoga, interferon-alpha represents the second choice among biotherapies. It acts both directly and indirectly on the tumor cells by inhibiting protein and hormone synthesis and by modulating immune response[28]. To date, recombinant IFN-alpha2a and IFN-alpha2b and their pegylated forms are being used in clinical situations. Interferon has been demonstrated as similarly effective in symptom control when compared to somatostatin analoga, with biochemical responses occurring in 40%-60%, and symptomatic improvement in 50%-60%[32]. However, partial tumor remission could only be noted in 10%-15% of the patients. Due to a larger range of side effects such as flu-like syndrome, weight loss, fatigue, autoimmune reactions and depression, interferon is generally used as a second-line therapy for symptomatic control[32].

CHEMOTHERAPY

Chemotherapy in gastrointestinal neuroendocrine tumors is mainly reserved for poorly differentiated metastatic tumors, but may also be used in selected well or moderately differentiated carcinomas which are either not eligible or resistant to other therapies. Generally, foregut tumors respond better to cytoreductive chemotherapies when compared to midgut tumors.

In most metastatic foregut tumors, first-line treatment consists of streptozotocin (STZ) in combination with 5-FU or doxorubicin, achieving a response rate of between 39%-63%[33,34]. In poorly differentiated, highly proliferating tumors (Ki67 > 20%), cisplatin or carboplatin in combination with etoposide are being used in analogy to regimens used for small-cell lung cancer[28]. With this regimen, response rates can be achieved in up to 67% of the patients[35]. At initiation of chemotherapy, all functionally active tumors should be treated concomitantly with somatostatin analoga in order to avoid a hormonal crisis due to cell lyses[28]. Several agents including temozolomide[36] and thalidomide[37] have been positively evaluated in clinical trials, representing alternative strategies after failure of standard chemotherapies.

For patients with metastatic midgut or hindgut tumors, the results with systemic chemotherapy have been generally poor, with response rates below 10%[28]. It is therefore generally not indicated except in poorly differentiated neuroendocrine carcinomas.

NEW TARGETED AGENTS

During recent years, several small molecule inhibitors targeting one or several kinases have been, or are currently being evaluated in clinical trials, including the multi-kinase inhibitor sunitinib[38] and the mTOR inhibitor everolimus[39]. A recent phase II trial tested everolimus +/- long-acting somatostatin analoga: Everolimus alone resulted in stable disease rates of 68.7% (PFS 9.7 mo), in combination with somatostatin analoga in 77.8% of the patients (PFS 16.7 mo) in patients with pancreatic NETs progressive after chemotherapy[39]. Furthermore, new somatostatin analoga such as pasireotide or anti-angiogenetic strategies using anti-VEGF agents are also being clinically evaluated.

SOMATOSTATIN RECEPTOR RADIONUCLIDE THERAPY

The fact that most neuroendocrine midgut tumors express somatostatin receptors can be used for therapeutic targeting of these receptors with radio-labeled somatostatin analoga. Different analoga have been investigated for somatostatin receptor radionuclide therapy (SRRT), (^{90}Y-DOTA-Tyr3) octreotide and (^{177}Lu-DOTA-Tyr3) octreotate[40], with response rates of up to 35%, according to phase Ⅰ and Ⅱ trials in patients with progressive disease[28,40]. Generally, SRRT is indicated in metastatic endocrine midgut tumors with a positive somatostatin receptor scintigraphy which failed other therapies, in particular, in cases where the metastatic load is not only confined to the liver.

INTERVENTIONAL APPROACHES IN THE TREATMENT OF LIVER METASTASES

Interventional strategies and procedures provide a multitude of options in the treatment of neuroendocrine liver metastases. The main aim of these procedures is firstly, the control of hormonal symptoms in patients with active tumors, and secondly, to control tumor growth and symptoms arising from tumor size.

Two principals behind the procedures can be identified: (1) ablative therapies, such as radiofrequency ablation (RFA) or laser interstitial thermotherapy (LITT); and (2) transarterial approaches, such as transarterial embolization (TAE), transarterial chemoembolization (TACE) and selective intraarterial radiotherapy (SIRT).

Ablative strategies can be used in oligonodular, bilobular liver metastases. These procedures are limited if the metastasis is localized in the vicinity of a liver vein or portal vein, as this leads to a temperature steal phenomenon, lowering the heat in the metastasis needed to ablate the lesion. Furthermore, RFA can be applied in combination with liver resections (in the same setting), or percutaneously with CT-guidance. Henn *et al*[41] treated up to 12 lesions in one RFA setting under CT-guidance with a maximum lesion size of 7.1 cm. Other groups reported successful treatment of lesions with a maximum size of 9 cm[42]. Complications of RFA have mostly been related to electrode application, such as pneumothorax and neuritis at the site of skin entry. Other complications include skin burn, liver abscess and transient elevation of liver enzymes[43].

Laser interstitial thermotherapy (LITT) is a thermal ablation technique that uses a ND-YAG laser, which transports its energy *via* a cannulation needle and a special protective catheter system to the liver metastases. The

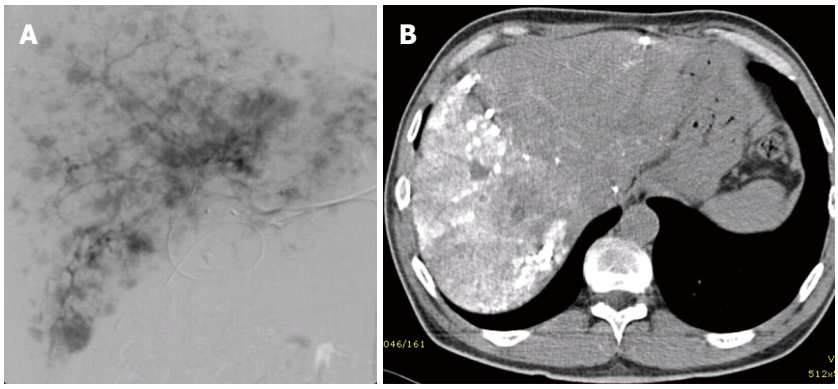

Figure 3 Diffuse liver metastases of a non-functional pancreatic endocrine tumors. Angiography (A) and chemoembolization of the right liver lobe (B).

advantage of this laser application system is that it can be performed under MR-guidance. Furthermore, the efficacy of this procedure can be simultaneously evaluated under MRI[44]. Complications arising from this procedure are similar to those of RFA, being liver enzyme elevation, pleural effusion and subcapsular hematomas.

Loco-regional transarterial therapy procedures can further be subdivided into transarterial embolization (TAE) and transarterial chemoembolization (TACE). The rationale behind these endovascular procedures is the fact that neuroendocrine tumors produce highly vascular metastases in the liver, and those metastases draw their blood supply predominantly (> 90%) from the hepatic artery, rather than the surrounding liver tissue, which receives only 20%-30% of its supply from the hepatic artery, but 70%-80% from the portal vein[43]. In TAE, embolization is performed using lipiodol, gel foam particles, polyvinyl alcohol foam (PVA) and microspheres[45]. As the tumor-supplying artery can be superselectively embolized, the effect of devascularization can be achieved more effectively with a lower possibility of collateral supply, in comparison to surgical ligation. Another advantage of TAE and TACE is that in case of recurrence or revascularization, the procedure can be repeated.

TACE follows the same principles as those of TAE, but an intra-arterial administration of a chemotherapeutic agent is added, prior to the embolization procedure (Figure 3). The advantage of this technique is the synergistic effect of chemotherapy, which has a more than 20 times higher intra-tumoral concentration when compared to a systemic administration, and the effect of tumor ischemia due to embolization[46]. The chemotherapeutic agents and the embolization particles used vary between the different groups and publications, but doxorubicin and streptozocin have mostly been used.

The symptomatic response rate, by which is meant the improvement of symptoms of hormonal syndromes, is estimated for TAE in 64%-93% of patients in a time period of 1-18 mo. TACE is associated with a symptomatic response in between 53%-95% of patients for a period of 1-55 mo[43]. Complications of TAE and TACE vary in the literature. 80%-90% of all patients experience fever, leukocytosis, abdominal pain and liver enzyme elevation. More severe complications range from pleural effusion, liver abscess, bowel ischemia to hepatic infarction.

Selective intra-arterial radiotherapy (SIRT) provides a selective, loco-regional radiotherapy of the liver metastases. In this procedure, ^{90}Y-DOTA-lantreotide is applied directly to the metastases using an interventional approach, and is targeted to the somatostatin receptors expressed by the metastases. The metastases usually express somatostatin receptors 2-5, but the expression has to be verified prior to this procedure using somatostatin-receptor-scintigraphy or ^{18}Fluordesoxyglucose-(DOTA(0)-Phe(1)-Tyr(3) octreotid-PET[47].

CONCLUSION

Neuroendocrine tumors are uncommon but clinically challenging and fascinating tumors with an annual incidence of 1 per 100 000 people. They present either as functional tumors or as non-functional pancreatic tumors. The natural history of NPTs is highly variable. Small, benign neoplasms, such as 90% of all insulinomas, are readily curable by surgical resection; however, most other functional and all non-functional pancreatic tumors have a much less favorable prognosis. The existence or development of liver metastases is the worst prognostic factor. This review describes the current status of surgical, interventional and medical treatment of liver metastases for pancreatic endocrine tumors, and discusses the new developments in this field.

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