

Systemic treatment of neuroendocrine tumors with hepatic metastases

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Neuroendocrine tumors, 1-2% of all malignancies, are relatively slow-growing neoplasms. The majority of neuroendocrine tumors belong to the World Health Organization Group 2 with well-differentiated endocrine carcinomas, but some tumors can be aggressive. The most common are gastroenteropancreatic-neuroendocrine tumors, followed by bronchopulmonary neuroendocrine tumors; less frequent locations are the ovaries, testis and hepatobiliary locations. They can be either non-functioning tumors with symptoms related to mass effects and malignant tumor disease or functioning tumors with specific hormones/neuropeptides autonomously secreted to induce specific clinical syndromes. Localized neuroendocrine tumors are less frequent than metastatic ones; in fact, up to 75% of patients with small bowel neuroendocrine tumors and 30-85% of pancreatic neuroendocrine tumors present with liver metastases either at the time of diagnosis or during the course of the disease. The predominant metastatic site is the liver, which is the best prognostic marker of survival regardless of the primary site. If surgical resection or interventional therapies of the hepatic tumor burden are not feasible, or if the metastases are not confined to the liver, systemic treatment remains the only option. None of the systemic therapies is liver-specific, but rather acts on all metastatic sites. The lack of prospective studies comparing different treatment modalities in homogeneous cohorts of patients makes the best treatment strategy poorly defined. Standard systemic therapy options are somatostatin analogues (octreotide and lanreotide), interferon- α and chemotherapy. Somatostatin analogues not only control symptoms related to functioning tumors but tumor growth as well. Because of the studies challenging its efficacy, as well as the potential for side effects, the more widespread acceptance of interferon- α in the treatment of metastatic neuroendocrine tumors has been limited. Well-differentiated neuroendocrine tumors do not show high sensitivity to chemotherapy because of their low mitotic rates, high levels of antiapoptotic protein bcl-2 and increased expression of the multi-drug resistant gene. Traditional chemotherapeutic agents are streptozotocin in combination with 5-fluorouracil or doxorubicin, or to some extent dacarbazine. Temozolomide, capecitabine and oxaliplatin, as monoagents or in combination therapy, show efficacy in phase II trials. Patients with poorly differentiated neuroendocrine tumor, regardless of the primary tumor localization, are candidates for cisplatin and etoposide chemotherapy regimen. Peptide receptor radionuclide therapy is reported to be an effective treatment option for patients with good performance status and high somatostatin-receptor scintigraphy uptake as well as without major liver involvement. Basic fibroblast growth factor, vascular endothelial growth factor, platelet-derived growth factor, transforming growth factor alpha and beta, insulin-like growth factor type 1, epidermal growth factor, stem cell factor (c-kit), and corresponding receptors have been shown to be expressed in Neuroendocrine tumors. Current phase II-III clinical trials with molecular-targeted therapies revealed promising agents such as everolimus (RAD001), an oral mTOR inhibitor, and sunitinib malate (SU-11248), an oral multitargeted tyrosine kinase inhibitor against vascular endothelial growth factor receptors, platelet-derived growth factor receptors, c-kit receptors, glial cell line-derived neurotrophic factor, and FMS-like tyrosine kinase-3 (Flt 3), which were approved for the treatment of advanced pancreatic neuroendocrine tumors. Ongoing clinical trials with bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, will further define the role of angiogenesis inhibitors in advanced intestinal neuroendocrine tumors. Various further novel strategies of targeted therapy and microRNA-regulated pathways in neuroendocrine tumors are under development.

Key words: Neuroendocrine tumor, hepatic metastasis, chemotherapy, molecular-targeted therapy, biologic agents, peptide receptor radionuclide therapy

Karaciğer metastazları olan nöroendokrin tümörlerde sistemik tedavi

Nöroendokrin tümörler, tüm malignitelerin %1-2'sini oluşturan, oldukça yavaş büyüyen tümörlerdir. Nöroendokrin tümörlerin büyük bir kısmı Dünya Sağlık Örgütü Grup 2 iyi differansiye endokrin karsinomlardır, fakat bazı tümörler agresif seyirli olabilir. En sık görülenler gastroenteropancreatik-nöroendokrin tümörler, daha sonra bronkopulmoner nöroendokrin tümörler ve daha az sıklıkta görülen lokalizasyonlar ise overler, testisler ve hepatobiliyer sistemdir. Kitle etkisi veya malign tümör ile ilişkili semptomlar içeren fonksiyon görmeyen (hormon inaktif) tümörler olabilir veya spesifik klinik sendromlara neden olan otonom olarak spesifik hor-

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mon/nöropeptid salgılayan fonksiyon gören tümörler olabilirler. Lokalize nöroendokrin tümörler metastatik olanlardan daha nadirdir, aslında incebarsak nöroendokrin tümörlerin yaklaşık olarak %75'inde ve pankreas nöroendokrin tümörlerin %30-85'inde tanı anında veya hastalık seyri sırasında karaciğer metastazı mevcuttur. Ana metastatik bölge, primer bölgeden bağımsız olarak sağkalımın en fazla belirleyicisi olan karaciğerdir. Eğer cerrahi rezeksiyon veya hepatik tümöre girişimsel tedaviler uygulanamıyorsa, veya metastazlar karaciğer ile sınırlı değilse sistemik tedavi tek seçenektir. Hiçbir cerrahi tedavi karaciğere spesifik değildir, fakat tüm metastatik bölgelere etki eder. Homojen hasta gruplarında farklı tedavi modellerini karşılaştıran prospektif çalışmaların olmaması, en iyi tedavi stratejisinin tanımlanmamasına neden olmaktadır. Standart sistemik tedavi seçenekleri somatostatin analogları (oktreotide ve lanreotide), interferon- α ve kemoterapidir. Somatostatin analogları sadece fonksiyon gören tümörlerle ilişkili semptomların kontrolünde değil fakat tümör büyümesini de kontrol ederler. Etkinliği ile ilgili çelişkili çalışmalar aynı zamanda potansiyel yan etki profili, metastatik nöroendokrin tümörlerin tedavisinde interferon- α 'nın daha yaygın kullanımını sınırlamıştır. İyi differansiye nöroendokrin tümörler, düşük mitotik indeks, antiapoptotik protein bcl-2 ve artmış çoklu ilaç direnç ekspresyonu nedeniyle kemoterapiye fazla duyarlılık göstermezler. Geleneksel kemoterapi ajanları, 5-florourasil veya doksorubisin veya bir ölçüde dakarbazindir. Faz II çalışmalarda, tek ajan veya kombine tedavi olarak, temozolamid, kapesitabin, veya okzaliptatin etkinlik göstermektedir. Kötü differansiye nöroendokrin tümörlü hastalar, primer tümör lokalizasyonundan bağımsız olarak sisplatin ve etoposid kemoterapi rejimine adaydırlar. Peptid reseptör radyonüklid tedavi, iyi performans durumu ve yüksek somatostatin reseptör sintigrafi tutulumu olan aynı zamanda yaygın karaciğer metastazı olmayan hastalar için etkili bir tedavi seçeneği olarak bildirilmektedir. Temel fibroblast büyüme faktörü, vasküler endotelial büyüme faktörü, trombosit derive büyüme faktörü, transforme büyüme faktörü alfa ve beta, insülin benzeri büyüme faktörü 1, epidermal büyüme faktörü, kök hücre faktörü (c-kit) ve bunlara karşılık gelen reseptörlerin nöroendokrin tümörlerde eksprese olduğu gösterilmiştir. Moleküler hedefe yönelik tedavilerle yapılan güncel faz II-III çalışmaları; ileri evre pankreatik nöroendokrin tümör tedavisinde kullanımı onaylanan oral bir mTOR inhibitörü olan everolimus (RAD001) ve vasküler endotelial büyüme faktörü, trombosit derive büyüme faktörü, c-kit reseptörleri, glial hücre dizisinden köken alan nörotropik faktör ve FMS-benzeri tirozin kinaz-3 (Flt-3) inhibitörü olan oral kullanılan sunitinib malate (SU-11248) gibi ajanları belirlemiştir. Vasküler endotelial büyüme faktörüne karşı geliştirilmiş humanize bir monoklonal antikor olan bevacizumab ile devam etmekte olan klinik çalışmalar, ileri evre intestinal nöroendokrin tümörlerde angiogenesis inhibitörlerinin rolünü daha iyi tanımlayacaktır. Nöroendokrin tümörlerde mikroRNA ile regüle yollar ve hedefe yönelik tedavilerle ilgili farklı yeni stratejiler geliştirilmektedir.

Anahtar kelimeler: Nöroendokrin tümör, karaciğer metastazı, kemoterapi, hedefe yönelik tedavi, biyolojik ajanlar, peptid reseptör radyonüklid tedavi

INTRODUCTION

It is reported that neuroendocrine tumors (NETs) have increased in the last 30 years (1-2% of all malignancies) according to the SEER (United States Surveillance Epidemiology and End Results) database in 2004 (2.5-5 patients per 100,000) (1,2). In another epidemiologic study, the SEER and Norwegian Registry of Cancer (NRC) were compared, and the overall Caucasian SEER NET incidence was 4.44, compared with 3.24 in the NRC, and African Americans exhibited a remarkably high overall NET incidence of 6.50 (3). These epidemiologic observations can be due to increased awareness of the disease, widespread use of advanced diagnostic techniques or true changes in incidence.

In Japan, overall prevalence of GastroEnteroPancreatic (GEP)-NET in 2005 was 2.23 patients per 100,000 population (95% confidence interval (CI): 1.93-2.76) per year, and the incidence of pancreatic NETs (PNET) in 2005 was estimated to be 1.01 per 100,000 population per year (95%CI: 0.88-1.25). As the incidence of PNET in the United States (US) has been reported to be about 0.32 per year per 100,000 population, these tumors seem to develop about three times more frequently in Japan compared to that in the US (4).

The incidence of PNETs is <1 in 100,000 in Asian and European population-based studies.

There is a need for epidemiologic data of NETs in Turkey; case reports or case series related with treatment outcomes, imaging or prognostic factors are the ones most reported (5-7).

Although the majority of tumors are malignant, they are relatively slow-growing neoplasms. World Health Organization (WHO) and tumor node metastasis staging systems of the European Neuroendocrine Tumor Society (ENETS) and American Joint Committee on Cancer (AJCC) have provided the new classification systems. The majority of NETs belong to WHO group 2 with well-differentiated NETs, but some tumors can be aggressive (neuroendocrine carcinomas -G3) (Table 1) (8-10).

The most common ones are GEP-NETs (66%), followed by bronchopulmonary NETs (31%), and less frequent locations are the ovaries, testis and hepatobiliary locations. They are defined as either non-functioning tumors with symptoms related to mass effects and malignant tumor disease or functioning tumors with specific hormones/neuropeptides autonomously secreted to induce specific clinical syndromes. The tumor cells also have the ability to take up amine precursors and/or express somatostatin receptors (SSTRs or ssts). NETs can develop either in a sporadic form or as a compo-

Table 1. WHO classification of gastroenteropancreatic neuroendocrine tumors (8)

WHO 2000	WHO 2010
1. Well-differentiated endocrine tumor	1. Neuroendocrine tumor (NET) G1 (carcinoid)
2. Well-differentiated endocrine carcinoma	NET G2 (carcinoid) (If the Ki67 index exceeds 20%, it can be G3)
3. Poorly differentiated endocrine carcinoma/small cell carcinoma	2. Neuroendocrine carcinoma G3 large or small cell type
4. Mixed exocrine-endocrine carcinoma	3. Mixed adenoneuroendocrine carcinoma
5. Tumor-like lesions	4. Hyperplastic and preneoplastic lesions

nent of inherited endocrine tumor susceptibility syndromes such as multiple endocrine neoplasia (MEN), von Hippel-Lindau syndrome (VHL) and neurofibromatosis-type 1 (NF-1) (11,12).

Secretory markers are important for the biochemical diagnosis of “functioning NETs”. A breakdown product of serotonin, 5-HIAA (5-hydroxyindoleacetic acid) can be measured in a urine sample obtained over 24 hours (h). Although elevated urinary 5-HIAA levels are highly specific for NETs, they are not particularly sensitive. The use of 5-HIAA levels is not limited only by false-positives; they are also generally elevated almost solely in patients who have primary midgut (jejunum, ileum, appendix, and proximal colon) NETs, and are not useful for either foregut (lungs, thymus, stomach, and duodenum) or hindgut (distal colon and rectum) NETs. For detection of tumors with low serotonin production or those lacking DOPA decarboxylase, measurement of platelet and urine serotonin, respectively, has been recommended, but it is not widely applied in clinical practice. Other circulating non-specific peptide markers for NET with lower clinical relevance are synaptophysin, neuron-specific enolase (NSE), pancreatic polypeptide, human chorionic gonadotropin, parathyroid hormone-related protein, or calcitonin (11,13-15).

For PNETS related with specific clinical syndromes, markers for insulinomas, gastrinomas, glucagonomas, and VIPomas include insulin/proinsulin C-peptide, gastrin, glucagon, and vasoactive intestinal polypeptide (VIP) levels, respectively. A common marker for many types of GEP-NETs is chromogranin A (CGA), a soluble secretory glycoprotein localized in neuroendocrine cell vesicles. Levels of circulating CGA are especially useful for non-functioning tumors, which constitute approximately 70-90% of GEP-NETs (16).

Localized NETs are less frequent than metastatic ones; in fact, up to 75% of patients with small bowel NETs and 30-85% of PNETs present with li-

ver metastases either at the time of diagnosis or during the course of the disease (1,11,17).

The predominant metastatic site in patients with NET is the liver (75%), which is the best prognostic marker of survival regardless of the primary site (11,18-20).

Imaging of Liver Metastases

Assessment of the location and extent of disease is crucial for management. Conventional radiology (transabdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI)); selective angiography with or without hormonal sampling; and nuclear imaging (somatostatin-receptor scintigraphy (SRS) (octreotide scan-111 In-DTPAOC), bone scintigraphy and positron emission tomography (PET)/CT) are commonly used imaging modalities. DOTA-d-Phe(1)-Tyr(3)-Octreotide (DOTATOC) or DOTA-1-Nal3-Octreotide (DOTANOC) are highly specific and more sensitive radiopharmaceuticals with high affinity to SSTR-2 and SSTR-2, -3, and -5, respectively. Labelling of DOTATOC or DOTANOC with the positron emitter gallium-68 (68Ga) (68Ga-DOTATOC or 68Ga-DOTANOC) increases the diagnostic sensitivity of PET imaging (18,21-27). Patients with negative 68Ga-DOTATOC or 68Ga-DOTANOC PET/CT results or those with elevated plasma serotonin levels, serotonin and catecholamine precursors 18 F-dihydroxy-phenyl-alanine and 11 C-5-hydroxy-tryptophan, respectively, as tracers are recommended (28). However, for the routine clinical practice of the new imaging technologies, more clinical data are still needed.

All imaging modalities can frequently fail to detect small liver metastases (i.e., tumors <0.5 cm in diameter), underestimating the true disease extent, and give little prognostic information.

Three morphologic patterns of liver metastases have been defined: single metastasis of any size (type I); isolated metastatic bulk accompanied by smaller deposits, with both liver lobes always in-

volved (Type II); and disseminated metastatic spread with both liver lobes always involved, a single lesion of varying size, and virtually no normal liver parenchyma (Type III). The three growth types reflect a different grade of aggressiveness of the disease (G1-3) (11,14,29).

Systemic Treatment of Liver Metastases

If surgical resection or interventional therapies of the hepatic tumor burden are not feasible, or if the metastases are not confined to the liver, systemic treatment remains the only option. 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, hindgut) has to be taken into account. None of the systemic therapies is liver-specific, but rather acts on all metastatic sites.

In metastatic disease, multiple therapeutic approaches are possible. In these cases, the goal is to improve quality of life and to extend survival. Medical treatment can control the associated symptoms and signs of the specific tumors and shrink the tumor mass.

The lack of prospective studies comparing different treatment modalities in homogeneous cohorts of patients makes the best treatment strategy poorly defined. Two recent Cochrane reviews on the optimal management of liver metastases of GEP-NETs did not reveal any evidence for existence of optimal therapeutic strategies (30-47).

Standard Medical Therapies

Biotherapy

Somatostatin Analogues

More than 80% of NETs express SSTRs located on the cell membrane (Table 2).

Long-acting somatostatin (SST) analogues (octreotide and lanreotide) are used frequently to con-

trol hormone-related symptoms and, although their anti-neoplastic activity has not been widely studied and the available data are discordant, it seems to result prevalently in tumor stabilization. The analogues bind with high affinity to sst2 and sst5 and with a lower affinity to sst3. Two long-acting formulations administered every four weeks are available (octreotide-LAR and lanreotide autogel) (48-53).

A few patients who fail to respond or cease to respond to standard SST analogues seem to have a response to higher doses of these drugs.

To clarify the issue of tumor growth control, the PROMID study (**P**lacebo-**C**ontrolled, **D**ouble-**B**lind, **P**rospective **R**andomized Study of the Effect of **O**ctreotide LAR in the control of tumor growth in patients with Metastatic Neuroendocrine **M**idgut Tumors) was published in 2009. This placebo-controlled study included 85 out of 162 planned treatment-naïve metastatic well-differentiated midgut carcinoids (95.3% of cases with low Ki67 <2%). Not only did octreotide-LAR significantly lengthen the time to progression (TTP) compared with placebo (15.6 versus 5.9 months, $p=0.000072$), but stable disease (SD) was achieved in 66.7% and 37.2% of patients with octreotide-LAR and placebo, respectively, as well. It was effective in both functioning and non-functioning tumors. Patients with a tumor burden in the liver of less than 10% and the primary tumor resected benefited the most (median 72 months versus 27.1 months, $p=0.0001$) (54).

Novel somatostatin analogues, SOM230 or pasireotide, have high affinity to sst1, sst2, sst3, and sst5 (30-40 times higher binding affinity to sst1 and sst5 than octreotide and lanreotide). Ongoing clinical trials will show their clinical efficacy (48,55).

Interferon (IFN)- α

Leukocyte IFN can stimulate T-lymphocyte func-

Table 2. Somatostatin receptors in neuroendocrine gastroenteropancreatic tumors [%] (48,49)

Tumor	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
All	68	86	46	93	57
Insulinoma	33	100	33	100	67
Gastrinoma	33	50	17	83	50
Glucagonoma	67	100	67	67	67
VIPoma	100	100	100	100	100
N-F	80	100	40	100	60

SSTR: Somatostatin receptor. VIP: Vasoactive intestinal polypeptide. N-F: Non-functioning.

on and control the secretion of tumor products. It was first used in patients with carcinoid syndrome in 1983. Patients with carcinoid syndrome who may be resistant to somatostatin analogues alone have been reported to benefit from combination therapy with IFN- α for control of symptoms. In 2003, the International Lanreotide and Interferon Alpha Study Group published a prospective randomized multicenter trial on the antiproliferative effect of lanreotide, IFN- α and their combination for therapy of 80 patients with metastatic GEP-NETs (midgut and foregut). No significant difference in the overall survival but apparent disease stabilization in a higher proportion of patients (28%, 26%, and 18% for lanreotide, IFN- α and combined therapy, respectively) suggested that they had a cytostatic effect. Because of the studies challenging its efficacy, as well as the risk of side effects including myelosuppression, fatigue, depression, and alteration of thyroid function, the more widespread acceptance of IFN- α in the treatment of metastatic NETs has been limited (56-61).

Cytotoxic Therapy

Well-differentiated NETs do not show high sensitivity to chemotherapy because of their low mitotic rates, high levels of antiapoptotic protein bcl-2 and increased expression of the multi-drug resistant (MDR) gene. Well-differentiated midgut NETs show low response rates (10-15%) to traditional chemotherapeutic agents such as streptozotocin in combination with 5-fluorouracil (FU) or doxorubicin. However, low-to-moderately differentiated PNET trials with streptozotocin plus 5-FU/doxorubicin or to some extent dacarbazine as a monoagent have produced objective response rates (RR) of 39% and 33%, respectively, and an improved overall survival (OS) (62-70).

On the basis of the activity of dacarbazine, temozolomide (TMZ), a new oral alkylating agent sharing its active metabolite (methyltriazene-1-yl-imidazole-4-carboxamide) with dacarbazine, has been studied in phase II trials including patients with bronchial carcinoids and PNET. Fifteen percent partial responses (PR) and 53% SD with a median TTP of 7 months have been reported (71,72). Because of the *in-vitro* synergistic effects between TMZ and capecitabine, combination therapy for PNET patients as first-line treatment or after a prior chemotherapy revealed 71% and 59% RR, respectively (73). Oxaliplatin-based regimens also have efficacy and may be considered as salvage chemotherapy in well-differentiated NETs. In a

trial including XELOX protocol, 40 patients, 13 poorly differentiated NETs and 27 well-differentiated NETs, were treated with capecitabine plus oxaliplatin (74). 30% PR and 48% SD with a median duration of remission of 20 months and a median survival of 40 months were achieved. Patients with poorly differentiated NET, regardless of the primary tumor localization, are candidates for cisplatin and etoposide treatment, with reported RR of 55-80% and a median duration of response of 8-11 months (75).

Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy (PRRT) targets a molecule to specific receptors located on the surface of tumor cells. After interacting with the receptor, the molecule is internalized to deliver specific and localized radiotherapy for the precise destruction of tumor cells with little effect on non-tumorous tissue, but some exposure of renal, bladder and bone marrow tissues (20,52,76). Radionuclides linked with a somatostatin analogue (octreotide, octreotate and lanreotide) are ^{90}Y trium (^{90}Y), ^{177}Lu lutetium (^{177}Lu), or ^{111}In indium (^{111}In). If the tumor expresses more SSTRs than the surrounding tissue, the PRRT will be more effective; thus, SRS can predict the benefit of the treatment (low and high uptake indicate 20% and 60% chance of effect on liver metastases, respectively), and also the best results are observed in patients with good performance status and without major liver involvement (77). It is reported that RR and response duration are better with ^{177}Lu -DOTATATE therapy than ^{90}Y -DOTATATE therapy (20,78). Side effects of PRRT are hematological and/or renal toxicity, which are rare and usually mild. For up to 25% of patients with neuroendocrine hepatic metastases, PRRT can be useful (30,79,80).

Molecular-Targeted Therapies

Basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor alpha and beta (TGF- α , β), insulin-like growth factor type 1 (IGF-1), epidermal growth factor (EGF), stem cell factor (c-kit), and corresponding receptors have been shown to be expressed in NETs.

mTOR is a serine/threonine kinase involved in the regulation of cell growth and death through apoptosis. A rationale for targeting this pathway in GEP-NETs is the recognized relation existing between tuberous sclerosis complex (TSC), phospho-

tase and tensin homolog (PTEN), NF-1, and the VHL genes and the development of GEP-NETs. In a recent study, TSC2 and PTEN downregulation in a large series of PNETs was shown to be a poor prognostic factor, supporting an important role for the PI3K/Akt/mTOR pathway and its inhibition in the treatment of PNETs (81-84).

Everolimus (RAD001), an oral mTOR inhibitor, has been shown to have activity in GEP-NETs. Furthermore, octreotide can inhibit IGF-1, which is an upstream activator of the PI3K/Akt/mTOR pathway.

RADIANT-1 (RAD In Advanced Neuroendocrine Tumor), a phase II trial, studied everolimus for its activity in patients with advanced well- and moderately differentiated PNETs after failure of a previous chemotherapy. One hundred and sixty patients were enrolled and received everolimus 10 mg/day. Patients were stratified as follows: stratum 1 received everolimus alone (115 patients) and stratum 2 received everolimus and octreotide LAR (45 patients). Overall RR was 9.6% and 4.4% and SD was 68% and 80% in stratum 1 and 2, respectively. Median progression-free survival (PFS) was 16.7 months (95%CI, 11.1 months to NA) in the combined stratum, and 9.7 months (95%CI, 8.3 to 13.3 months) in single agent stratum. Median OS in stratum 1 was 24.9 months (95%CI, 20.2 to 27.1 months) and not reached for stratum 2. An early CGA and NSE response, defined as normalization or $\geq 30\%$ decrease at week 4, significantly correlated with PFS, suggesting a role of these two circulating biomarkers as predictors of response and survival. Although better results were obtained in stratum 2, it is not possible to conclude that the combination is better than everolimus alone due to the design of the study (85).

In another prospective randomized phase III trial comparing everolimus 10 mg/day plus octreotide LAR 30 mg/28 days (216 patients) to placebo plus octreotide LAR 30 mg/28 days (213 patients) in advanced carcinoid tumors of various origin (RADIANT-2 Study), the preliminary data revealed that median PFS was 16.4 months in the combined group versus 11.3 months in the octreotide LAR group (hazard ratio (HR) 0.77; 95%CI, 0.59 to 1.00, $p=0.026$). The study failed to reach the prespecified significance level of $p=0.0246$ (86).

RADIANT-3 is a prospective randomized phase III trial that investigated everolimus 10 mg/day plus best supportive care (207 patients) versus placebo

plus best supportive care (203 patients) in advanced PNET. There was a 2.4-fold prolongation in median PFS with 11.0 months in the everolimus group versus 4.6 months in the placebo group (HR 0.35, $p=0.0001$) (87). Everolimus has been approved by the Food and Drug Administration (FDA) for advanced PNETs.

Current clinical phase II studies with everolimus in NETs are sorafenib and everolimus (<http://ClinicalTrials.gov/identifier:NCT00942682>), bevacizumab and everolimus (<http://ClinicalTrials.gov/identifier:NCT00607113>), and erlotinib and everolimus (<http://ClinicalTrials.gov/identifier:NCT00610129>).

Sunitinib malate (SU-11248), an oral multitargeted tyrosine kinase inhibitor (TKI), is active against VEGFRs, PDGFRs, c-kit receptors, glial cell line-derived neurotrophic factor, and FMS-like tyrosine kinase-3 (Flt 3).

In a phase II study, 107 patients with NETS (41 carcinoids and 66 PNETs) and documented tumor progression received sunitinib 50 mg/day orally for 2 weeks, followed by 2 weeks off. PR was higher in PNETs (16.7%) than in carcinoids (2.4%), and SD was observed in 68% and 83%, respectively. Median TTP was 7.7 months for PNETs and 10.2 months for intestinal NETs (88).

In a prospective randomized phase III study of sunitinib versus placebo in advanced PNETs, patients received either sunitinib 37.5 mg/day (75 patients) or placebo (79 patients). The trial was halted prematurely due to more events in the placebo arm. Sunitinib significantly prolonged PFS with 11.4 months compared with 5.5 months in the placebo group (HR 0.418, $p=0.0001$). Although median OS was not reached, sunitinib was favored by a HR 0.409 ($p=0.0204$), but with longer follow-up there was no statistical difference in OS (89,90). The FDA and European Medicines Agency (EMA) have approved sunitinib for the treatment of unresectable or metastatic, well-differentiated PNETs with disease progression in adults (90,91).

Bevacizumab is a humanized monoclonal antibody against VEGF. Neuroendocrine malignancies are highly vascularized solid tumors. VEGF expression correlates with a more aggressive tumor behavior (92,93).

In a randomized phase II trial in advanced carcinoid tumors, 44 patients with SD on octreotide received bevacizumab 15 mg/kg every 3 weeks or weekly pegylated IFN- $\alpha 2b$ 0.5 μ g/kg during 18 weeks

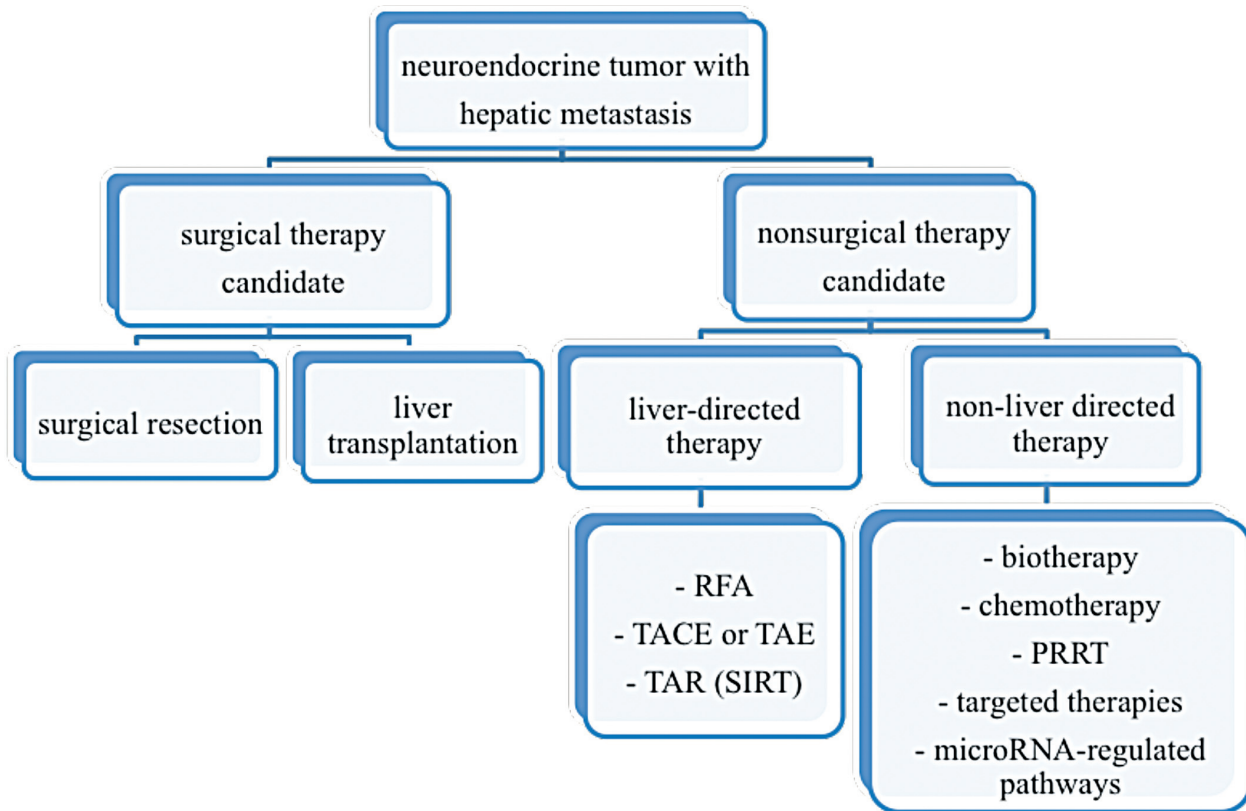


Figure 1. Algorithm for treatment of neuroendocrine tumors with hepatic metastases. RFA: Radiofrequency ablation. TACE: Transarterial chemoembolization, TAE: Transarterial embolization. TAR: Transarterial radioembolization (or SIRT: Selective internal radiation therapy). PRRT: Peptide receptor radionuclide therapy.

(94). The bevacizumab arm showed higher RRs (18% versus 0%), less disease progression (5% versus 27%) and longer PFS after 18 weeks (95% versus 68%). In this study, using a functional CT scan, a significant decrease in tumor perfusion was demonstrated in the bevacizumab arm (49% at day 2 and 28% at week 18).

A prospective randomized phase III study of bevacizumab plus octreotide LAR versus IFN- α plus octreotide LAR in metastatic or locally advanced intestinal NETs (<http://ClinicalTrials.gov/identifier:NCT00569127>), as well as phase II clinical studies of temozolomide plus bevacizumab (<http://ClinicalTrials.gov/identifier:NCT00137774>), CAPOX plus bevacizumab (<http://ClinicalTrials.gov/identifier:NCT00398320>), FOLFOX plus bevacizumab (<http://ClinicalTrials.gov/identifier:NCT00227617>), and RAD001 plus bevacizumab (<http://ClinicalTrials.gov/identifier:NCT00607113>) are still ongoing (92-94).

Various further novel strategies of targeted therapy in NETs are under development.

MicroRNA-Regulated Pathways

MicroRNAs are small, noncoding RNAs that can function as gene regulators by posttranscriptional processing, such as inducing mRNA degradation or repression of translation. MicroRNAs are usually downregulated in cancers (95-97).

While microRNA-133a, -145, -146, -222, -106 are important in primary NETs, microRNA-183, -488, -19a+b are important in metastatic NETs (96). MicroRNA-142-3p, -142-5p, -155, -146a and -483 are upregulated in PNETs as compared to normal tissue. MicroRNA-210, -431, and -424 are upregulated in metastases as compared with tumors, so that microRNAs could be used to predict the probability of metastasis (98,99). Additional studies are needed to understand microRNA-regulated pathways and possible therapeutic targets.

CONCLUSION

Systemic treatment options for a patient with neuroendocrine liver metastases who is not a candi-

date for surgical resection or interventional therapies because of the hepatic tumor burden or because of extrahepatic metastases are vast (Figure 1). The treatment must be tailored specifically to the patient. Systemic therapies can produce longer lifespans as salvage treatment. Although it is hard to conduct large, randomized-controlled trials because metastatic NETs are rare tumors, newer technologies and increased knowledge of pathways will enable the development of new treatment options that may improve survival. The use of prognostic factors for NETs may be helpful for clinical management and for deciding the appropriate treatment for an individual patient (100, 101).

Evidence-based data on therapeutic sequence strategies in inoperable metastatic NETs are not available at present. Consensus recommendations provided by ENETS (European Neuroendocrine Tumor Society), NCCN (National Comprehensive Cancer Network), NANETS (North American Neuroendocrine Tumor Society), NORDIC Neuroendocrine Tumor Group, and ESMO (European Society for Medical Oncology) Clinical Practice Guidelines are useful for clinicians in decision-making (102-106).

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