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Topic: Neuroendocrine Tumors

Management of hepatic metastases of well/moderately differentiated neuroendocrine tumors of the digestive tract

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ABSTRACT

In neuroendocrine tumors (NETs), liver metastases (LM) represent the most crucial prognostic factor, irrespective of the primary tumor site. At diagnosis, about 65-95% of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) show hepatic metastasis. Management strategies of LM are heterogeneous and range from systemic therapy to liver-directed procedures. The type of systemic therapy used is dependent on the grade and proliferation of the tumor and includes somatostatin analogues, interferon, m-Tor and tyrosine kinase inhibitors, and chemotherapy. Angiographic liver-directed techniques, such as transarterial embolization/chemoembolization and selective internal radiation therapy, offer excellent palliation for patients with liver-predominant disease. In highly selected cases, liver transplantation and peptide receptor radionuclide therapy are considered. The relatively low disease incidence and the diversity of presentation have led to a lack of well-conducted randomized controlled trials comparing the efficacy of different treatment options. Experience indicates that surgery is the only treatment that offers potential for cure. For unresectable lesions, the absence of data from rigorous trials limits the validity of many publications that detail management. In this review we will discuss the existing approaches for hepatic metastases from GEP-NETs.

Key words: Gastroenteropancreatic carcinoids; metastases; systemic treatment

INTRODUCTION

Neuroendocrine tumors (NETs) are rare neoplasms originating from diffuse neuroendocrine cells. Even though site of origin could sometimes be unknown, NETs frequently involve any part of the gastrointestinal tract (including endocrine pancreas), bronchopulmonary tree, thyroid, and thymus and have a wide range of malignant potential. The rapid evolution of clinical and pathological findings has hampered a systematic classification of this inhomogeneous family of tumors. The last World Health Organization (WHO) classification was published in 2010.[1] Basically, NETs are classified according to tumor differentiation and site of occurrence. Highly aggressive, poorly differentiated neoplasms were defined as Grade-3 neuroendocrine carcinomas (NECs) when originating from the gastrointestinal tract, or as small- or large-cell NECs when appearing in the lung.[2] Well- to moderately differentiated neuroendocrine neoplasms (WMD-NEN) are a highly heterogeneous group of tumors comprising low-grade (G1) and intermediate-grade (G2) NETs of the gastrointestinal tract, typical and atypical carcinoids of the lung and thymus, and other cancers such as medullary thyroid carcinoma and pheochromocytoma/paraganglioma.[1,2] Finally, NETs could be associated with paraneoplastic syndromes or with a supranormal production of hormones responsible for specific syndromes.

The gastroenteropancreatic NETs (GEP-NETs) are the most common NETs. Due to their relatively indolent course, they are frequently diagnosed in an advanced stage,[3,4] with the development of liver metastases (LM) being the most frequent clinical occurrence.[3-5] Metastatic spread to the liver may be accompanied by a wide spectrum of clinical presentations, from asymptomatic disease incidentally

Access this article online

Quick Response Code:

Website: www.jcmtjournal.com

DOI: 10.20517/2394-4722.2016.37

How to cite this article: La Salvia A, Partelli S, Tampellini M, Tamburrino D, Falconi M, Scagliotti GV, Brizzi MP. Management of hepatic metastases of well/moderately differentiated neuroendocrine tumors of the digestive tract. J Cancer Metasta Treat 2016;2:294-303.

Received: 20-06-2016; **Accepted:** 18-07-2016.

vs. 37.2%).[72] CLARINET trial, a double-blind, phase-III study, randomized 204 patients with well- or moderately differentiated, Octreoscan-positive, nonfunctioning GEP-NETs to receive lanreotide depot 120 mg monthly versus placebo. SSAs therapy obtained a significant improvement in PFS, with a median time not reached in the experimental arm versus 18 months in the placebo group. The estimated rates of PFS at 24 months were 65.1% in the lanreotide group and 33% in the placebo group. No information on disease control rate was reported.[73]

Recently, the clinical activity of the new SSA pasireotide has been evaluated in an open-label, phase-II study enrolling advanced pancreatic and extrapancreatic Grade 1 and 2 NETs.[74] Median PFS of the 29 treated patients was the primary endpoint of the study and was 11 months. According to the RECIST criteria, one patient obtained a partial response and 17 experienced disease stabilization, for a disease control rate of 64%. In all the above-reported trials, treatment with SSAs resulted in low cytoreductive activity as demonstrated by the low objective response rates reported (around 5%). This finding was recently confirmed in an extensive review.[75] Thus, while SSAs can be considered the mainstay of treatment in well- or moderately well-differentiated NETs, both functioning or not, when a disease control is needed, there is no evidence to support the use of SSAs in the "neoadjuvant" setting.

Targeted therapies

Recently, novel targeted therapies such as everolimus and sunitinib have been introduced in the clinical management of G1 and G2 NETs.

Following exciting preclinical data demonstrating mTOR signaling pathway activation in NET cells, everolimus was extensively studied in cancer patients.[76-78]

A randomized, phase-III, double-blind study (RADIANT-3) enrolled 410 patients with locally advanced or metastatic well- to moderately differentiated pancreatic NETs, comparing the PFS of patients treated with everolimus 10 mg/day to that of patients receiving placebo. The study met its primary endpoint as patients treated with everolimus presented a longer median PFS (11.0 *vs*. 4.6 months). Response rate was low, with only 5% of the patients randomized to receive everolimus achieving a partial response.[79] Similar encouraging results have been obtained in the phase-III placebo-controlled RADIANT-2 study enrolling patients with well- and moderately differentiated locally advanced or metastatic NETs and carcinoid syndrome. Patients receiving everolimus plus SSA (octreotide LAR) presented a longer PFS than those treated with octreotide LAR plus placebo (16.4 *vs*. 11.3 months, $P = 0.026$). Overall response rate was similar in both groups, with 2% of patients achieving a partial response and 82% disease stabilization.[80] The advantages of treating patients with everolimus have recently been confirmed in a randomized, double-blind, placebo-controlled, phase-III RADIANT-4 trial. The study evaluated everolimus efficacy in patients with advanced, well-differentiated NETs of different origin and with nonfunctional disease. Patients in the everolimus arm of the study presented a significant improvement in PFS (11.0 *vs*. 3.9 months).[81] Interestingly, according to subgroup analysis, the positive treatment effect was confirmed irrespective of the extent of liver metastasis. Objective responses were recorded in four (2%) patients receiving everolimus and in one patient (1%) receiving placebo. Disease stabilization was the best overall response in 165 patients (81%) in the everolimus group, compared with 62 patients (64%) in the placebo group. The findings of these three studies were consistent with the role of everolimus in prolonging PFS and not in achieving tumor shrinkage. Thus, everolimus cannot be proposed as a preferred therapy in the neoadjuvant setting.

The activity of sunitinib, a multityrosine kinase inhibitor of vascular endothelial and platelet-derived growth factor receptors, was explored in a double-blind, placebo-controlled, phase-III trial enrolling 171 patients with advanced, well-differentiated progressing pancreatic NETs.[82] The study met its primary endpoint, as median PFS of patients receiving sunitinib was significantly longer than that of patients treated with placebo (11.4 *vs*. 5.5 months). In contrast to what was observed in patients with renal cell carcinoma,[83] tumor shrinkage rate in patients with pancreatic NET was low; only 9% of those treated with sunitinib achieved an objective response according to the RECIST criteria.

The high rate of vascularization of NETs led to initial interest in angiogenesis inhibition as a promising field of research. Furthermore, an overexpression of vascular endothelial growth factor (VEGF) has been observed in both carcinoid and p-NET (either in serum or in tissue), thus making VEGF and VEGFR excellent targets to be inhibited.[84] The anti-angiogenetic agent bevacizumab has been investigated combined with IFNα in a randomized phase-II trial of 44 patients with advanced (unresectable or metastatic) carcinoid tumors. Patients were randomized to receive 18 weeks of single agent bevacizumab or IFN. At disease progression or after 18 weeks of treatment, patients were allowed to receive the combination of these two treatments. The results obtained in the bevacizumab arm were encouraging; a partial response was achieved in 18% of the patients, with a better 18-week PFS than in the IFN group (95% *vs*. 67%, respectively).[85] However, even though bevacizumab monotherapy has been associated with improvement in response rate and survival, the results obtained in terms of tumor shrinkage were not encouraging, probably because of the cytostatic rather than cytotoxic effect of antiangiogenic therapies. Therefore, the role of bevacizumab-based combination therapy has been evaluated, mostly with chemotherapy agents or with mTOR inhibitors in the management of advanced GEP-NETs. In the randomized phase-II study CALGB80701 (Alliance), patients with metastatic pNETs were randomly

treated with everolimus or everolimus plus bevacizumab. The overall response rate was 31% and 12% for the combination treatment and everolimus alone, respectively. The current evidence from this available clinical trial suggests that combination strategy was more active but not more effective in terms of PFS.[86]

Chemotherapy

While chemotherapy is the standard of care for aggressive, poorly differentiated (G3), advanced, or metastatic NECs,[87] it could represent a therapeutic option in symptomatic and progressive well- or moderately differentiated NETs. Notwithstanding a relatively high number of agents which have been demonstrated to be active in this latter tumor setting (platinum salts, 5-fluorouracil, doxorubicin, streptozotocin, temozolomide, and capecitabine), the best chemotherapeutic strategy remains controversial.[88]

As far as unresectable or metastatic pancreatic NETs are concerned, polychemotherapy was more active than monotherapy, with a response rate in this latter group lower than 20%. A retrospective study evaluating the combination of streptozotocin (STZ) with doxorubicin and 5-fluorouracil (5-FU) reported a response rate of 39%, with a median response duration of 9.3 months. The 2-year PFS rate was 41%, and the 2-year OS rate was 74%. Tumor burden clearly affected survival outcomes in both univariate and multivariate analyses. In fact, the PFS rate at 2 years for patients with LM involving ≤ 75% of the parenchyma was 41%, whereas all 12 patients with LM involving more than 75% of the organ had experienced disease progression by 14.2 months ($P = 0.01$). At 2 years, the OS rate for patients with LM ≤ 75% was 83%, whereas all 12 patients with LM more than 75% had died at 15.5 months ($P = 0.0001$).[89]

The combination of temozolomide with capecitabine was demonstrated to be more active and better tolerated than STZ-based regimens. In a retrospective study enrolling metastatic pancreatic NETs, objective response rate of temozolomide combination was reported to be 70%. It has to be noted, however, that in this study only 30% of the patients had moderately differentiated (G2) tumors.[90] The combination of octreotide LAR 20 mg, metronomic capecitabine, and intravenous bevacizumab was explored in the XELBEVOCT phase-II study enrolling 45 patients with well- to moderately differentiated NETs from various primary origins (pancreas, intestinal tract, lungs, and unknown site). Objective response rate was 17.8% with a median PFS of 14.9 months. This study demonstrated that the combination of SSA plus capecitabine and bevacizumab was active and well tolerated in this group of patients.[91]

Finally, a retrospective study evaluated the combination of 5-fluorouracil, dacarbazine, and epirubicin in patients with well-differentiated NETs originating from pancreas, intestine, stomach, gallbladder, kidney, or an unknown site. Chemotherapy was well tolerated and outcome results were encouraging. Tumor shrinkage was obtained in 44% of the patients, with a median duration of response of 12 months. Objective response rates recorded in pancreatic, gastrointestinal, and extradigestive NETs were 58%, 25%, and 36%, respectively. Interestingly, disease control was achieved in 83% of the patients progressing at the time of study inclusion. Median PFS was 11 months and OS was 21 months.[92]

Notwithstanding this body of evidence, the number of patients enrolled in each study was relatively low, thus preventing any definitive conclusion on which could be the best chemotherapeutic strategy for each subset of patients. New multicenter, well designed, randomized clinical trials are needed.

CONCLUSION

About one in seven patients diagnosed with digestive NETs presents with metastatic disease at the time of diagnosis, with the liver being the most frequently involved organ. Moreover, 25% to 90% of patients who are nonmetastatic at diagnosis are expected to develop metastases during the course of the disease. In clinical practice, hepatic failure represents the primary cause of death in these patients. Surgery is the only technique that may permit curability of liver involvement. Thus, all treatments should primarily be focused on tumor shrinkage, especially when unresectable liver lesions could become resectable if reduced in size. When complete resection is not possible, treatment goals should be tumor control and symptom relief.

Complete resection of primary and metastatic disease (when possible) and surgical debulking of symptomatic diseases are standard procedures for G1 and G2 NETs. To patients with Grade 1 or 2 NETs (either pNETs or gastrointestinal NETs) with LM and without extra-abdominal metastasis and peritoneal carcinomatosis, surgery permits the best results in terms of recurrence-free survival and outcome. Unfortunately only 10-25% of patients can be directly submitted to surgical resection. These considerations suggest that "neoadjuvant strategies" should be explored in patients with liver-confined metastatic disease. Despite the proven efficacy of different systemic treatment strategies for metastatic NETs (SSAs, PRRT, chemotherapy, or target therapies such as everolimus, sunitinib, and bevacizumab), none of these approaches resulted in significant tumor shrinkage. Few studies have explored systemic therapies in the neoadjuvant setting. Unfortunately, trial designs, inhomogeneous inclusion and exclusion criteria, and the relatively low number of patients have hampered definitive conclusions in this patient setting.

Further research is needed to determine the value of these medical treatments as a cytoreductive strategy against LM from NETs. Moreover, loco-regional approaches to LM, such as radiofrequency ablation, laser ablation, or intra-

arterial therapies (embolization/chemoembolization), may be useful in reducing tumor burden only in selected cases. Application of the concept of tumor response as defined by RECIST or WHO criteria in patients with metastatic NETs is worthy of mention. Often it is difficult to select the target lesions to be monitored over time. Furthermore, necrosis or hemorrhage within other clinical occurrences may be misinterpreted as a stable disease instead of a response.

In conclusion, while surgical management of resectable LM from NETs is a standardized procedure, there is no consensus on the best therapeutic strategy for all other patients. For example, it is a matter of debate whether incomplete surgical resection of bulky but asymptomatic metastasis from NETs is preferable to systemic biotherapy. Extremely promising recent data have been reported in the Radiant 4 trial, suggesting that novel therapies (in particular the mTOR inhibitor everolimus) will play an increasingly important role in the management of advanced LM irrespective of the extent of liver metastasis.

Large prospective studies are needed to evaluate the optimal management of hepatic metastases from NETs, defining common guidelines and allowing the choice of the best treatment strategy for each individual patient.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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