MEDICAL TREATMENT OF NEUROENDOCRINE TUMORS (NETs) OF THE LUNG

Aija Gerina-Berzina
Department of Oncology, Riga Stradiņš University,
Ilze Strumfa
Institute of Pathology, Riga Stradiņš University, Latvia
Andrejs Vanags
Department of surgery, Riga Stradiņš University, Latvia

Abstract

The improvement in histological diagnostic tools, including neuroendocrine markers by immunohistochemistry (IHC), has led to an increased recognition of pulmonary neuroendocrine tumors. This may explain their rapid increase in incidence, representing roughly 30% of all neuroendocrine tumors. NETs represent about 3% of all lung cancers. The incidence of pulmonary NETs is low, although reported to have increased over the past 30 years. According to the surveillance, epidemiology and end results program (SEER) database from 2003, the combined incidence has been 1.57/100 000 inhabitants. The median age at diagnosis for bronchial NETs is 64 years and for thymic NETs 59 years. The main therapy for bronchial NETs is surgical resection. The surgical approach is dependent on the size, location and tissue type. Bronchoscopic laser excision of intraluminal typical bronchial NETs should be considered a suboptimal treatment and reserved for inoperable patients or performed as preoperative disobliterating procedure. Cytotoxic treatment combined with surgical resection when indicated has been the standard for metastatic bronchial and thymic NETs, although the available chemotherapy regimens demonstrate a rather poor effect. Chemotherapy for small-cell lung cancer (SCLC), which is a chemosensitive but not curable cancer, is discussed in the appropriate guidelines.

Keywords: Neuroendocrine tumors (NETs), somatostatin analogs, chemotherapy, targeted therapy

Introduction:

The improvement in histological diagnostic tools, including neuroendocrine markers by immunohistochemistry (IHC), has led to an

increased recognition of pulmonary neuroendocrine tumors. This may explain their rapid increase in incidence, representing roughly 30% of all neuroendocrine tumors. NETs represent about 3% of all lung cancers. Unfortunately, with the exclusion of small-cell lung cancer (SCLC), no large phase II and III trials for pulmonary neuroendocrine tumors have been published.

Neuroendocrine tumors (NETs) of the lung comprise a heterogeneous population of tumors ranging from well-differentiated bronchial NETs to highly malignant and poorly differentiated small-cell lung cancer (SCLC) and large-cell neuroendocrine carcinoma (LCNEC). The incidence of pulmonary NETs is low, although reported to have increased over the past 30 years (Yao JC, et al., 2008) (Skuladottir H, et al.,2002). Typical carcinoids (TCs) comprise~1%–2% and atypical carcinoids (ACs) only 0.1%–0.2% of pulmonary neoplasms. According to the surveillance, epidemiology and end results program (SEER) database from 2003, the combined incidence has been 1.57/100 000 inhabitants (Gustafsson BI, Kidd M, Chan A et al., 2008). SCLC is the most common bronchial NET reported to account for 15%–20% of invasive lung cancers. LCNEC comprise 1.6%–3% of resectable lung cancers. The prevalence of thymic NET is~3% of the total number of NETs at all sites. In the last SEER database, a reported incidence of thymic NETs is 0.02/100 000 population per year (Gaur P., et al., 2010). They constitute~5% of all thymic tumors. The median age at diagnosis for bronchial NETs is 64 years and for thymic NETs 59 years.

NETs of the lung include the low-grade TC (well-differentiated), the high-grade LCNEC (poorly differentiated) and SCLC. Mixed tumors are found in < 5% of patients and are more frequently found in the peripheral areas of the lung. About 70% of all bronchial NETs are located in the major bronchi and the remainder in the periphery of the lungs. They occur more frequently (60%) in the right than in the left lung, and particularly in the middle lobe (Travis WD,et al., 1998). The cell of origin for bronchial NETs have been suggested to be pulmonary neuroendocrine cells (PNECs) that usually exist as solitary cells, but sometimes aggregate to form small nodules termed neuroepithelial bodies (NEBs), which are located within the ciliated epithelium. PNECs express serotonin and neuron-specific enolase (NSE) and also gastrin-releasing peptide (GRP) (Righi L, Volante M, Rapa I et al., 2007). Up to 90% of patients with central bronchial NETs are symptomatic, presenting with hemoptysis, cough, recurrent pulmonary infection, fever, chest discomfort and unilateral wheezing, while peripheral carcinoids are incidentally discovered in most of the cases (Travis WD,et al., 1998). The carcinoid syndrome is very rare in patients with bronchial NETs. Nevertheless, a carcinoid crisis may occasionally occur in previously

asymptomatic patients following bronchoscopic biopsy laser disobliteration, surgical manipulation or peptide receptors radiotherapy (PRRT).

Well-Differentiated Neuroendocrine Tumors of the Thorax (Includes Lung and Thymus)

Adjuvant Therapy

There are currently no data to suggest that adjuvant therapy (radiation, chemotherapy, or chemoradiation) will prolong a disease-free interval or median survival. Therefore, at this time, there are insufficient data to recommend the use of adjuvant therapy after complete resection of local-regional disease (Fukai I, Masaoka A, Fujii Y, et al. 1999) (de Montpreville VT, et al., 1996).

Perioperative Treatment of Carcinoid Syndrome

Treatment is centered on prevention. Premedication with octreotide, such as a single subcutaneous injection of 250 to 500µg, should be a sufficient prevention for most minor procedures (Parris WC, et al., 1988). Recommend having extra doses available in the operating room or treatment area, to be given in 250µg amounts or greater, should the need arise. For major procedures, a preoperative intravenosus bolus of 250 to 500 µg, followed by a continuous infusion of 100 to 500 µg/h during the procedure, has been reported (Weingarten TN, Abel MD, Connolly HM, et al., 2007). The infusion is then weaned by 50% daily for a few days until it can be safely discontinued and is sometimes supplemented by a dose of long-acting depot somatostatin analog. Additional preoperative preparation can include short-acting corticosteroids and antihistamines (H1-and H2-blocking agents). Hypotension, which is not attributable to acute blood loss, should be treated with boluses of octreotide, steroids, and volume expansion. Bronchospasm can also be reversed similarly to most allergic reactions with steroids. Vasopressors should be avoided because these agents are known to potentiate the release of serotonin and vasoactive amines from these tumors. Low doses of dopamine, vasopressin, and neosynephrine after pretreatment with a high-dose octreotide infusion can effectively prevent perioperative precipitation of carcinoid crises (Weingarten TN, Abel MD, Connolly HM, et al., 2007).

Treatment of Refractory Carcinoid Syndrome

The causes for refractory carcinoid syndrome in NETs, particularly refractory diarrhea, include an increase in hormone production by the tumor, development of steatorrhea because of pancreatic exocrine insufficiency secondary to somatostatin analogs, and development of pellagra because of niacin deficiency (Alexandria T. Phan et al., 2010).

Somatostatin Analogs

The short-acting somatostatin analog is administered initially as a test compound to determine safety and tolerability of the long-acting formulation and as a rescue injection for periods when the patient is exhibiting severe or recalcitrant symptoms. Currently, the long-acting release form of octreotide is offered in 10-, 20-, and 30mg formulations, and the currently recommended starting dosage is 20 mg/mo. Careful review of the octreotide drug registration data reveals that octreotide blood levels are weight dependent (Rubin J, et al., 1999) (Harris AG, et al., 1995).

Recent data suggest that up to 40% of patients who are treated with the long-acting release formulation may need additional rescue injections of short-acting somatostatin at somepoint during their disease course. The need for a short-acting rescue medication to optimize symptom management is further supported by the data from the registration trial for octreotide long-acting release. In that trial, 40% of patients required weekly rescue medication (regardless of long-acting release dose) and 70% of patients required rescue injections at some time during the registration trial.

Interferon alpha

Most investigational trials have studied recombinant IFN-α2a or IFN-α2b. In 30% to 70% of the patients with carcinoid syndrome, symptomatic remission with IFN therapy is observed, with a superior effect on flushing compared with diarrhea (Wymenga AN, et al., 1998). The effectiveness of IFN to control the symptoms of carcinoid syndrome is similar to that of somatostatin analogs, but the onset of response is more delayed. In patients with the carcinoid syndrome, comparing IFN to somatostatin analog, remission or stabilization of tumor markers and/or urinary 5-HIAA excretion was observed in 36% to 44% and in 30% to 35%, respectively. In most patients, symptoms of flulike syndrome occur during the first 5 days of IFN administration. Other common adverse effects include anorexia, weight loss, fatigue, and dose-dependent bone marrow toxicity including anemia, leucopenia, and thrombocytopenia. Less common adverse effects include hepatotoxicity, depression, mental disturbances, and visual impairment (Shah T, Caplin M., 2005) (Plockinger U, et al. 2008). The combination of octreotide and IFN-α has also been studied. Patients for whom octreotide alone produced suboptimal symptom control were included in 3 studies of 24, 19, and 9 patients (Frank M, et al., 1999). Patients for whom monotherapy with IFN had no benefit were also included in 1 of these studies (Janson ET, et al., 1992). Biochemical responses were reported in 77%, 72%, and 75% of patients treated with combination therapy. Results of these studies suggest that there may be synergism between somatostatin analogs and IFN in controlling symptoms of carcinoid syndrome.

Serotonin Receptor Antagonists

Serotonin receptor subtype 5-HT1 and 5-HT2 antagonists, such as methysergide, cyproheptadine, and ketanserin, and 5-HT3 antagonists, such as ondansetron, have also been used in patients with the carcinoid syndrome. These drugs generally result in symptomatic improvements of diarrhea and nausea but not of flushing (Orbach-Zinger S, et al., 2002).

Anti diarrheal Agents

Like in other causes of secretory diarrhea, opiates and loperamide have been used for a symptomatic improvement of diarrhea in patients with the carcinoid syndrome.

Cushing Syndrome

Bronchial and thymic NETs can cause Cushing syndrome because of the ectopic production of adrenocorticotropic hormone (ACTH). A bronchial NET is the most common cause of ectopic ACTH production.

Cushing syndrome could be treated with commonly available agents such as ketoconazole, metyrapone, aminoglutethimide, etomidate, mitotane, or mifepristone. Ketoconazole is the most popular and effective; it acts on several of the P450 enzymes, including the first step in cortisol synthesis, cholesterol side-chain cleavage, and conversion of 11-deoxycortisol to cortisol. A daily dose of 600 to 800 mg of ketoconazole can effectively decrease cortisol production. Adverse effects of ketoconazole include headache, sedation, nausea, irregular menses, decreased libido, impotence, gynecomastia, and elevated liver function tests. Metyrapone blocks 11-β-hydroxylase activity, the final step in cortisol synthesis. Therapy with metyrapone starts at 1 g/d divided into 4 doses and increases to a maximum dose of 4.5 g/d. Adverse effects are secondary to an increase in androgen and mineralocorticoid precursors and include hypertension, acne, and hirsutism. Aminoglutethimide is an anticonvulsant agent that blocks cholesterol side-chain cleavage to pregnenolone, with a relatively weak adrenal enzyme inhibitor at doses that patients can tolerate. Currently, ami-noglutethimide is not commercially available for use. Similar to metyrapone, etomidate, an imidazole-derivative anesthetic agent, blocks 11-β-hydroxylase. Its use is limited to short-term duration because it has a short half-life and its route of administration is intravenous. Etomidate dosage is usually started at 0.3 mg/kg per hour. Mitotane is an adrenolytic agent that acts by inhibiting 11-β-hydroxylase and cholesterol side-chain cleavage enzymes. This drug also leads to mitochondrial destruction and necrosis of the adrenocortical cells in the zona fasciculate and reticularis. For this reason, it is used in the treatment of patients with adrenal cortical carcinoma. Mitotane can be used in combination with metyrapone. Mitotane is expensive with a very narrow

therapeutic index. Adverse effects include moderate gastrointestinal and neurologic toxicity: nausea, vomiting, diarrhea, dizziness, and ataxia. Another important limitation of mitotane is that it is potentially teratogenic and can cause abortion. Mifepristone (RU 486) is an antiprogestational agent, which, at high doses, competitively binds to the glucocorticoid and progesterone receptors. Although it may be effective, availability and use are currently restricted. In some patients, bilateral adrenalectomy may be necessary to control for Cushing syndrome when all medical therapy failed. For ectopic growth hormone-releasing hormone (GHRH) secretion and acromegaly, somatostatin analogs can be of value. Some patients with ectopic ACTH syndrome might respond to a somatostatin analog as well (Scanagatta P, et al., 2004).

Acromegaly from the ectopic production of GHRH is a rare manifestation of bronchial NETs. Bronchial NETs are the most common cause of extrapituitary GHRH secretion. These patients will likely respond to Somatostatin Analog or to surgical debulking (Scheithauer BW, et al., 1984).

Treatment of Advanced Disease

The decision to initiate therapy is based on a number of clinical and pathological factors including tumor grade, symptoms, performance status, and organ functions. Initiation of therapy for progressive disease should be considered if patients have symptoms, bulky disease, or evidence of tumor growth. Treatment of asymptomatic patients with limited evaluable disease and no evidence of progression can also be considered using agents with a favorable safety profile such as a somatostatin analog. For patients with unresectable disease confined to the liver, liver-directed therapy should be considered (Rubin J, et al., 1999).

Somatostatin Analogs

Somatostatin analogs have been widely used in NETs for the control of hormonal syndromes. Although somatostatin analogs have also been frequently used for theoretical cytostatic activity, until recently there were no prospective data to support the antiproliferative role of somatostatin analogs. In 2009, a somatostatin analog was demonstrated to have an antiproliferative activity, where progression-free survival duration of patients with well-differentiated NETs treated with 30 mg of octreotide long-acting release was prolonged compared with those patients who only received placebo (median progression-free survival, 14 vs 6 months; hazard ratio, 0.34; 95% confidence interval, 0.2- 0.6; $P<0.0001$) (Rinke A, et al., 2009).

Interferon-α

Interferon-α has been reported to induce disease stabilization and to lead to objective responses in a small number of patients. Most of these studies, however, are underpowered. Pooling the data from patients with NETs involved in these studies, only 37 (12%) of 309 had objective tumor responses (Schnirer II, et al., 2003).

Combining somatostatin analogs with IFN can theoretically enhance antitumor activity. Two underpowered random assignment studies have attempted to compare single-agent and combination therapy. In 1 study, NET patients who have undergone debulking by surgery and hepatic artery embolization were randomly assigned to octreotide or octreotide plus IFN. A significant improvement in time to progression was observed in the IFN arm (hazard ratio, 0.28; 95% confidence interval, 0.16-0.45) (Kolby L, et al., 2003). In a second random assignment trial, patients were treated with lanreotide, IFN or lanreotide plus IFN. Objective response rates were 4%, 4%, and 7%, respectively (Faiss S, et al., 2003). Although there is no defined standard therapy for NET patients with progressive disease, somatostatin analog plus IFN can be considered as an accepted option.

Chemotherapy

For metastatic well-differentiated NETs as a group, multiple cytotoxic drugs have been tried in various combinations; however, randomized trials have revealed only minor activity. As a result, there is no standard regimen, and the role of chemotherapy for advanced well-differentiated NETs, in general, continues to be debated. Patients with foregut NETs such as those originating from the lung and thymus may derive some benefit from cytotoxic chemotherapy. Results from a published phase 2 study suggest antitumor activity with singleagent temozolomide for well-differentiated NETs, particularly those with foregut NETs. Patients with metastatic or inoperable advanced NETs included 13 bronchial NETs (10 typical and 3 atypical); all received oral temozolomide for 5 consecutive days every 28 days (Ekeblad S, et al., 2007). Four (31%) had a partial response, whereas 4 others (31%) had stable disease. The limited efficacy of chemotherapy has prompted investigation of novel therapeutic approaches for patients with advanced NETs. These include targeted radiotherapy (eg, therapeutic ^{131}I-MIBG, lutetium Lu 177 octreotate), inhibitors of angiogenesis (eg, bevacizumab), small molecule tyrosine kinase inhibitors (eg, sunitinib), and mammalian target of rapamyacin small molecule inhibitor (eg, everolimus). These novel treatments, although demonstrating promising efficacy in clinical studies, are still considered investigational therapy and are currently only available to patients on clinical trials.

Liver-Directed Therapy

Many patients with NETs have extensive liver involvement and may require regional liver therapy. Regional arterial therapies are administered through angiographic catheters and can be delivered in a segmental, lobar, or whole liver distribution. These include bland embolization, chemoembolization, radioactive microsphere embolization, and percutaneous hepatic perfusion. Particle embolization with or without chemotherapy has long been the standard therapy for NET patients with extensive liver involvement (Pommier RF, et al., 1996) (Gupta S, et al., 2005). Patients can frequently develop postembolization syndrome (fever, pain, nausea, and vomiting), requiring a short stay in the hospital. Prospective randomized controlled comparison of hepatic artery embolization and chemoembolization is lacking. Therefore, the question of whether hepatic chemoembolization is better than hepatic bland embolization for patients with NETs remains unresolved. In recent years, radioactive microsphere embolization is emerging as a well-tolerated outpatient procedure, providing symptom relief and encouraging response rates (Kennedy AS, et al., 2008). Preliminary data with percutaneous hepatic perfu- sion using melphalan in patients with NETs are also encouraging. Regional treatments have also been used to convert patients with unresectable to resectable disease; the frequency of conversion remains rare.

These nonsurgical therapies are reserved for patients who have no surgical options. A multidisciplinary team approach to formulate individual therapy specific and optimal for each NET patient consisting of surgical and/or nonsurgical treatment is highly recommended. Often, hepatic tumor burden can be safely cytoreduced using a multispecialty approach involving experienced interventional radiologists, hepatobiliary surgeons, and medical oncologists. Even in the setting of unresectable disease, patients with NETs should be periodically assessed for disease status (stable or progressive disease) and surgical candidacy.

Follow-Up of Patients with Thymic and Bronchial NETs

General guidelines consist of identifying any disease-related symptom(s), biochemical markers (specific and nonspecific), and imaging assessment to determine the precise tumor localization and possible metastases by CT or MRI and [^{111}In-DTPA^{0}]octreotide scintig- raphy (Octreoscan). After surgery, patients are typically reevaluated 3 months postoperatively to establish a new ‘baseline’. The term ‘as clinically indicated’ refers to changes of symptoms or signs from baseline, rising tumor marker(s), and CT/MRI changes suggestive of tumor growth. Tumor markers to consider are dependent on the primary NET site. Serum CgA is the most sensitive but the least specific, whereas urine 5-HIAA is the most specific

but not sensitive for diagnosing early disease. Serotonin is recognized as a variable and labile tumor marker when followed serially, but it may be useful in making a diagnosis. Elevated or abnormal 24-hour urinary 5-HIAA level has a sensitivity of 75% and a specificity of up to 100% in making a diagnosis of thymic or bronchial NET (Feldman JM., 1986). This test may help to confirm the diagnosis, it is fraught with human errors that may be induced by certain drugs or activities. In fact, thymic or bronchial NET cells often lack aromatic amino acid decarboxylase, which is necessary to convert tryptophan to serotonin and ultimately to urine 5-HIAA. Thus, in patients with thymic or bronchial NETs, measurement for urine 5-HIAA is not as helpful or as useful as urinary serotonin. Triple-phase helical CT and MRI are the preferred imaging modality when hepatic tumor infiltration is present or strongly suspected. For NET patients with contrast allergy, MRI (enhanced and unenhanced) is recommended. Ultimately, for patients unable to undergo CT or MRI, serial [^{111}In-DTPA^{0}]octreotide scintigraphy (Octreoscan) is suggested. Although no prospective study has been attempted to demonstrate the utility of any specific follow-up protocol, it is accepted that after curative resection, an active surveillance program can detect early tumor relapse. The toretically, early detection of tumor recurrence or relapse can lead to an improved chance of achieving complete resection and allow for early initiation of therapy. Because of the indolent nature of well-differentiated NETs, patients need not be followed up at short intervals, but they can be followed up with long-intervening periods. Recommend that patients with NETs be reassessed once between 3 and 6 months after complete curative resection. Subsequently, patients should be evaluated every 6 to 12 months for at least 7 years after curative surgical resection. Follow-up evaluation should consist of interval history, physical examination, and laboratory testing including CgA and 5-HIAA at a minimum.

Among patients undergoing surveillance after complete resection, we recommend cross-sectional imaging (CT) of the soft tissues of the head and neck and the chest and periodic (every 6-12 months) cross-sectional imaging (CT or MRI) of the abdomen and pelvis. The role of routine [^{11}I^{1}n-DTPA^{0}]octreotide scintigraphy (Octreoscan) has not been defined by prospective studies. Many experts, however, would advocate the use of [^{111}In-DTPA^{0}]octreotide scintigraphy (Octreoscan) yearly as follow-up for patients without evidence of disease or on an as-needed basis to define indeterminate radiologic findings. For patients with advanced disease, we generally recommend the use of cross-sectional imaging for known sites of disease. [^{111}In-DTPA^{0}]octreotide scintigraphy (Octreoscan) can be used to test in vivo for the presence of somatostatin receptors 2 and 5. It can also be

used to evaluate if peptide receptor radiotherapy represents a reasonable treatment option (Alexandria T. et al., 2010).

Poorly Differentiated Neuroendocrine Tumors/Large or Small Cell Tumors

Primary Treatment of Poorly Differentiated/Large or Small Cell Tumors (chemotherapy with a small cell lung cancer regimen with or without radiotherapy).

For resectable poorly differentiated/small cell tumors, surgical resection and chemotherapy with a small cell lung cancer regimen with or without radiotherapy are advised. In general, cisplatin or carboplatin and etoposide are recommended as primary treatment.

Envolving data suggest that patients with intermediate Ki-67 levels (in the 20%–50% range) may not respond as well to platinum/etoposide as patients with small cell histology or those with extremely high Ki-67. Clinical judgement should be used in selecting chemotherapy regimens for patients with Ki-67 levels in this intermediate range (NCCN Guidelines Version 2., 2014).

Treatment of loco-regional disease (limited disease)

Poorly differentiated NECAs are characterized by a high proclivity for metastatic dissemination even in patients with clinically localized tumors. This principle is validated by retrospective studies confirming that surgery alone is rarely curative (Casas F, et al., 1997) (Brenner B, et al., 2004). Based on the treatment paradigm for limited-stage small-cell lung cancer, a course of definitive chemotherapy (cisplatin or carboplatin and etoposide for 4-6 cycles) and radiation can be considered in many patients with loco-regional extrapulmonary PD (poorly differentiate) NECAs (neuroendocrine carcinoma), particularly when surgical resection is difficult. Clinical trials in small-cell lung cancer suggest that concurrent chemoradiation is more efficacious than sequential treatment but at the expense of increased toxicity (Takada M, et al., 2002). The optimal sequencing of chemotherapy with radiation in extrapulmonary PD NECA is unknown. Likewise, the benefit of surgery among patients who have completed a course of chemoradiation is uncertain. Whereas there are no studies examining adjuvant postoperative treatment in PD NECAs, their aggressive behavior warrants consideration of adjuvant therapy in most cases. Chemotherapy (4-6 cycles of cisplatin or carboplatin and etoposide) is recommended. Sequential radiation can also be considered in cases where the risk of local recurrence is thought to be higher than average (eg, carcinomas of the rectum or cervix).

The incidence of brain micrometastases in small-cell lung cancer is high, necessitating prophylactic cranial irradiation for patients with

successfully treated limited-stage disease (Meert AP, al., 2001). Data on extrapulmonary PD NECAs suggest a lower frequency of central nervous system metastases (Cicin I, et al., 2007). Consequently, routine prophylactic cranial irradiation cannot be recommended in this population but may be considered among patients with PD NECAs of the head and neck or unknown primary site.

Treatment of metastatic disease (extensive disease)

Based on the established role of cisplatin and etoposide in metastatic small-cell lung cancer, this combination has been investigated in metastatic NECAs of the GI tract. The first such study explored infusional cisplatin and etoposide among 45 patients with metastatic NECAs, of whom 18 had PD tumors. A response rate of 67% was reported in patients with PD NECAs, with response duration of 8 months and a median survival of 19 months (Moertel CG, et al., 1991). A subsequent study of 53 patients with PD NECAs of the GI tract treated with a bolus regimen of cisplatin and etoposide reported a response rate of 42% with response duration of 9 months and a median survival of 15 months (Mitry E, et al., 1999). Based on these studies, the combination of cisplatin and etoposide is recommended as first-line therapy for metastatic PD NECAs. Alternative regimens substituting carboplatin for cisplatin (Lassen U, et al., 1996) or irinotecan for etoposide (Hanna N, et al., 2006) have been validated in metastatic small-cell lung cancer and are therefore thought to be acceptable options for management of extrapulmonary PD NECAs. The optimal duration of chemotherapy has not been clearly defined, and it remains unclear whether treatment beyond 4 cycles is associated with a survival benefit. There are no studies of salvage chemotherapy in extrapulmonary PD NECAs. Second-line chemotherapy regimens in refractory or relapsed small-cell lung cancer are typically associated with modest response rates of 0% to 20%. One study ooral topotecan versus supportive care in relapsed small-cell lung cancer demonstrated a 3-month improvement in median survival (O'Brien ME, et al., 2006).

Based on this data, topotecan can be recommended as a salvage option for relapsed PD NECAs. Alternatively, retreatment with a platinum and etoposide or irinotecan regimen can be considered in patients who relapse more than 3 to 6 months after termination of first-line chemotherapy. Other agents with similar reported activity in small-cell lung cancer include paclitaxel, docetaxel, vinorelbine, and gemcitabine (Walenkamp AM, et al., 2009).

Octreotide therapy can be considered for symptom control in the rare cases of hormone-secreting tumors that are unresectable or metastatic. Lanreotide, which is approved for symptom control in Europe, has a similar

mechanism of action as octreotide. Because it is injected subcutaneously, it may be preferable in patients who have difficulty tolerating an intramuscular injection.

Follow-Up of Patients with Poorly Differentiated/Large or Small Cell Tumors

After surgery, surveillance consists of a routine H&P along with appropriate imaging studies every 3 months for the first year and every 6 months thereafter. Patients with locoregional, unresectable disease and with metastatic disease should be monitored at least every 3 months (NCCN Guidelines Version 2., 2014).

Summary:

NETs of the lung comprise a heterogeneous population of tumors ranging from well-differentiated bronchial NETs to highly malignant and poorly differentiated small-cell lung cancer and large-cell neuroendocrine carcinoma. The improvement in histological diagnostic tools, including neuroendocrine markers by immunohistochemistry, has led to an increased recognition of pulmonary neuroendocrine tumors. No large phase II and III trials for pulmonary neuroendocrine tumors have been published. Several treatment approaches are available for their treatment but none of them has been validated in appropriately designed and adequately sized clinical trials. The main problem of the published studies is that they include neuroendocrine tumors from various sites of origin with different clinical behavior.

Acknowledgements:

The present work was carried out within the frames of scientific project Nr. 2013/0004/1DP/1.1.1.2.0/13/APIA/VIAA/020, supported by the European Social Fund (ESF).

References:

Alexandria T. Phan et al., NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors. Volume 39, Number 6, August 2010.

Brenner B, Shah MA, Gonen M, et al. Small-cell carcinoma of the gastrointestinal tract: a retrospective study of 64 cases. Br J Cancer 2004;90(9):1720-1726.

Casas F, Ferrer F, Farrus B, et al. Primary small cell carcinoma of the esophagus: a review of the literature with emphasis on therapy and prognosis. Cancer.1997;80(8):1366-1372.

Cicin I, Karagol H, Uzunoglu S, et al. Extrapulmonary small-cell carcinoma compared with small-cell lung carcinoma: a retrospective single-center study. Cancer. 2007;110(5):1068-1076.
de Montpreville VT, Macchiarini P, Dulmet E. Thymic neuroendocrine carcinoma (carcinoid): a clinicopathologic study of fourteen cases. J Thorac Cardiovasc Surg 1996;111(1):134-141.
Ekeblad S, Sundin A, Janson ET, et al. Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors. Clin Cancer Res. 2007;13(10):2986-2991.
Gaur P, Leary C, Yao JC. Thymic neuroendocrine tumors: a SEER database analysis of 160 patients. Ann Surg 2010; 251(6): 1117–1121.
Faiss S, Pape UF, Bohmig M, et al. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors-the International Lanreotide and Interferon Alfa Study Group. J Clin Oncol. 2003;21(14):2689-2696.
Feldman JM. Urinary serotonin in the diagnosis of carcinoid tumors. Clin Chem. 1986;32(5):840-844.
Frank M, Klose KJ, Wied M, et al. Combination therapy with octreotide and alpha-interferon: effect on tumor growth in metastatic endocrine gastroenteropancreatic tumors. Am J Gastroenterol 1999; 94(5):1381-1387
Fukai I, Masaoka A, Fujii Y, et al. Thymic neuroendocrine tumor (thymic carcinoid): a clinicopathologic study in 15 patients. Ann Thorac Surg.1999;67(1):208-211.
Gupta S, Johnson MM, Murthy R, et al. Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rates and survival. Cancer. 2005;104(8):1590-1602.
Gustafsson BI, Kidd M, Chan A et al. Bronchopulmonary neuroendocrine tumors. Cancer 2008; 113(1): 5–21.
Hanna N, Bunn PA Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol. 2006;24(13):2038-2043.
Harris AG, O'Dorisio TM, Woltering EA, et al. Consensus statement: octreotide dose titration in secretory diarrhea. Diarrhea Management Consensus Development Panel.Dig Dis Sci.1995;40(7):1464-1473.
Janson ET, Ronnblom L, Ahlstrom H, et al. Treatment with alpha interferonversus alpha-interferon in combination with streptozocin and doxorubicin in patients with malignant carcinoid tumors: a randomized trial. Ann Oncol.1992;3(8):635-638.

Kennedy AS, Dezarn WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. Am J Clin Oncol. 2008;31(3):271-279.
Kolby L, Persson G, Franzen S, et al. Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours. Br J Surg. 2003;90(6):687-693.
Lassen U, Kristjansen PE, Osterlind K, et al. Superiority of cisplatin or carboplatin in combination with teniposide and vincristine in the induction chemotherapy of small-cell lung cancer. A randomized trial with 5 years follow up. Ann Oncol. 1996;7(4):365-371.
Meert AP, Paesmans M, Berghmans T, et al. Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. BMC Cancer. 2001;1:5.
Mitry E, Baudin E, Ducreux M, et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. Br J Cancer.1999;81(8):1351-1355.
Moertel CG, Kvols LK, O'Connell MJ, et al. Treatment of neuroendocrin carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. Cancer.1991;68(2):227-232.
NCCN Guidelines Version 2.2014 Neuroendocrine Tumors Version 2.2014, 12/11/13 © National Comprehensive Cancer Network, Inc. 2013, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.
O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol.2006;24(34):5441-5447.
Orbach-Zinger S, Lombroso R, Eidelman LA. Uneventful spinal anesthesia for a patient with carcinoid syndrome managed with long-acting octreotide. Can J Anaesth 2002;49:678-681.
Parris WC, Oates JA, Kambam J, et al. Pre-treatment with somatostatin in the anaesthetic management of a patient with carcinoid syndrome. Can J Anaesth. 1988;35(4):413-416.
Plockinger U, Couvelard A, Falconi M, et al. Consensus guideline for the management of patients with digestive neuroendocrine tumours: well-differentiated tumour/carcinoma of the appendix and goblet cell carcinoma. Neuroendocrinology. 2008;87(1):20-30.
Pommier RF, Vetto JT, Lee JT, et al. Synchronous non-small cell lung cancers. Am J Surg. 1996;171(5):521-524.

Righi L, Volante M, Rapa I et al. Neuro-endocrine tumors of the lung. A review of relevant pathological and molecular data. Virchows Arch 2007; 451(Suppl.1):S51–S59.
Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009;27:4656-4663.
Rubin J, Ajani J, Schirmer W, et al. Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. J Clin Oncol 1999;17:600-606.
Scanagatta P, Montresor E, Pergher S, et al. Cushing's syndrome induced by bronchopulmonary carcinoid tumours: a review of 98 cases and our experience of two cases. Chir Ital. 2004;56(1):63-70.
Scheithauer BW, Carpenter PC, Bloch B, et al. Ectopic secretion of a growth hormone releasing factor. Report of a case of acromegaly with bronchial carcinoid tumor. Am J Med.1984;76(4):605-616.
Schnirer II, Yao JC, Ajani JA. Carcinoid: a comprehensive review. Acta Oncol. 2003;42:672-692.
Shah T, Caplin M. Endocrine tumours of the gastrointestinal tract. Biotherapy for metastatic endocrine tumours. Best Pract Res Clin Gastroenterol. 2005;19(4):617-636.
Skuladottir H, Hirsch FR, Hansen HH et al. Pulmonary neuroendocrine tumors: incidence and prognosis of histological subtypes. A population-based study in Denmark. Lung Cancer 2002; 37(2): 127–135.
Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104.J Clin Oncol.2002;20(14):3054-3060.
Travis WD, Rush W, Flieder DB et al. Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. Am J Surg Pathol 1998; 22(8): 934–944.
Walenkamp AM, Sonke GS, Sleijfer DT. Clinical and therapeutic aspects of extrapulmonary small cell carcinoma. Cancer Treat Rev. 2009;35(3):228-236.
Weingarten TN, Abel MD, Connolly HM, et al. Intraoperative management of patients with carcinoid heart disease having valvular surgery: a review of one hundred consecutive cases. Anesth Analg. 2007;105(5):1192-1199.
Wymenga AN, de Vries EG, Leijsma MK, et al. Effects of ondansetron on gastrointestinal symptoms in carcinoid syndrome. Eur J Cancer. 1998;34(8):1293-1294.

Yao JC, Hassan M, Phan A et al. One hundred years after carcinoid epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008; 26(18): 3063–3072.