Medical Treatment of Advanced Thoracic Neuroendocrine Tumors

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KEYWORDS

• Carcinoid • Neuroendocrine tumors • Target therapy • Biologic therapy

KEY POINTS

- The bronchial tree represents one of the most frequent sites of origin of neuroendocrine tumors (NET), with a prevalence that reaches 25% of all the NET.
- Furthermore, they are the subgroup of NET with a higher increase in incidence among all the NET in recent years, mainly because of the development of new diagnostic techniques in the last 3 decades.
- Thymic NET share with the bronchial NET the same histologic subdivision but are much more rare (<2%–3% of all the NET).
- Both of these tumors may be associated with multiple endocrine neoplasia type 1 syndrome.
- Thoracic NET (TNET) is a heterogeneous group of neoplasm, ranging from the more indolent behavior of the well-differentiated forms (typical and atypical carcinoids) to the highly aggressive behavior of the poorly differentiated forms (large cell neuroendocrine and small cell carcinoma).
- These 2 groups require a clinical approach totally different in terms of diagnosis and, above all, treatment.
- Chemotherapy and radiotherapy are the treatments of choice in poorly differentiated forms, whereas biological (mainly somatostatin analogues) and target therapy (mainly everolimus). Peptide Receptor Radionuclide Therapy (PRRT) and temozolomide have shown efficacy in small series or in the subgroup analysis of larger trials. The clinical response to these drugs does not significantly differ when compared with other well-differentiated NET, including gastro-entero-pancreatic-NET; however, no specific trials have been performed before this year.
- The first large, prospective, randomized trial (LUNA trial) entirely dedicated to TNET is ongoing at the time of this publication.

INTRODUCTION

The bronchial tree represents one of the most frequent sites of origin of neuroendocrine tumors (NET), with a prevalence that reaches 25% of all the NET.[1] Furthermore, they are the subgroup of NET with the higher increase in incidence among all the NET in recent years,[2] mainly because of the development of new diagnostic techniques in the last 3 decades. Thymic NET share with the bronchial NET the same histologic subdivision but are much more rare (<2%–3% of all the NET). Both of these tumors may be associated with multiple endocrine neoplasia type 1 syndrome.[3]

Thoracic NET (TNET) is a heterogeneous group of neoplasms, ranging from the more indolent behavior of the well-differentiated forms (typical

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and atypical carcinoids) to the highly aggressive behavior of the poorly differentiated forms (large cell neuroendocrine and small cell carcinoma).[4]

The clinical management of advanced TNET always requires a multidisciplinary approach. Every decision on the therapeutic strategy should be taken in the course of tumor boards that allow the evaluation of the different possibility of treatment including, whenever possible, the surgical treatment of local recurrences. A referral to third-level centers dedicated to these tumors is always recommended.

The main aims of the treatment are the control of the tumor growth and the control of the secretory pattern of the neuroendocrine tumor cells whenever endocrine syndromes are associated.

The clinicians approaching the cure of these tumors should always take in mind that, also after curative R0 surgery, only an accurate and protracted follow-up may assure that patients have been cured (also in typical carcinoid). The peak of recurrences is, in fact, located after more than 10 years from surgery in typical carcinoids and within the first 5 years in atypical carcinoids.[5–7] No evidence is available, at the moment, supporting the use of adjuvant treatment after radical surgery; however, in some subgroups with worse prognostic factors, such as atypical carcinoids N1 or N2, the design of clinical trials dedicated to assess the possible role of an adjuvant treatment with low-toxicity drugs, like as somatostatin analogues (SSA), is urgently needed.

CONTROL OF ASSOCIATED NEUROENDOCRINE HYPERSECRETIONS

TNET are associated with clinically evident endocrine hypersecretions in a percentage of cases inferior to the gastro-entero-pancreatic (GEP) counterpart (about 10%–15% vs 30%); however, if the subclinical secretions are also considered, the percentage increases up to 25% of the cases.[7] Long-acting SSA represent the drug of choice in the control of most of the associated hypersecretions, including carcinoid syndrome, which, in TNET, are more frequently atypical.[6,8,9] It should be remembered that atypical carcinoid syndrome, if not recognized, may be associated with an high mortality rate. Although reported only in small series, the percentage of response to these drugs in TNET seems similar to the GEP-NETs. H_1 and H_2 blockers, loperamide, and symptomatic therapies may be used in association with SSA with the intent to control some of the symptoms. In atypical carcinoid syndrome, the use of steroids may be required in association with SSA to control bronchostenosis and carcinoid crises; it should always be remembered that the beta-2 agonist may exacerbate the symptoms, increasing the degranulation of secretory granules. Teloristat etipirate acts as an inhibitor of the enzyme tryptophan hydroxylase. This drug is actually under investigation in the course of phase II and III trials to increase the percentage of control of the carcinoid syndrome in patients not completely controlled by SSA.[10] Furthermore, it will be of interest to assess if an earlier reduction of the circulating levels of serotonin in patients affected by NET may be associated with a prevention of some complication of carcinoid syndrome and if the supposed reduction of the fibrotic phenomenons inducted by high serotonin levels may be associated with an antiproliferative effect.

Ectopic corticotropin hypersecretion and consequent cushing disease, growth hormone releasing hormone secretion and consequent ectopic acromegaly, and inappropriate antidiuretic hormone secretion may be less frequently associated with TNET. The treatment in these cases does not differ from the codified standard treatment. In order to reduce the amount of secreting cells, debulking strategies may be considered of some value. These strategies include partial surgical resections, hepatectomies, locoregional treatments (both radiofrequency and chemoembolizations), radioactive microsphere, and PRRT. The addition of alpha-interferon to SSA has been reported to be of some value in increasing their efficacy. All the listed procedures should be evaluated in terms of the risk-benefit ratio in the course of a multidisciplinary tumor board.

MEDICAL THERAPY FOR PRIMARY TUMOR IN PATIENTS NOT CANDIDATES FOR SURGERY, IN MULTICENTRIC FORMS, AND IN PATIENTS WITH ADVANCED METASTATIC DISEASE

The first multicentric randomized prospective trial entirely dedicated to TNET (LUNA trial, ClinicalTrials.gov Identifier: NCT01563354), started in the last months of 2013, is actually ongoing and will probably complete the accrual within 2014. No other prospective trial focused on bronchial NET have been published; therefore, the only available results come from small retrospective series and from the subgroup analysis of a few larger multicentric studies that allowed the inclusion of TNET.

Since all the neuroendocrine cells originate from the same neuroendocrine diffuse system and share most of the biologic features, it is reasonable to speculate that some of the results obtained in other neuroendocrine cell like as in the ileal carcinoid may be applicable also in bronchial carcinoid.