Review Article

New options for neuroendocrine thymic tumors medical treatment

Giovannella Palmieri, Margaret Ottaviano

Department of Clinical Medicine and Surgery, University of Naples Federico II and CRTR Rare Tumours Reference Center, Naples, Italy

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: M Ottaviano; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Giovannella Palmieri. Department of Clinical Medicine and Surgery, University of Naples Federico II and CRTR Rare Tumours Reference Center, Via Pansini 5, 80128 Naples, Italy. Email: giovpalm@unina.it.

Abstract: Neuroendocrine neoplasms (NENs) consist of a group of heterogenic malignancies, mainly arising from the gastroenteropancreatic (GEP) and the bronchopulmonary tract. Thymic neuroendocrine tumors (TNETs) are included in the thymic carcinoma group, due to the biological aggressiveness and the poor prognosis for the high incidence of local recurrences and distant metastases. The pathological classification of TNETs slightly differs from other NENs, considering in addition to Ki-67, also the grade of necrosis. Furthermore, almost 50% of these tumors can be complicated by endocrine diseases, either due to ectopic adrenocorticotropic hormone secretion (Cushing syndrome) or because of its association with other endocrine tumors, such as in multiple endocrine neoplasia type 1 syndrome (MEN1). Surgery remains the mainstay of therapy for resectable disease, whereas induction/adjuvant chemotherapy/radiotherapy play a role in case of incomplete resections or unresectable tumors. Somatostatin analogs (SSAs) play a fundamental role since the majority of well differentiated NETs expresses high levels of somatostatin receptors so that SSAs therapy is selected as first line treatment in functional and no functional NETs. In the complex scenario of treatment strategies, a pivotal role is acted by the inhibition of mTOR protein with everolimus. The angiogenesis is another important pathway in NETs. Pazopanib, a multi-targeted agent, has been recently evaluated in advanced NETs including patients who received mTOR inhibitors. Because comparative clinical trials are still lacking and the different therapies cannot be placed in a specific sequence, future clinical research will aim to clarify these issues in randomized trial.

Keywords: Neuroendocrine tumors (NETs); thymus; somatostatin analogs (SAs); everolimus; angiogenesis; combination therapy

Received: 11 December 2017; Accepted: 14 March 2018; Published: 13 April 2018.
doi: 10.21037/med.2018.03.19
View this article at: http://dx.doi.org/10.21037/med.2018.03.19

Neuroendocrine neoplasms (NENs) consist of a group of heterogenic malignancies, which share the same histological origin from the neuroendocrine cells and are most commonly originated from the gastroenteropancreatic (GEP) and the bronchopulmonary tract.

Rosai and Higa firstly described in 1972 thymic neuroendocrine tumors (TNETs) that arose from thymic neuroendocrine cells and constituted a minor cell population scattered in the normal human thymus (1). The incidence is approximately 0.4% of all carcinoid tumors (2) and are included in the thymic carcinoma group because the carcinoid tumors arising in this anatomic site (mediastinal) may behave more aggressively than the foregut counterparts (3). The prognosis of patients with TNET is poor because of the high incidence of local recurrences and distant metastases, even after a radical tumor resection, in fact the reported overall 5-year survival rate may vary from 30% to 70% (4). According to the Surveillance, Epidemiology and End-Result (SEER) database, the International Thymic Malignancy Interest Group (ITMIG) and the European Society of Thoracic Surgeons databases, pathologic stage and radical resection were demonstrated to be strong

prognostic factors, whereas histology did not influence patient's outcome (2-5).

The pathological classification of lung and thymus NENs slightly differs from other NENs: in addition to Ki-67, it considers also the grade of necrosis and so defines three distinct subgroups: typical carcinoid, atypical carcinoid (that would correspond to NET grades 1 and 2, respectively) and large- and small-cell NECs (equivalent to grade 3). Almost 50% of these tumors can be complicated by endocrine diseases, either due to ectopic adrenocorticotropic hormone secretion (Cushing syndrome) or because of its association with other endocrine tumors, such as in multiple endocrine neoplasia type 1 syndrome (MEN1).

The aim of therapy for patients with advanced NETs is to achieve tumor control through the eradication or the stabilization of disease, prolonging survival and relieving the symptoms of functional tumors, while maintaining the quality of life. Due to the rarity and the consequent limited number of both retrospective and prospective studies, very few progresses have been made for the acquisition of new data about the treatment and the survival of patients affected by TNETs, thus a clear consensus concerning the optimal treatment actually does not exist and there are no uniform treatment strategies (2). Surgery remains the mainstay of therapy for resectable disease, whereas induction/adjuvant chemotherapy/radiotherapy play a role in case of incomplete resections or unresectable tumors. The reported resectability rate may vary from 28% to 100% (mean 86%), strongly depending on the single center experience.

Fortunately, now, different options in the setting of functional and non-functional metastatic NENs are suitable, specifically for grades 1 and 2, which include systemic treatment with somatostatin analogs (SSAs), interferon-α (INF-α), peptide receptor radiotargeted therapy (PRRT), cytotoxic chemotherapy and molecular target agents. SSAs play a fundamental role in the diagnostic work up: a majority of well differentiated NETs expresses high levels of somatostatin receptors (to which SSAs bind). Generally, SSAs therapy is selected as first line treatment in functional and no functional NETs (6). Two double-blind placebo controlled prospective randomized studies, demonstrated that octreotide LAR and lanreotide Autogel respectively, significantly prolonged the time to progression (TTP) in patients enrolled with diagnosis of metastatic G1 and G1–G2 NETs in PROMID and CLARINET respectively (7). Another observational Italian multicentre study evaluated the efficacy of long-acting SSAs in NETs according to Ki67 index. A Ki67 index cut off ≤5% seems to indicate the most suitable patients for SSA therapy (8).

Since 1992, radio-labeled SSA therapy (peptide receptor radionuclide therapy) has shown considerable promise for the treatment of advanced, well-differentiated neuroendocrine tumors. Recently, a phase 3 trial of ^{177}Lu-Dotatate, in patients with advanced midgut neuroendocrine tumors demonstrated a markedly longer progression-free survival (PFS) and a significantly higher response rate than high-dose octreotide (9). Another poor explored strategy in this setting of patients is the use of SSAs at high dose. In the complex scenario of treatment strategies, a pivotal role is acted by the inhibition of mTOR protein with everolimus, since, due to its upregulation, the mTOR pathway is widely recognized as involved in the NET pathogenesis.

Everolimus has shown a significant improvement in PFS among patients with pancreatic NETs and non-functional GEP and lung NETs in the phase III trials, RADIANT-3 and RADIANT-4. Moreover, in RADIANT studies the role of combination therapy with everolimus and SSAs is not defined, only in RADIANT-2 trial the combination of everolimus with octreotide showed a clinically significant improvement versus octreotide alone in functional disease (10). Firstly, the phase 2 randomized 3 arms LUNA trial, evaluated the efficacy and safety of pasireotide LAR or everolimus alone or in combination in patients with advanced carcinoids (NET) of the lung/thymus. The primary endpoint of progression-free rate (PFR)-9 months has been reached in all arms (P =30.0%, 95% CI, 24.2–55.5%; E =33.3%, 95% CI, 19.6–49.5%); P + E =58.5%), with a better trend in favour of the combination army (11). The angiogenesis is another important pathway in NETs. Pazopanib, a multi-targeted agent against vascular endothelial growth factor receptors (VEGFR-1, -2 and -3), platelet-derived growth factor receptor α and β (PDGFRα and β) and proto-oncogene c-Kit, showed in the PAZONET study activity in previously treated, advanced NETs including patients who received mTOR inhibitors (12). VEGFR and mTOR inhibitors are active in NETs; thus, the combination of these agents could be another possible synergistic strategy to investigate in further studies (10).

There are a growing number of ongoing studies that are evaluating other agents alone or in combination with everolimus in patients with NETs. To date in our institution are ongoing two studies: the pilot phase II ATLANT trial, that includes non-resectable thoracic NETs (lung and thymus) patients with progressive disease, administering lanreotide every 28 days in combination with temozolomide

(250 mg) for 5 days a month, and the phase II single-arm IMMUNeOCT trial to evaluate the efficacy and safety of PDR001, a check-point inhibitor, in patients with advanced or metastatic non-functional neuroendocrine tumors of GEP and thoracic origin who progressed on previous treatment (Oncology Clinical Protocol CPDR001E2201). Because comparative clinical trials are still lacking and the different therapies cannot be placed in a specific sequence, future clinical research will aim to clarify these issues in randomized trial.

Acknowledgments

We thank Dr. Marianna Tortora, CRTR Rare Tumours Reference Center, Naples, Italy for collection and assembly of data , Dr. Pasqualina Perrone and Dr. Carmen Forino, CRTR Rare Tumours Reference Center, Naples, Italy for administrative support.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors Mirella Marino and Brett W. Carter for the series "Dedicated to the 8th International Thymic Malignancy Interest Group Annual Meeting (ITMIG 2017)" published in *Mediastinum*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/med.2018.03.19). The series "Dedicated to the 8th International Thymic Malignancy Interest Group Annual Meeting (ITMIG 2017)" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Rosai J, Higa E. Mediastinal endocrine neoplasm, of probable thymic origin, related to carcinoid tumor. Clinicopathologic study of 8 cases. Cancer 1972;29:1061-74.
2. Gaur P, Leary C, Yao JC. Thymic neuroendocrine tumors: a SEER database analysis of 160 patients. Ann Surg 2010;251:1117-21.
3. Moran CA, Suster S. Neuroendocrine carcinomas (carcinoid tumor) of the thymus. A clinicopathologic analysis of 80 cases. Am J Clin Pathol 2000;114:100-10.
4. Filosso PL, Yao X, Ahmad U, et al. Outcome of primary neuroendocrine tumors of the thymus: a joint analysis of the International Thymic Malignancy Interest Group and the European Society of Thoracic Surgeons databases. J Thorac Cardiovasc Surg 2015;149:103-9.e2.
5. Gaur P, Leary C, Yao JC. Thymic neuroendocrine tumors: a SEER database analysis of 160 patients. Ann Surg 2010;251:1117-21.
6. Kos-Kudła B. Treatment of neuroendocrine tumors: new recommendations based on the CLARINET study. Contemp Oncol (Pozn) 2015;19:345-9.
7. Rinke A, Wittenberg M, 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 (PROMID): Results of Long-Term Survival. Neuroendocrinology 2017;104:26-32.
8. Faggiano A, Carratù AC, Guadagno E, et al. Somatostatin analogues according to Ki67 index in neuroendocrine tumours: an observational retrospective-prospective analysis from real life. Oncotarget 2016;7:5538-47.
9. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med 2017;376:125-35.
10. Gajate P, Martínez-Sáez O, Alonso-Gordoa T, et al. Emerging use of everolimus in the treatment of neuroendocrine tumors. Cancer Manag Res 2017;9:215-24.
11. Ferolla P, Brizzi MP, Meyer T, et al. Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced carcinoids of the

lung and thymus (LUNA): an open-label, multicentre, randomised, phase 2 trial. Lancet Oncol 2017;18:1652-64.
12. Grande E, Capdevila J, Castellano D, et al. Pazopanib in pretreated advanced neuroendocrine tumors: a phase II, open-label trial of the Spanish Task Force Group for Neuroendocrine Tumors (GETNE). Ann Oncol 2015;26:1987-93.

doi: 10.21037/med.2018.03.19
Cite this article as: Palmieri G, Ottaviano M. New options for neuroendocrine thymic tumors medical treatment. Mediastinum 2018;2:30.