## Chapter 24

## WHAT IS THE PLACE OF THE PEPTIDE RECEPTOR RADIONUCLIDE THERAPY IN NEUROENDOCRINE TUMORS?

Tulay KUS<sup>1</sup> Umut ELBOGA<sup>2</sup>

## **INTRODUCTION**

Neuroendocrine tumors (NETs) are a heterogeneous malignancies arising from neuroendocrine cells whole the body. While well-differentiated gastrointestinal neuroendocrine tumors (GINET) and lung/thymus NETs were classified as low-grade (G1) and intermediate-grade (G2), pancreatic NETs are classified as low-grade (G1), intermediate-grade (G2), and high-grade (G3) based upon mitotic count and proliferative index (Ki-67). The main curative treatment of NETs is surgery for patients with potentially resectable disease, however, approximately half of the patients initially harbor metastases. Prolonged control of symptoms and prevention of tumor growth can be provided by octreotide and lantreotide, which are somatostatin analogues, based on PROMID and CLARINET studies in patients who are not candidate for curative intent surgery (Rinke A et al., 2009, Caplin ME et al., 2014).

GINETs and pancreatic NETs have morphologically similar histology, but, their biological behavior and response to treatment are different. Wheares pancreatic NETs have a worse prognosis than gastrointestinal NETs, response to treatment is better. Among pacreatic NETs, patients with gastrinomas, which have faster growth pattern, have a shorter time to progression than other nonfunctioning endocrine pancreatic NETs. Among GINET, wheares colon NETs are associated with the worst median survival (7 months), jejenum, ileum, and ceacum are associated with better survival as 55 to 65 months (Yao JC et al., 2008). Differentiated neuroendocrine tumors mostly express subtypes of the somatostatin receptor. This allows not only treatment with the somatostatin analogs, but

<sup>&</sup>lt;sup>1</sup> Associated Proffesor, Adıyaman University Education and Research Hospital, Medical Oncology, drtulaykus83@hotmail.com

<sup>&</sup>lt;sup>2</sup> Associated Proffesor, Gaziantep University, Faculty of Medicine, Department of Nuclear Medicine, umutelboga@hotmail.com

there are non-randomised studies indicating the efectivity of sunitinib and everolimus after PRRT which have better toxicity profile compared to targeted therapies. Therefore, PRRT may be considered as a second-line therapy for patients with high uptake on pretherapy somatostatin receptor imaging, limited number of liver metastases, and low performance score in pancreatic NETs.

## REFERENCES

- Caplin ME, Pavel M, Ćwikła JB, et al; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014 Jul 17;371:224-33.
- De Jong M, Valkema R, Jamar F, et al. Somatostatin receptor-targeted radionuclide therapyof tumors: preclinical and clinical findings. Semin Nucl Med 2002;32:133–40.
- Hörsch D, Ezziddin S, Haug A, et al. Peptide receptor radionuclide therapy for neuroendocrine tumors in Germany: first results of a multi-institutional cancer registry. Recent Results Cancer Res. 2013;194:457-65.
- Imhof A, Brunner P, Marincek N, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol. 2011 Jun 10;29:2416-23.
- Kwekkeboom DJ, Bakker WH, Kam BL, et al. Treatment of patients with gastro-entero-pancreatic (GEP) tumours with the novel radiolabelled somatostatin analogue [177Lu-DOTA(0),Tyr3]octreotate. Eur J Nucl Med Mol Imaging. 2003 Mar;30:417-22.
- Kwekkeboom DJ, Krenning EP. Peptide Receptor Radionuclide Therapy in the Treatment of Neuroendocrine Tumors. Hematol Oncol Clin North Am. 2016 Feb;30:179-91.
- Kwekkeboom DJ, Teunissen JJ, Bakker WH, et al. Radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3]octreotate in patients with endocrine gastroenteropancreatic tumors. J Clin Oncol. 2005 Apr 20;23:2754-62.
- Panzuto F, Rinzivillo M, Fazio N, et al. Real-world study of everolimus in advanced progressive neuroendocrine tumors. Oncologist. 2014 Sep;19:966-74.
- Pavel ME, Hainsworth JD, Baudin E, et al. ; RADIANT-2 Study Group. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011 Dec 10;378(9808):2005-2012.
- Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011 Feb 10;364:501-13.
- Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. 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 Oct 1;27:4656-63.
- Rinzivillo M, Fazio N, Pusceddu S, et al. Sunitinib in patients with pre-treated pancreatic neuroendocrine tumors: A real-world study. Pancreatology. 2018 Mar;18:198-203.
- Strosberg J, El-Haddad G, Wolin E, et al. ; NETTER-1 Trial Investigators. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017 Jan 12;376:125-135.
- Van Essen M, Krenning EP, Kam BL, et al. Salvage therapy with (177)Lu-octreotate in patients with bronchial and gastroenteropancreatic neuroendocrine tumors. J Nucl

Med. 2010 Mar;51:383-90.

- Villard L, Romer A, Marincek N, et al. Cohort study of somatostatin-based radiopeptide therapy with [(90)Y-DOTA]-TOC versus [(90)Y-DOTA]-TOC plus [(177)Lu-DO-TA]-TOC in neuroendocrine cancers. J Clin Oncol. 2012 Apr 1;30:1100-6.
- Yao JC, Fazio N, Singh S, et al.; RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016 Mar 5;387(10022):968-977.
- 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: 3063–72.
- Yao JC, Shah MH, Ito T, et al.; RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011 Feb 10;364:514-23.
- Yordanova A, Wicharz MM, Mayer K, et al. The Role of Adding Somatostatin Analogues to Peptide Receptor Radionuclide Therapy as a Combination and Maintenance Therapy. Clin Cancer Res. 2018 Oct 1;24:4672-4679.