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Management of neuroendocrine tumors: state of the art

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Neuroendocrine neoplasms comprise a heterogeneous group of diseases derived from the diffuse neuroendocrine system and arising from several organs and tissues. The available systemic treatments for advanced GEPNENs are diverse, including cytotoxic chemotherapy, somatostatin analog (SSA), radionuclide therapy, and molecular targeted therapeutics.

The clinical management of neuroendocrine tumors always requires a multidisciplinary approach. Currently available international classifications are important to choose for each patient the best treatment strategy. The WHO 2010 classification divides the neuroendocrine neoplasms (NENs) from the Gastroenteropancreatic (GEP) tract into the well differentiated neuroendocrine tumors (NETs) or poorly differentiated neuroendocrine carcinomas (NECs). In addition, according to their proliferative activity, GEP NENs are classified as grade 1 (G1), when show a Ki67 index equal to or less than 2%, NET G2 with a Ki67 index between 3 and 20%, and neuroendocrine carcinoma (NEC) G3 with a Ki67 index greater than 20% (1).

According to the Travis classification, the neuroendocrine (NE) tumours of the lung include the low grade typical carcinoid (TC), intermediate grade atypical carcinoid (AC) and the high grade large cell NE carcinoma (LCNEC) and small cell carcinoma (SCLC). Recently a new grading system of neuroendocrine lung carcinomas, which consider mitosis, Ki67 and necrosis, was introduced. It clearly identifies 3 tumor categories with different prognosis (2). In patients with well to moderately differentiated neuroendocrine tumors, surgery is the mainstay of therapy and systemic therapies are usually prescribed in patients with advanced disease not amenable to surgery. Among them, somatostatin analogs, radionuclide therapy and molecular target therapies are generally preferred, while chemotherapy is reserved in cases of disease progression to these treatments. In patients with poorly differentiated neuroendocrine carcinoma, cytotoxic chemotherapy is frequently adopted as first line treatment.

In the last 5 years, randomized clinical trials have demonstrated the efficacy in improving patient outcome of somatostatin analogues and molecular target agents (3, 4), Somatostatin analogs, mainly targeting the type 2 somatostatin receptor, are available in clinics for decades and they were generally prescribed to control the endocrine syndromes. Only recently 2 prospective randomized clinical trials have demonstrated their antineoplastic activity (3, 4).

In the PROMID trial (3) published in 2009, Octreotide LAR demonstrated to significantly lengthen the time to tumor progression compared with placebo in a subset of patients with functionally active and inactive metastatic, well differentiated midgut NETs. Median time to tumor progression in the octreotide LAR and placebo groups was 14.3 and 6 months, respectively (hazard ratio [HR) 0.34; 95% CI, 0.20 to 0.59). The antineoplastic activity of somatostatin analogs was confirmed by the results of the CLARINET trial (4) published in 2014. In this study the antiproliferative effects of the long-acting somatostatin analogue lanreotide was tested in more than 200 patients with nonfunctioning, somatostatin receptor-positive, enteropancreatic neuroendocrine tumors with Ki67

values of less than 10%. Patients enrolled in the trial had NET from pancreas, midgut, hindgut and unknown primary origin. The overall results showed that Lanreotide, as compared with placebo, was associated with significantly prolonged progression-free survival (median not reached vs. median of 18.0 months; HR: 0.47; 95% CI, 0.30 to 0.73).

In both trials, lung carcinoids, in which type 2 somatostatin receptor is also frequently expressed, were not included, therefore the administration of somatostatin analogs in these patients is not supported by a clear demonstration of antineoplastic efficacy.

As far as molecular target therapy is concerned, the pathways that have been investigated most extensively in NET are the VEGF/VEGF receptor pathway and the PI3K-Akt-mTOR pathway. The results of a randomized phase III trial that compared sunitinib (a mutitarget anti-angiogenetic drug) administered at a continuous dose of 37.5 mg to placebo in 171 patients with progressive pancreatic NET (5) showed a superiority of sunitinib versus placebo in terms of PFS prolongation (11.4 vs. 5.5 months, respectively), that was the study primary aim. The cross over to sunitinib at progression in patients randomized in the placebo arm was not permitted and the trial also observed a significant survival prolongation associated with sunitinib therapy (5). The efficacy of everolimus, an oral m-TOR inhibitor, in prolonging PFS was tested in a randomized double-blind placebo-controlled trial in 410 patients with progressive well-differentiated pancreatic NET (RADIANT-3) (6). In this trial everolimus administration obtained an 11 months of PFS that was significantly higher than the 4.6 months of the placebo arm. The cross over to everolimus was offered to patients randomized in the placebo arm at disease progression. This may be the reason why the trial failed to demonstrate a survival advantage. A recent update of the RADIANT-3 trial was presented at the last ESMO meeting (7). After a longer follow-up, everolimus administration was associated to a modest survival improvement. An additional large phase III randomized placebo-controlled trial (RADIANT-2), that enrolled 423 advanced NET (carcinoids) associated with the carcinoid syndrome, failed to demonstrate a significant advantage in terms of PFS of everolimus versus placebo, according to the prespecified P value (8) Radionuclide therapy is another important therapeutic approach but its efficacy is not supported by the results of randomized clinical trials.

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