Year in Review 2018 by the Brazilian Gastrointestinal Tumors Group: Neuroendocrine Tumors
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ABSTRACT
Neuroendocrine tumors (NET) constitute a heterogeneous group of neoplasms with variable prognoses and clinical presentations. Therefore their therapeutic management is challenging, involving a real multidisciplinary approach composed of medical oncologists, surgeons, endocrinologists, nuclear medicine physicians and interventionist radiologists. Here in this article, we have summarized the studies that have changed (or are likely to influence) the clinical management of patients with NET in 2018: the new WHO pathology classification for pancreatic NET, the use of peptide receptor radionuclide therapy (PRRT) in G3 NET, re-treatment with PRRT, randomized data on the CapTem regimen and new data on carcinoid heart disease.

Keywords: Neuroendocrine Tumors. Malignant Carcinoid Syndrome. Antineoplastic Agents.
INTRODUCTION
In the recent years, a plethora of studies, including randomized clinical trials, have been conducted in neuroendocrine tumors (NET). This has led to many insights into the biology of NET and has helped to tailor treatment approaches to specific subgroups of NET patients. Give the rapid advances on the overall knowledge of NET, treatment decisions have become much more complex. This article aims to review and contextualize the most important studies in NET from 2018 that, from the authors’ opinions, have changed – or significantly influence - the current management of patients with NET.

The new WHO Pathology classification for pancreatic neuroendocrine tumors
NET share a common phenotype with immunoreactivity for pan-neuroendocrine markers, including chromogranin A and synaptophysin, and neuron-specific enolase and CD56, often positive, although not specific of NET. The correct classification, staging and grading demand detailed description of the macroscopic, microscopic and immunohistochemical findings, including the immunohistochemistry (IHC) evaluation of the Ki-67 staining index, which is mandatory to grade the tumor according to the World Health Organization (WHO) classification.(1) According to the WHO 2010 classification, the entire group of gastroenteropancreatic (GEP) NET were classified into the three following grading subgroups, based on their mitotic activity and Ki-67 IHC expression index: G1 (mitotic count <2/10 high power fields [HPF] and/or Ki-67 index ≤2%), G2 (mitotic count 2 to 20/10 HPF and/or Ki-67 3 to 20%), and G3 (mitotic count >20/10 HPF and/or Ki-67 higher than 20%).

The new WHO Pathology 2017 classification subdivided the G3 pancreatic group into two different subgroups based on cell differentiation. Therefore, G3 pancreatic tumours (pNET) are now classified as either well differentiated G3 pNETs, often with Ki-67 of less than 50%, or poorly differentiated G3 pancreatic neuroendocrine carcinoma (NEC). The G3 pNETs at the lower range of proliferative index resemble G2 pNETs in terms of clinical course and molecular features(2) as for example, the presence of mutations in MEN1 (44%) and DAXX/ATRX (43%). In contrast, G3 NEC often harbor TP53 (56%) and RB1 (72%) mutations, present small cell or large cell morphology and often a Ki-6 index higher than 50%.(3,4) Immunohistochemistry staining of p53 can be used to differentiate NEC from NET G3 of the pancreas. The new WHO classification for pNET brings important information that directly impacts on treatment decisions because patients with NET G3 can benefit from other therapies beyond platinum-based chemotherapy, as for example PRRT (discussed ahead) and targeted therapies(5).

The expanding role of PRRT in NET
Two abstracts presented at 2018 European Neuroendocrine Tumor Society (ENETS) meeting explored expanded indications of peptide receptor radionuclide therapy (PRRT) in NET. Salvage PRRT is commonly performed in patients with previous response to PRRT, but no randomized trial has endorsed that practice. The efficacy and toxicity of salvage PRRT with [177 Lu-DOTA,Tyr3] octreotate was evaluated retrospectively in a large group of GEP or bronchial NET patients treated at Erasmus Medical Center.(7) Patients were selected for salvage PRRT if they had had a progression free survival (PFS) of at least 18 months after the first cycle of initial PRRT (I-PRRT) and presented new progression. Intended dose for salvage PRRT was 14.8 GBq divided over 2 administrations. A total of 181 and 14 patients had PRRT retreatment (R-PRRT) and second retreatment with PRRT (RR-PRRT), respectively. In a median follow-up of 91 months, the median PFS and overall survival (OS) times after R-PRRT were 14 months and 26 months, respectively. Median PFS was 14 months and median OS was 29 months after RR-PRRT. Overall response rate was 15.5% after R-PRRT and 38.5% after RR-PRRT. The incidence of myeloproliferative disease, including acute myeloid leukemia and myelodysplastic syndrome, was 3.5% in a historical control group and 2.2% in R-PRRT group (p=0.56). The authors concluded that salvage PRRT is a feasible and an effective option in GEP or bronchial neuroendocrine tumors and that the toxicity is not higher than previously reported. While the results suggest that some patients do benefit from R-PRRT, we should not disregard that these results are likely inflated due to selection bias.

The role of PRRT in G3 octreoscan- or PET-CT galio68-positive NET patients was investigated in a retrospective international multicenter study(8). A total of 149 patients were included, of whom, 59% had pancreatic primary tumors. PRRT was mainly given as second (n=62) or later line of treatment (n=47). In a median follow up of 34 months, median PFS was 14 months and median OS was 29 months for all patients. Of 114 patients evaluable by RECIST, 48 (42%) experienced complete or partial tumor response. There was a difference in PFS (16 vs. 5 months; p<0.001) and OS (31 vs. 8 months; p<0.001) according to Ki-67 index below (n=126) or above (n=22) the 55% cut off value. Based on these results, PRRT can be considered in patients with G3 NET whose tumors are positive in octreoscan or PET-CT scan gallium68.

The phase 3 trial of 177 Lu-Dotatate for NET, the NETTER-1 trial,(9) was presented in the 2018 ENETS Conference(10) and at 2018 ASCO Annual Meeting.(11) This trial evaluated the safety and efficacy of 177 Lu-Dotatate for NET, the NETTER-1 trial,(9) was presented in the 2018 ENETS Conference(10) and at 2018 ASCO Annual Meeting.(11)
Lu-Dotataate at a dose of 7.4 GBq every 8 weeks for 4 cycles combined with Octreotide LAR (30mg every 4 weeks) compared to high-dose Octreotide LAR alone (60 mg every 4 weeks) in advanced somatostatin-receptor-positive midgut NET patients whose tumor had progressed during first-line somatostatin analogue at usual doses (30 mg). The final results showed a median PFS of 28.4 months vs 8.5 months, (HR 0.21 [0.14-0.33], p<0.0001) in favor of the 177 Lu-Dotataate group and suggested an OS benefit for this group to be confirmed in future analyzes with longer follow up. In a recent updated analyses, patients in the 177 Lu-Dotataate group experienced improved quality of life, represented by longer time-to-deterioration (TTD) to global health status when compared to the group of Octreotide LAR 60mg (28.8 vs 6.1 months; HR 0.41 [0.24-0.69], p=0.006), longer TTD to physical functioning (25.2 vs 11.5 months; HR 0.52 [0.30-0.89], p=0.0096) and better control of symptoms of diarrhea, fatigue and pain.[12] Such findings demonstrate the efficacy of PRRT to treat symptoms from functioning NET, in this case, carcinoid syndrome.

**CapTem for pancreatic neuroendocrine tumors**

The ECOG-ACRIN study E2211 presented in the 2018 ASCO Annual Meeting is a randomized phase II trial of 144 patients with advanced and progressive low or intermediate grade pancreatic NETs randomly assigned to capecitabine (750mg/m² twice daily, days 1-14) plus temozolomide (200mg/m² days 10-14), the CapTem regimen, or single-agent temozolomide (200mg/m² days 1-5) every 4 weeks. With a median follow up of 29 months, the CapTem group presented a significant improvement in PFS, the study primary endpoint, with a median of 22.7 vs 14.4 months (HR=0.58 [0.36 – 0.93], p=0.023), and in median OS (not reached vs 38.0 months; HR=0.41 [0.21-0.82], p=0.012). Grade was not significantly associated with PFS (p=0.41) or with OS (0.28). The objective response rate was numerically higher but not statistically different between the groups (27.8% for temozolomide alone and 33.3% for CapTem, p=0.47).[13] This is the first randomized data of CapTem in pancreatic NET and it reinforces the activity of this regimen in this setting. Given the good tolerability of CapTem, we consider this regimen a good option for patients with progressive G1, 2 or 3 pancreatic NET, where tumor shrinkage is intended, as for example, in patients with high tumor burden and/or tumor-related symptoms.

**Carcinoid heart syndrome**

Carcinoid syndrome (CS), characterized by flushing, diarrhea, wheezing, cramping and swelling, can be associated with fibrotic complications, such as retroperitoneal fibrosis and a serious heart condition named carcinoid heart disease (CHD). Endocardial deposition of fibrotic plaques generally happens in right-sided valves and may lead to valve stenosis, resulting in heart failure.[14] Given the unknown frequency of CHD in Brazil, investigators undertook a single-center retrospective study where patients with advanced well-differentiated NET of any origin (69% from midgut) and elevated 24-hour-urinary 5-hydroxi-indolacetic acid (5HIAA), with or without carcinoid syndrome treated in a large academic and public cancer center, were screened for CHD. Using the definition of CHD as at least echocardiographic evidence of moderate to severe tricuspid or pulmonary regurgitation, 16 out 47 patients (38% [95% confidence interval [CI]: 23%–54%]) developed CHD in median follow up of 45.3 months since the first echocardiogram. They also found that high hepatic tumor burden (OR: 13.86, 95 CI: 2.57–74.68, p=0.002), delayed diagnosis, and concurrent cardiovascular disease (mostly arterial hypertension and coronary insufficiency) increased the risk of CHD in adjusted analysis.[15] The importance of this study is to increase awareness about this life-threatening complication of carcinoid syndrome. In addition, because CHD was also diagnosed in patients without CS, we recommended that all patients with abnormal 24-hour-urinary 5HIAA perform a screening echocardiogram, regardless of carcinoid symptoms.

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