Implications of the new histological classification (WHO 2010) for pancreatic neuroendocrine neoplasms

Pancreatic neuroendocrine tumors (PanNETs) are rare neoplasms with a more favorable prognosis than pancreatic adenocarcinoma. However, up to 60% of patients with PanNETs present with advanced disease or will recur after surgical resection, requiring multimodal therapy to improve clinical outcomes [1].

In 2011, two phase 3, randomized, placebo-controlled trials provided optimism regarding the treatment of malignant PanNETs [1, 2]. The tyrosine kinase inhibitor sunitinib and the mTOR inhibitor everolimus were effective in improving progression-free survival in advanced PanNETs [1, 2]. These two trials involved patients with well-differentiated or intermediate/low-grade PanNETs as defined by previous histological classifications including the World Health Organization (WHO) 2000 system [3]. Patients with poorly differentiated endocrine carcinomas (PDECs) were excluded from these trials, as PDECs are highly malignant tumors commonly treated with cisplatin and etoposide [4].

The enthusiasm for these two trials is unfortunately limited by the application of the WHO 2010 classification system for PanNETs. Based on a grading scheme with mitotic count and Ki-67 index, the WHO 2010 system identifies three tumor categories: NET G1, NET G2 and NEC [5]. The latter comprises PDECs defined by a mitotic count >20 mitoses/10 HPF and/or Ki-67 index >20% [5]. Interestingly, a 'morphological' well-differentiated tumor showing >20 mitoses/10 HPF or Ki-67 index >20% is classified as NEC (WHO 2010). Therefore, the number of NEC (WHO 2010) likely encompasses all PDECs (WHO 2000) and some tumors previously classified as well-differentiated PanNETs (WHO 2000).

In the sunitinib trial, the Ki-67 index was available only in 42% of patients, and 19.5% of these had Ki-67 > 10% [1]. Of note, the 6-month PFS rate was 71% and 43.2% in the sunitinib and placebo groups, respectively, and the PFS was significantly improved after administration of sunitinib only in patients with Ki-67 ≤ 5% [1]. This 'early' progression rate may be related to the presence of tumors with more aggressive biological behavior within the well-differentiated PanNETs (WHO 2000) included in the study. But are all these tumors well-differentiated neoplasms according to the WHO 2010 system (NETG1/NETG2)? Considering the Ki-67 values, some 'well-differentiated' tumors with Ki-67 > 10% might be NEC. Based on these findings, the inclusion in the sunitinib trial of only patients with 'real well-differentiated neuroendocrine tumors' (NETG1/NETG2) could have improved the results of this study, with a better PFS in the sunitinib group, as this drug was more effective for Ki-67 ≤ 5%.

In advanced PanNETs, a tumor-biopsy is required for grading definition with mitotic count/Ki-67 index evaluation to obtain a thorough histological diagnosis (NET G1/G2 versus NEC). This strategy is necessary for the appropriate management of patients with PanNETs in our daily practice, and it is also mandatory for careful planning and interpretation of future trials.

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All authors gave substantial contributions to conception and analysis/interpretation of data. S. C. and S. P. drafted the manuscript. L. B. and M. F. revised it critically. All authors approved the final version of the present manuscript.

disclosure

The authors declare no conflicts of interest.

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