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Sunitinib and everolimus in pancreatic neuroendocrine tumors

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To the Editor: Pancreatic neuroendocrine tumors (pNETs) represent a heterogeneous group of rare neoplasms, accounting for about 1% of all primary pancreatic tumors. In approximately 60-70% of cases they are diagnosed at an advanced stage no longer amenable to surgical resection, and in such circumstances the prognosis is poor, with a median survival of 24 months and a 5-year survival of 40%[1,2].

The low incidence of these tumors along with their histological and biological heterogeneity have in the past prevented clinicians from conducting prospective clinical studies aiming to define an appropriate therapeutic approach. Therefore, biotherapy with somatostatin analogues and chemotherapy combinations including platinum or streptozocin have been considered the standard treatments so far, capable of slowing tumor growth in unresectable disease[3,4].

The results of 2 phase III studies aimed at evaluating the efficacy of sunitinib and everolimus have been recently published in the *New England Journal of Medicine*[5,6]. The investigators accrued a significantly representative number of pNET patients with homogeneous characteristics in 2 similar, well-designed, randomized, double-blind clinical trials whose primary endpoint was the evaluation of progression-free survival. Both studies showed a significant advantage of sunitinib and everolimus over placebo in terms of progression-free survival (sunitinib – HR: 0.42; 95% CI: 0.26-0.66; P <0.001, everolimus – HR: 0.35; 95% CI: 0.27-0.45; P <0.001). In addition, good antitumor activity in terms of objective response rates was observed with sunitinib (9.3%) and everolimus (5.0%), chiefly with 2 complete responses among patients treated with sunitinib. Lastly, tumor growth control (complete response+partial response+stable disease) was achieved in 73% and 78% of patients treated with sunitinib and everolimus, respectively.

Despite inducing several hematological, gastrointestinal, dermatological and metabolic adverse events, both treatments turned out to be feasible. In most cases the severity of the adverse events was mild (grades 1 and 2), while the most common grade 3 and 4 events consisted of neutropenia (12%) and hypertension for sunitinib, and stomatitis (7%) and anemia (6%) for everolimus.

The results of these studies undoubtedly deserve consideration because they are very likely the starting point of the use of sunitinib and everolimus in the treatment of advanced pNETs; nonetheless, some clarifications and considerations seem necessary. First of all, the clinical course of pNETs does not always evolve in such a way as to justify the use of targeted therapy. In fact, even though pNETs are more aggressive than other NETs such as those originating from the ileum or appendix, well-differentiated or low-proliferation-index forms can be characterized by a scarcely evolving course.

Moreover, the 2 above-mentioned studies fail to clarify whether one therapeutic option would be more effective than the other. Therefore, it is reasonable to assume that the choice of one treatment over the other should be strictly related to the objective to be reached (objective tumor regression or chronic stable disease, choosing sunitinib in the former case and everolimus in the latter).

A starting point for a good tailoring of the therapeutic approach could be the appropriate distinction between the incidence and type of adverse events on the one hand, and the comorbidities and life expectancy of the patients on the other. In particular, since we are dealing with long-term therapies, it appears essential to avoid those mild-moderate side effects which, when persisting, could lead to worsening of the patient's quality of life.

Lastly, similarly to what has already been observed for the treatment of kidney cancer, future studies should investigate the sequential use of sunitinib and everolimus.

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