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Oral Agents for Treatment of Patients with Advanced Pancreatic Neuroendocrine Tumors: Could Pharmaeconomic, Cost-Effectiveness Data Play a Significant Role?

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Neuroendocrine tumors involving the pancreas (pNETs) represent a small percentage of all pancreatic tumors, with an increasing incidence and prevalence over the last decades [1]. The majority of malignant pNETs was diagnosed in advanced stage with approximately 65% of patients presenting with unresectable or metastatic disease [2]. Fortunately, the disease has a slow progression even at this noncurable stage as is reflected by the 30-40% 5-year survival rate [2, 3]. Treatment is determined by the tumor stage and surgical management is mandatory for resecatble mass at moment of the first diagnosis and it is also suggested for locally advanced nonresectable disease or metastatic tumors in the context of a debulking surgery, which is justified because of the slow tumor progression in patients with PNETs [3]. R0 resection, if feasible, is the current standard of care, while no adjuvant treatment has been established as a standard approach, and the role of debulking surgery and liver metastases resection requires further investigation. Systemic treatment for patients with advanced or metastatic disease includes the cytotoxic chemotherapeutic drug streptozocin, alone or in combination with doxorubicin or 5-fluoruracil [4]. However, these options are associated with a modest response rate and adverse, disabling toxicity [5]. For patients with functional tumors and hormonal secretion, somatostatin analogues may relieve symptoms and provide a potential antitumor activity in selected patients [6]. Recently, alternative molecular targeting for the systemic treatment of pNETs has been evaluated. Mammalian target of rapamycin (mTOR) inhibitors and VEGF/VEGF-R/PDGF-R inhibitors are in the most advanced clinical phase of investigation [7]. mTOR, a serine-threonine kinase, represents a candidate target in cancer because it stimulates cell growth, proliferation and angiogenesis. An abnormal function of the mTOR signaling pathway is often observed in PNETs and everolimus, an oral agent inhibiting mTOR, showed therapeutic effects in these tumors. In the recent RAD001 in Advanced Neuroendocrine Tumors (RADIANT-3) study [8], a phase-III randomized controlled trial, 410 patients with advanced PNETs were randomly assigned to receive everolimus, at a dose of 10 mg once daily (207 patients) or placebo (203 patients). The median progression-free survival (PFS) was 11 months in the everolimus group, compared with 4.6 months in the placebo group (hazard ratio for disease progression: 0.35; 95% CI: 0.27-0.45; P<0.001). The proportion of patients who were alive and progression-free at 18 months were estimated to 34% (95% CI: 26-43%) with everolimus as compared with 9% (95% CI: 4-16%) with placebo Adverse events were more frequent with everolimus than with placebo but they were characterised by a low-grade toxicity and the patients well tolerated the drug. This study strongly indicated that everolimus is a safe drug with efficacy in improving PFS in patients with progressive advanced PNETs. In May and September 2011, everolimus was approved by the US Food and Drug Administration (FDA) and European Medicine Agency (EMA), respectively, for the treatment of patients with progressive pNET.

Another molecular target extensively investigated in pNETs is strictly related to the inhibition of tumoral angiogenesis. Vascular endothelial growth factor (VEGF) signaling pathway is involved into the shift from normal cells to cancer cells and metastasis in PNETs also [9]. Sunitinib, an oral multitargeted

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Abbreviations ICER: incremental cost-effectiveness ratio; LYG: life-year gained; mTOR: mammalian target of rapamycin; PDGF: platelet derived growth factor; PFS: progression-free survival; pNETs: pancreatic neuroendocrine tumors; QALY: quality-adjusted life-year; VEGF: vascular endothelial growth factor

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tyrosine kinase inhibitor, has demonstrated antitumor activity in preclinical and clinical phase-I and II studies by inhibiting the transduction of signals in VEGF recpetor and platelet derived growth factor (PDGF) receptor pathways [10]. Raymond *et al*. report the results of the first phase-III trials for assessment of the safety and efficacy of treatment with sunitinib for pNETs [11]. In this randomized, double-blind, placebo-controlled trial 171 patients with advanced PNETs were enrolled and randomly assigned to receive either sunitinib at a dose of 37.5 mg per day or placebo, to assess the efficacy and safety. After an interim analysis, the study was discontinued early because of therapeutic superiority of sunitinib. At the interruption time, median progression-free survival was twice as long (11.4 months) in the sunitinib group than in the placebo group (5.5 months; hazard ratio: 0.42; 95% CI: 0.26-0.66; P<0.001). The objective response and death rates were 9.3% and 10% in the sunitinib group, as compared with 0 and 25% in the placebo group, respectively. Adverse events were more frequent in the sunitinib group than in the placebo group.

In clinical practice, these two phase-III trials have established everolimus or sunitinib administration for the treatment of patients with advanced or metastatic PNETs. The oral form of administration of both drugs seems to be a great advantage in comparison with intravenous drugs, enabling treatment of patients in an outpatient setting. Moreover, length of treatment (continuous or intermittent) and best treatment regimen for tumor recurrences (switching to the other cytotoxic drugs or combination of sunitinib and everolimus or adding a somatostatin analogue) have to be clarified in the next future [12]. As there were no trials comparing everolimus and sunitib in advanced, progressive pNETs, an indirect comparison was performed by Signorovitch *et al*. [13] by using a subset of the population of the above-mentioned trials. The analysis demonstrated a trend towards improved PFS and overall survival with everolimus to sunitib. So, no definite data are available to support the choice between these two oral agents for the treatment of pNETs.

Recently, this question was addressed from a pharmacoeconomic standpoint. Cost-effectiveness of everolimus *vs*. sunitib was investigated by Casciano *et al*. [14] from United States perspective. The authors utilised a complex model to simulate two hypothetical patients cohorts with advanced, progressive pNETs (one treated with everolimus and the other with sunitib) and to estimate the cost per life-year gained (LYG) and per quality-adjusted life-year (QALY). The cohorts were modeled over a 20-year time horizon in monthly cycles. For health states were included in the model: stable disease with no adverse events, stable disease with adverse events, disease progression, and death. All patients started in health state "stable disease with no adverse events" and transitioned to the remaining health states according to PFS and overall survival estimates obtained from the above-mentioned indirect analysis [13]. Therapy costs were based on wholesale acquisition cost; other costs such as physician visits, tests, hospitalizations, and adverse event costs were obtained from literature and/or primary research. The authors performed appropriate sensitivity analyses to test the model's robustness. The results showed that, in the base-case analysis, everolimus was associated with an incremental 0.448 LYG (0.304 QALY) at an incremental cost of US$ 12,673, resulting in an incremental cost-effectiveness ratio (ICER) of 28,281 US$/LYG (41,702 US$/QALY gained). The ICER fell within the cost per QALY range for many widely used oncology drugs. In addition, sensitivity analyses demonstrated that, overall, there is a trend that everolimus is cost-effective compared to sunitib in this setting, even if the results were not statistically significant (P>0.05). Although this analysis is limited because of its reliance on an indirect comparison of two phase-III studies, everolimus is expected to be cost-effective relative to sutinib in advanced pNETs. On the other hand, cost-effectivenes of everolimus was recently addressed in metastatic renal cell carcinoma also by using the same methodology [15] and this oral agent was reported to be a cost-effective treatment relative to sorafenib for sunitinib-refractory disease.

Based upon these considerations, the question stated in the title of the present article may have an answer, at least in the United States health-payment model. But, the limits of the cost-effectiveness advantage of everolimus *vs*. sunitib in advanced, progressive pNETs are not so sharp-cut and, therefore, we need further studies, also from the European countries, to better understand whether pharmaeconomic data will represent a decision-making step in clinical management.

Conflict interests The authors have no potential conflict of interest

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