Control of carcinoid syndrome with everolimus

clinical case

In February 2004, a 50-year-old woman was diagnosed with well-differentiated neuroendocrine carcinoma of the ileum with multiple bilobar hepatic metastases that occupied nearly all the parenchyma. An immunohistochemical analysis was positive for chromogranin A, synaptophysin and Ki67 level of 2%.

In July 2004, the patient underwent treatment with octreotide LAR 30 mg/28 days. This resulted in a disappearance of the diarrhea and flushing and decrease in urinary 5-HIAA levels (up to 85% of reduction). In September 2006, interferon-α2b was added to octreotide due to disease progression. After 3 months of treatment with the combination, the radiological stabilization was achieved without improvement in the symptoms of carcinoid syndrome and a hepatic embolization of the larger lesion combined with three sessions of radiofrequency ablation to
other smaller lesions was performed. The patient improved until December 2007, after which flushing increased to >10 episodes in a day with incoercible diarrhea occurring both day and night. Coinciding with the worsening symptoms, the patient presented with clinical cardiac insufficiency. An ultrasound revealed pathological cardiac carcinoid disease with severe tricuspid and pulmonary insufficiency, right ventricular enlargement and moderate pulmonary hypertension. Symptomatic therapy and an increase in the frequency of octreotide LAR to 30 mg every 15 days along with 2.5 mg quick release octreotide every 12 h were initiated. In July 2008, the patient presented worsening of flushing episodes (10–15 daily) with increasing in duration (5–10 min). The patient began treatment with everolimus at a dose of 10 mg/day under compassionate use. After a month of treatment, the symptoms of carcinoid syndrome improved with a reduction in the flushing episodes to 1–2 per day, an improvement in diarrhea and a significant decrease in 5-HIA levels (up to 60%).

**Figure 1.** Hepatic metastases in computed tomographies, July 2008 and August 2009, where the patient had a partial response with everolimus (10 mg/day) and octreotide LAR (30 mg/day).

**Figure 2.** Scheme of intracellular signal transduction pathways. Ligands bind to the extracellular domain of membrane receptors, which are phosphorylated, leading to activation of several cytoplasmic messengers, which activate transcription factors in the nucleus. The activation of transcription factors in the nucleus involves some target genes that are implicated in the proliferation, angiogenesis, apoptosis, tumor invasion and hormonal secretion processes. EGFR, epidermal growth factor receptor; IGFR, insulin-like growth factor receptor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PDGFR, placent-derived growth factor receptor; PI3K, phosphoinositol-3-kinase; PTEN, phosphatase and tensin homolog deleted; SSTR 1-5, somatostatin receptors 1-5; STAT, signal transducers and activators of transcription; TGFBR, transforming growth factor beta receptor; VEGFR, vascular endothelial growth factor receptor.
In April 2009, a tricuspid and pulmonary valve replacement was carried out and everolimus treatment was held for 2 months. During this time, the patient’s symptoms of carcinoid syndrome reappeared. In June 2009, everolimus 10 mg daily was reintiated and the patient again experienced symptomatic improvement and after more than 1 year on treatment finally the patient achieved a radiological partial response by RECIST criteria, achieving a 50% reduction in the liver target lesions (Figure 1).

discussion

The therapeutic options for refractory carcinoid syndrome are limited. The development of new targeted agents for the treatment of neuroendocrine tumors (NET) has generated new hope for patients. Targeted agents in development include somatostatin analogues with high affinity to four of the five somatostatin receptor subtypes (pasireotide) [1], antiangiogenics such as bevacizumab [1], tyrosine kinase inhibitors such as sunitinib [2] and mammalian target of rapamycin (mTOR) inhibitors (everolimus). Everolimus has demonstrated antitumor activity in NETs in phase II clinical trials [3]. In a large, phase III, randomized placebo-controlled trial with advanced pancreatic NET patients, everolimus 10 mg daily demonstrated a significant improvement in progression-free survival (4.6 versus 11.04 months, hazard ratio = 0.35, P < 0.0001) [4]. The results of a placebo-controlled phase III trial in patients with advanced NET and symptoms attributed to carcinoid syndrome are expected in near future (RADIANT-2).

To our knowledge, this is the first report of a hormone syndrome control with a targeted therapy in a functioning nonpancreatic NET with a typical carcinoid syndrome. There are only few data available of the antisecretory activity of everolimus, especially in refractory insulinomas [5]. The rationale for inhibition of hormone release under mTOR inhibitor treatment is unclear. However, the antiproliferative and hormone secretion control effects of somatostatin and its analogs are well defined. Recently, a new antiproliferation and apoptosis induction mechanism has been described through the inhibition of the phosphoinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K-AKT-mTOR) pathway. The phosphorylation of the somatostatin receptor 2 subtype directly binds with the PI3K p85 subunit inducing dephosphorylation and inactivation of PI3K and therefore downregulation of AKT and mTOR [6]. This evidence should explain in part the antihormonal effect of mTOR inhibitors. The multiple downstream effects after somatostatin receptor activation showing the main pathways involved in the antihormonal and antitumoral effects is shown in Figure 2. With this picture, we can predict the activity of some targeted therapies that will reach the daily clinical practice in the near future. The expected results of the RADIANT-2 study will contribute to increase the evidence of the antihormonal effect of mTOR inhibitors and will attempt to differentiate if this is a drug class effect or related to reduction of tumor burden.

disclosure

The authors declare no conflict of interest.

references


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