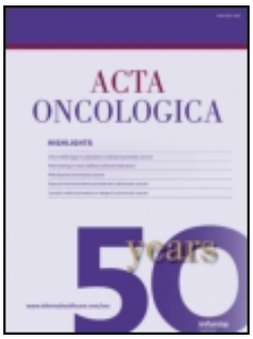

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LETTER TO THE EDITOR

Well-differentiated pancreatic islet cell carcinoma: Is there reversibility in mTOR inhibitor resistance?

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To the Editor,

In 2000, a 48-year-old man presented with epigastralgia. Computed tomography scan revealed a hypervascular pancreatic tumor with multiple liver and mediastinal lymph node metastases. The diagnosis of metastatic well-differentiated pancreatic islet cell carcinoma (pNET) was made by biopsy of the liver lesions. The mitotic index was 3/10 HPF (x40); Ki67 index was 5%. Serum levels of digestive hormones were within normal limits and chromogranin A levels was 220 µg/l. Octreotide scintigraphy showed high-grade activity in liver and mediastinal metastases. The patient was successively treated with chemotherapy (six cycles of streptozotocin-doxorubicin); surgery (cephalic duodenopancreatectomy in March 2002, due to the local risk of compression and presence segmental portal hypertension); without any treatment and stable disease until February 2004; alpha-interferon for 15 months; chemotherapy (ten cycles of Folfiri); and everolimus in December 2006 (RADIANT 1 trial). The treatment resulted in a decrease in tumor size (34% using RECIST criteria) at four months; the disease was controlled for 24 months. Because of occurrence of two new liver metastases, the patient was then included in a phase 3 trial and received sunitinib throughout 12 months; sunitinib was stopped because of occurrence of portal vein thrombosis under enoxaparin; the disease was stable. The patient was then treated with lanreotide in order to maintain disease stabilization; however, new progression (+10% among RECIST criteria and elevation of Chromogranin A from 1982 to 2932 µg/l) occurred three months later. In June 2010, as the patient refused cytotoxic chemotherapy and because of the particular initial good response to the everolimus, it was decided to add everolimus in association with lanreotide. Three months after starting the treatment, the weight of the patient had increased by 3 kg, fatigue had disappeared and imaging studies showed a response of 23% on RECIST criteria. His disease remains stable six months after this combination started.

To our knowledge, this is the first case showing a second efficacy of mTOR inhibitor for treatment of solid advanced cancer. It enables us to discuss the reversibility of resistance mechanisms of everolimus, and potential interest of a combined therapy with somatostatin analogs. It has recently been shown that, in patients with pNET, sunitinib or everolimus significantly increase progression-free survival [1,2]. However, even if a control of the disease is frequently achieved, objective responses, such as the one observed in our case, are rare. How can we explain the second efficacy of everolimus in combination with somatostatin analogs 18 months after the end of the first treatment, as reported here? Some hypotheses may be discussed: a) synergetic antitumor effect between everolimus and somatostatin analogs; b) emergence of a predominant tumor cell clone, responding to everolimus, after a break in treatment or maybe induced by

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sunitinib. There are at present no experimental studies or clinical trials to support this synergetic antitumor effect of a combined therapy, even if somatostatin analogs may interact with the PI3K/Akt/mTOR pathway [3]. Different studies demonstrated that mTOR inhibition induces feedback activation of Akt in different tumor cell types [4], and that dual targeting of the PI3K/Akt/mTOR pathway increases the anti-tumoral effect [4,5]. Furthermore, some experimental studies suggest the existence of a reversible compensatory feedback mechanism between PI3K/Akt/mTOR and MAP-kinases survival signaling [4] and provide a rationale for dual targeting of these pathways in pNET disease. The observations obtained in our case suggested a potential efficacy of somatostatin analogs to inhibit these feedbacks. Moreover our case also suggests that in pNET, with relative long disease evolution, sequential treatment with molecular targeted therapies could be also an option in comparison to combined therapy. Further preclinical studies are warranted to elucidate the mechanisms of adaptive resistance, so as to design therapeutic strategy.

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