Should everolimus be stopped after radiological progression in metastatic insulinoma? A "pro" point of view

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LETTER TO THE EDITOR

Should everolimus be stopped after radiological progression in metastatic insulinoma? A "pro" point of view

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We read with great interest the paper by Valeria Tovazzi and colleagues: "Should everolimus be stopped after radiological progression in metastatic insulinoma? A "cons" point of view as published in Endocrine [1].

The authors have described beneficial therapeutic effects of everolimus in a patient with refractory hypoglycaemia caused by a metastatic insulinoma. Treatment with everolimus was continued despite radiological progression. In this single case, everolimus significantly reduced the number of hypoglycaemic episodes. These hypoglycaemias in patients with metastatic insulinomas can indeed significantly decrease the quality of life and require multimodality treatment. In case of unresectable disease, systemic treatment is indicated to reduce hypoglycaemias and to inhibit tumour growth. Currently, somatostatin analogues (SSAs) are still considered first-line treatment and in the patient described by Tovazzi and colleagues, SSA treatment resulted in stable disease with well-controlled symptoms for 2 years. Thereafter, addition of everolimus again resulted in 2 years of disease and symptom control, but when radiological progression occurred discontinuation of everolimus resulted in the recurrence of refractory hypoglycaemias. Everolimus was, therefore, restarted, while treatment with chemotherapy was commenced. Indeed, mTOR inhibitors like everolimus can cause hyperglycaemia as a side effect and this effect is well-appreciated in patients suffering from hypoglycaemias. Everolimus prolongs progression-free survival (PFS)) in pancreatic neuroendocrine tumour (NET) patients (RADIANT-3 study).

However, at the time of further tumour progression, other therapies should also have been considered, with potentially fewer toxicities. Pasireotide is a multiligand SSA with higher affinity to somatostatin receptor subtype 5 as compared to first generation SSAs and has been shown to reduce hypoglycaemias in patients with insulinomas (case reports). However, pasireotide is not approved for the treatment of pancreatic NETs. Moreover, peptide receptor radionuclide therapy (PRRT) with radiolabelled SSAs (such as ^{177}Lu-DOTATATE) has been shown to be highly effective in the treatment of metastatic insulinomas. ^{177}Lu-DOTATATE is approved by the EMA and FDA for the treatment of pancreatic NET and in all subtypes of pancreatic NET it results in a radiological response in 55% of patients with a median PFS of 30 months [2]. Equally important, we have demonstrated that this radionuclide treatment results in symptomatic responses (e.g. reduction in hypoglycaemias) in 67% of patients and these symptomatic responses often persist despite radiological progression [3]. Other groups have also published very favourable results with PRRT in patients with metastatic insulinomas. Furthermore, in a recent meta-analysis, PRRT with radiolabelled SSAs showed better therapeutic efficacy and safety profiles as compared to everolimus in advanced pancreatic NETs [4]. Additionally, in NET patients pretreated with everolimus, no significant effect of prior/pretreatment with everolimus on the subacute haematotoxicity of ^{177}Lu-DOTATATE could be demonstrated [5]. In light of these results, switching to ^{177}Lu-DOTATATE, with proven tumour growth inhibition and symptom control, should be preferred above continuing everolimus after clinical and radiological progression, also considering other toxicities associated with this drug. In the case report described by Tovazzi and colleagues ^{68}Ga DOTA SSA PET showed somatostatin receptor expression on the primary tumour and its metastases making the patient a candidate for PRRT with ^{177}Lu-DOTATATE. The conclusion of the authors that "everolimus is the only drug capable of inducing a stable and long-lasting glycaemic control together with an

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antineoplastic effect in malignant insulinomas"(sic) is ignoring the favourable data on PRRT in such cases. PRRT with ^{177}Lu-DOTATATE should be considered as second or third line treatment for metastatic insulinomas because of the high symptomatic response.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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