OBSERVATIONS

Improved Glycemic Control With the Multi-Receptor Tyrosine Kinase Inhibitor Pazopanib

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Pazopanib is a novel antiangiogenic inhibitor of tyrosine kinases (TKIs) with high activity against vascular endothelial growth factor receptor (VEGFR1–3), platelet-derived growth factor receptor (PDGFR$\alpha+\beta$), and c-Kit. Here we report on a patient with prostate cancer and type 2 diabetes whose glycemic control has been significantly improved with pazopanib during anticancer therapy and describe a potential mechanism of action.

The 73-year-old patient was diagnosed with prostate cancer in 1999 and underwent prostatectomy and radiotherapy, sequential hormonal therapies, and, in 2008, first line chemotherapy. Due to disease progression he was enrolled in a phase I trial with pazopanib (400 mg p.o. daily, day 1 to 21 every 3 weeks) in combination with epirubicine (75 mg/m^2 i.v. q3w every 3 weeks). Type 2 diabetes was diagnosed when the patient was 69 years and weighed 103 kg (BMI 33.6 kg/m^2). He was treated with glibenclamide resulting in moderate to poor glycemic control (A1C 7.5–10.9%).

In February 2009, shortly after initiation of pazopanib, metformin was added but had to be withdrawn after a few days due to adverse gastrointestinal events. Surprisingly, however, self-measured blood glucose (SMBG) levels improved significantly. A1C decreased by 2.1% within 6 weeks (10.9% on 16 February 2009 to 8.8% on 26 March 2009), and fasting SMBG readings declined by more than 5 mmol/l on average (8.5–14.9 vs. 4.7–6.8 mmol/l). Glibenclamide was stopped, and no other medication affecting glucose metabolism was prescribed during follow up. Over the next 2 months, A1C levels decreased further (7.0% in May) and remained low even after stopping pazopanib in July 2009. Body weight and renal function did not change significantly over the same period of observation.

A blood glucose–lowering effect in patients has already been described for the multi-receptor TKIs sunitinib in type 1 and type 2 diabetes (1,2) and imatinib in type 2 diabetes (3). Despite their different pathogeneses, type 1 and type 2 diabetes seem to have potential overlapping inflammatory pathways. Louvet et al. (4) demonstrated in an animal model of type 1 diabetes in NOD mice that PDGF blockade (by means of a soluble PDGFβIg) could be the critical mechanism of improved glycemic control, probably by inhibition of a PDGF downstream-mediated nonspecific inflammatory response that promotes β-cell death and insulin resistance (4,5). TKIs targeting c-Kit and c-Fms (PLX647) showed only marginal efficacy, and TKIs affecting EGFR and the VEGF-antibody were, to our knowledge until now, not reported to have an impact on blood glucose levels. These findings suggest that inhibition of PDGFR is a key mechanism responsible for the antidiabetic class effect of the multi-receptor TKIs.

For clinicians, it is important to establish close monitoring of blood glucose levels in patients taking PDGFR targeting TKIs, but especially in patients with diabetes treated with sulfonylureas, meglitinides, or insulin in order to prevent hypoglycemia.

On the other hand, the observation of the glucose-lowering effect and the further identification of its molecular mechanisms could offer promising targets for innovative therapeutic concepts for treatment or even prevention of type 1 and type 2 diabetes.

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