Remission of diabetes while on sunitinib treatment for renal cell carcinoma

introduction

Sunitinib is an oral inhibitor of tyrosine kinases, including vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), and has been associated with higher response rates and longer progression-free survival in patients with metastatic renal cell carcinoma (RCC) as compared with interferon [1]. We describe a long-term remission from recent-onset type 1 diabetes mellitus in a patient with metastatic RCC during sunitinib therapy.

case report

We report on a 64-year-old man who had undergone nephrectomy for clear cell RCC in 1996. Because of systemic relapse in 2003 that ultimately failed interferon-alpha therapy, the patient was treated in an investigational vaccination protocol with dendritic cells fused to his own tumor cells beginning in March 2005. In May 2005, diabetes mellitus was diagnosed after a 2-week history of polydypsia, polyuria and weight loss with a plasma glucose level of 36.8 mmol/l (662 mg/dl), HbA1c 11.5%. The patient was of normal weight and stature (body mass index 20.3 kg/m²), had no dyslipidemia and his family history was negative for type 2 diabetes suggesting type 1 diabetes. Diagnosis of type 1 diabetes was confirmed by clearly elevated glutamic acid decarboxylase (GAD) antibodies with 28,680 U/l (<9.5 U/l). Intensive multiple-dose insulin therapy using a basal-bolus approach was started (42 IU daily). Vaccinations were stopped because of disease progression in November 2005 and sunitinib treatment was started in January 2006 (37.5 mg daily). Gradually, the insulin dose could be tapered off until September 2006 (Figure 1), from that time point on the patient was euglycemic without insulin. There was a slight increase in weight during these 8 months (74 to 74.9 kg). Initially, the response to sunitinib treatment was stable disease (according to Response Evaluation Criteria in Solid Tumors criteria), but in February 2007 the computed tomography scan showed progressive disease and the treatment with sunitinib was stopped.

The patient’s glycemic control including postprandial insulin secretion remained nearly normal without medication up to the present (HbA1c 6.6%, postprandial plasma glucose 8.8 mmol/l and postprandial C-peptide 3475 pmol/l while anti-GAD antibodies were still elevated (2770 U/l).

discussion

In a 64-year-old patient with metastatic RCC and recent-onset type 1 diabetes, we have observed sustained normoglycemia without insulin treatment after 9 months of treatment with sunitinib. Although the onset of type 2 diabetes is more common at this age, type 1 diabetes also occurs at a low incidence in the elderly [2]. The clinically suspected diagnosis of type 1 diabetes was confirmed by the clearly elevated GAD antibodies in our patient. Although we cannot exclude the possibility that autoimmune insulitis with beta-cell failure was triggered by the vaccinations that reversed after vaccine treatment discontinuation, it is more likely that the recovery of diabetes mellitus was caused by sunitinib treatment since anti-GAD antibodies were still elevated 15 months after the last

Figure 1. During sunitinib treatment insulin could be tapered off.
vaccination. The potential mechanism of recovery with sunitinib is not known. In animal models for diabetes due to beta-cell destruction, the tyrosine kinase imatinib mesylate was shown to enhance beta-cell survival by promoting a state similar to ischemic preconditioning, as evidenced by NF-kappaB activation, increased nitric oxide and hydrogen peroxidation and depolarization of the inner mitochondrial membrane [3]. We speculate that similar effects of sunitinib may prevent further loss of residual beta cells in our patient with type 1 diabetes. To evaluate these potentially beneficial effects on beta-cell survival further trials in diabetic cancer patients would be warranted.

It was recently observed that a modest number of patients suffering from both chronic myeloic leukemia and type 2 diabetes were successfully treated not only for leukemia but also for diabetes, when given imatinib [4]. The molecular mechanisms underlying the beneficial effect of imatinib in these cases are unknown, but may be related to the property of imatinib to inhibit the nonreceptor tyrosine kinase c-Abl which, when activated, leads to cell cycle arrest and apoptosis playing a pathogenic role in type 1 and type 2 diabetes [3]. Furthermore, imatinib has been shown to retard the development of atherosclerosis in the context of diabetes by inhibition of PDGFR which is also targeted by sunitinib suggesting not only amelioration of diabetes and glycemia but also beneficial effects on the development and progression of diabetic macrovascular complications [5].

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