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Long Term Survival of a Patient with Metastatic Renal Cell Carcinoma Treated with Half-Dose Pazopanib: A Case Report

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Abstract

We describe the case of a 59-year-old woman who underwent a radical left nephrectomy for renal cell cancer in 1993. After 7 years, the disease relapsed as thyroid and pulmonary metastases and she has been initially treated with chemotherapy. At further progression we administered an antiangiogenic drug, Sunitinib for 9 months then we switched to Pazopanib. The patient is still receiving a half-dose of Pazopanib (46 months) and she is showing a long-lasting response with an optimal safety profile.

In this patient, Pazopanib demonstrated a significant improvement in PFS and tumor response also with half a dose. Nephrectomy, metastasectomy, medical therapy and targeted treatments have been shown able to prolong survival and improve quality of life. This is an example of chronicized disease in a patient who can be defined as a long-term survivor.

Keywords: Long-term survivor; Metastatic renal cell cancer; Pazopanib; Quality life; Thyroid

Introduction

The incidence of all stages of Renal Cell Carcinoma (RCC) has increased over the past several years, accounting for 2%-3% of all adult malignancies [1]. All stages of RCC patients have a 5-year survival rate of approximately 62%, but untreated metastatic patients (mRCC) have a 5-year survival rate ranging from 0% to 18% [2,3].

The systemic management of metastatic RCC (mRCC), traditionally resistant to conventional chemotherapy [4,5] has changed rapidly over the past five years with FDA approval of six targeted agents directed against aberrant VEGF and mTOR pathways. VEGF-pathway antagonists have largely replaced cytokine-based therapies as the first-line treatment for many patients with clear cell RCC.

Materials and Methods

A 59 years-old Caucasian woman underwent a left radical nephrectomy for a renal mass in February 1993. Histology revealed a grade II clear-cell carcinoma without invasion of the capsule or major vessels. No lymph nodes were removed during surgery. The patient was followed up with 6-monthly abdominal computed tomography (CT) scans and chest X-rays. After seven years, due to the appearance of dysphagia and dysphonia, a total body CT scan was performed and multiple thyroid lesions were detected. A total thyroidectomy was done in April 2000 and metastases of mRCC were diagnosed. No specific oncological therapy was started, and in February 2001 bilateral lung metastases were highlighted by CT scan. A first line chemotherapy with vinblastine was started; due to hematological G4 toxicity (requiring hospitalization), it was stopped after two cycles. In September 2001, lung progression disease was documented and a second-line therapy with Fluorodeoxyuridine (FUDR) 0,15 mg/kg/day, 14 days ON and 14 days OFF, was performed for 2 years with stable disease until December 2005. Lung disease progression was highlighted in February 2009 and biological first-line therapy started with dose-escalation of oral Sunitinib (from 37.5 mg to 50 mg daily, 4 weeks ON/2 weeks OFF). Due to hematological G4 toxicity (pancytopenia requiring hospitalization), Sunitinib therapy was stopped after 6 month and no further therapy was started for patient's refusal. In January 2012, due to severe clinical and radiological lung disease progression, the patient was treated with Pazopanib at a reduced dose of 400 mg/day considering previous toxicities. Treatment was well tolerated and in July 2012, after six months of therapy, partial response to treatment was highlighted, showing number and size reduction of bilateral lung metastases. There were neither hematological toxicity nor laboratory abnormalities; the only adverse events were fatigue (G1) and changes in hair color (G1). Patient is still continuing Pazopanib therapy, now achieving a 46 months Progression Free Survival (PFS).

Results

In patients with mRCC, chemotherapy as monotherapy is not considered effective. In contrast, a systematic review on phase I/II/III studies, published between 2003 and 2012, indicated that chemotherapy can still play a promising role in mRCC when immunotherapy and target therapy have not yielded lasting and satisfactory results [6].

Recent advances in molecular biology have led to the development of several novel agents for the treatment of mRCC. Many targeted agents have been introduced for the treatment of advanced and/or metastatic renal cell carcinoma and have demonstrated a substantial improvement in PFS. Tyrosine kinase inhibitors (TKIs) are able to increase the progression-free survival and/or overall survival as both first-line and second-line treatments for mRCC.

Our case represents the transition between two different settings of care: chemotherapy was the past and TKI drugs were the future.

In our case report, thyroid was the first metastatic site during follow-up for CCRC that had been diagnosed 7 years earlier. In the literature there are only 10 cases of CCRC with metastasis to thyroid [7].

After chemotherapy, the patient was initially treated with

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Sunitinib, an oral inhibitor of tyrosine kinases, that demonstrated a longer progression-free survival and response rates than patients receiving interferon alfa [8]. Grade 4 hematological toxicity occurred in our patient and treatment was stopped. Conversely, Pazopanib, a similar TKI inhibitor, demonstrated in pre-clinical models a low affinity for Flt-3, in contrast to a higher affinity for VEGFR1-2-3 (higher than, for example, to that of sunitinib) and similar affinity for PDGF α and PDGFR α [9]. The low off-target activity of Pazopanib seems to be responsible for the lower toxicity of this molecule compared to other tyrosine kinase inhibitors [10]. Escudier et al. [11] suggests that, in the context of a comparable efficacy, patients preferred Pazopanib over Sunitinib due to a lower incidence of adverse events and a better quality of life.

Our work suggests that switching to another anti-VEGF agent, even after toxicity-related changes, could offer excellent results, in terms of tolerability and efficacy. As well as previous clinical experiences [12], this report suggests that biological agents seem promising for stabilizing mRCC over a long period of time. However, this promise has to be balanced against their toxicity profile and the patient's quality of life.

Pazopanib, administrated at a dose of 400 mg orally in a single daily, demonstrated a significant effect in terms of PFS (46 months) and objective response, all associated with an excellent tolerability profile. In literature there are no studies for Pazopanib with schedule changing as in Sunitinib. Motzer et al. [13] determined, according to the severity of adverse events, dose reductions for Pazopanib (to 600 mg and to 400 mg) nevertheless the efficacy of treatment was demonstrated. Tolerability profile is important in patients with kidney cancer in advanced stage or in elderly patients, just to preserve the quality of life and allow to stay in treatment for a long period of time , with an impact important to the stability of the disease. This case proves that treatment with Pazopanib can be offered to patients with pre-existing hematological abnormalities and in the future, personalized treatment based on clinical and laboratoristic criteria will surely lead to the development of new treatment schedule.

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