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Case Report

Pazopanib-induced trismus in a young male with metastatic renal cell carcinoma: a case report and literature review

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Abstract

The treatment landscape of advanced kidney cancer has radically changed over the years. Targeting tumor angiogenesis from historical cytokines to multi-tyrosine kinase inhibitors and recently the advent of immunotherapy resulted in a radical improvement in survival but presented substantial challenges in terms of toxicity management. In countries where the access to immune checkpoints inhibitors is still very limited, tyrosine-kinase inhibitors remain the optimal choice. The toxicity profile of these agents can influence both the clinician and the patient's preference for one molecule over another. This report describes the case of a young man treated with Pazopanib in a first-line setting for stage IV renal carcinoma who developed trismus under treatment. The occurrence of this off-target toxicity has made the patient ineligible for anti-angiogenic drugs. Although side effects of tyrosine kinase inhibitors seem manageable and reversible, some less known and unusual effects may evolve into severe and irreversible complications.

Keywords: Oncology, Palliative medicine, pharmacology and pharmacy

INTRODUCTION

Tyrosine kinase inhibitors TKI have revolutionized the treatment landscape of many aggressive cancers, including metastatic renal cell carcinoma. The recent approval of immunotherapy-based combinations led to significant improvement in survival rates, never achieved before. TKI monotherapy remains however the frontline therapy due to limited access to immune checkpoint inhibitors ICI in many countries. Tyrosine kinase inhibitors are small molecules able to target tyrosine kinase receptors, essential components involved in intra- and inter-cellular signal transduction pathways that maintain fundamental cellular tissue homeostasis such as proliferation, differentiation, migration, and apoptosis. These agents generate a distinct toxicity profile, resulting from ubiquitous inhibition of angiogenic signals in endothelial cells of normal tissues. Although the promise of a fairly well-tolerated toxicity profile, some rare and serious events have been reported since the development of TKIs.

Herein, we report the case of a young patient treated with Pazopanib in first line setting for a metastatic renal carcinoma who developed trismus under treatment. To the best of our knowledge, this is one of the first cases to be reported in the medical literature.

CASE REPORT

A 23-year-old male with no prior significant medical history presented to his primary care physician with a 3 months history of decreased visual acuity and ptosis in his left eye, associated with a tender, painless and fixed scalp swelling. The patient also described persistent pelvic and lumbar pain resistant to first-line analgesics. Physical examination shows a limitation of intrinsic motility and low reactivity to light with no significant anomalies.

MRI brain imaging showed a lesion of the sellar and infrasellar region of lobular contours, measuring 30∗28∗28 mm, in hyposignal T1, hypersignal T2, with diffuse restriction in diffusion-weighted imaging and homogeneously enhances after contrast injection. Systemic investigation revealed a locally infiltrant tumor of the right kidney measuring 150×120×180 mm well limited and spontaneously heterogeneous after contrast injection, with intratumoral calcifications and delimiting areas of necrosis, associated with secondary liver, spleen and diffuse lytic bone lesions. A surgical biopsy of the scalp lesion revealed a poorly differentiated proliferation of clear cell carcinoma. Immunohistochemical staining (IHC) demonstrated negative staining for CK7, CK20 with positive staining for PAX8 suggestive of clear cell renal carcinoma. First-line Pazopanib, the only treatment option available to us, was started in September 2021, with best response of stable disease (RECIST1.1: −13%). The patient tolerated well the treatment and showed adequate compliance. He achieved an improvement in his systemic symptoms and quality of life, with no immediate grade 3–4 adverse events. After nine months of treatment, the patient presented a painful tightening of the jaw muscles, causing sudden difficulty in mouth opening and speaking. The patient

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had no history of dental infections and was not taking any other medication. He had no evidence of mucositis, neuromuscular or striking symptoms. The panoramic X-ray did not show any structural alterations or fractures. Head and neck imaging showed no evidence of metastatic disease or other pathology. After the elimination of traumatic, infectious, and dental causes, the diagnosis of Pazopanib-induced trismus was retained. The symptoms improved within two weeks after discontinuing the treatment and resumed when reintroduced. The occurrence of this off-target adverse event has made the patient ineligible for anti-angiogenic drugs. Following that, Everolimus was given as second-line treatment at standard doses. Four months later, the patient was hospitalized due to severe deterioration in his general condition. He died after rapid progression of the disease in July 2022.

DISCUSSION

Angiogenesis is a physiological process of growth and cellular regeneration by which new blood vessels are formed from pre-existing vessels. It is acquired as a fundamental step in tumor growth, progression and metastasis. Our understanding of tumor angiogenesis has continued to evolve and has made possible the development of antiangiogenic agents. VEGFs, a family of five circulating ligands involved in cancer angiogenesis, bind to three endothelial tyrosine kinase receptors VEGFR and initiate pro-angiogenic intracellular downstream signaling pathways [1]. Over the past decades, targeting tumor angiogenesis via inhibition of VEGF overexpression through monoclonal antibodies bunding (e.g. Bevacizumab) or intracellular blockade of VEFGR signaling by oral multitarget TKIs has made a substantial breakthrough.

Renal cancer has been a proof-of-concept model for targeting angiogenesis [2]. Hereditary and most sporadic renal cell carcinoma originate from the loss-of-function mutation of the Von-Hippel Lindau (VHL) gene, which leads to hyperactivation of the hypoxia-inducible factors (HIF-1α and HIF-2α) normally expressed under hypoxia, and thus an overexpression of VEGF and other proangiogenic factors [3]. **Sorafenib** is the first oral tyrosine kinase inhibitor approved for advanced RCC in 2006. The Target trial showed increased PFS of 5.5 months versus 2.8 months in the placebo group (HR: 0.44; 95% CI, 0.35–0.55; $P < 0.01$) in patients whom previous therapy has failed, with no overall survival benefit [4]. **Sunitinib** was approved the following year for first-line treatment after demonstrating a statistically significant reduction in the risk of progression (11 vs. 5 months, HR = 0.42, 95% CI, 0.32–0.54; $P < 0.001$) and in the risk of death (26.4 vs 21.8 months, HR = 0.818; 95% CI 0.669–0.999; $p = 0.049$) compared to INF alfa [5]. The efficacy and safety of **Pazopanib** was first evaluated in a phase III trial in locally advanced and metastatic RCC where treatment-naïve patients were randomized to receive either Pazopanib at 800 mg daily or matching placebo [6]. First-line Pazopanib results of 8 months PFS compared with placebo and 11 months PFS compared with sunitinib, and offered similar efficacy in overall survival [7]. On the basis of this data, Pazopanib obtained approval of the FDA in 2009. Of note, the PISCES study showed that toxicity can influence both patient and clinician preference for pazopanib over sunitinib [8].

With the coming of age of ICI/immunotherapy and the array of combined approaches expands, the management of renal cancer has radically changed. The first clinically relevant improvements in overall survival (OS) occurring with TKI and ICI combinations have marked the new era, overtaking TKI as standard of care [9]. Although, the exponentially higher cost of this change of approach has made it difficult to adopt in limited-resources countries. In this context, TKIs are still largely prescribed in the first-line setting [10].

The association between TKIs-related toxicity and therapeutic outcomes is well known and widely investigated. Patients experiencing high-grade toxicities are more likely to achieve optimal response rates [11]. The hypothesis that the VEGFR, the major target of these agents, is a potent angiogenic factor expressed on numerous endothelial, non-endothelial, and cancer cells with varying levels of expression depending on the tissue from which they originate. The occurrence of toxic effects results from the effective inhibition of signaling pathways mediated by the VEFGR and is therefore an indicator for effective anti-tumor activity. Gastro-intestinal symptoms, stomatitis, skin rash, hypertension, fatigue, and hypothyroidism are the most reported adverse events. Few of these agents are selective for one tyrosine kinase receptor [12]. The pan-inhibition of other tyrosine kinase receptors explains the rare side effects that most TKIs induce through their multi-targeted activity. To illustrate, hemorrhagic events may occur under TKI secondary to the inhibition of PDFGR signaling [13]. Most of these side effects are common, reversible, often respond to symptomatic measures, and do not require the discontinuation of treatment. Alongside, some less-known yet more serious AE have been associated with TKIs. Their etiopathogenesis is multifactorial and involves the deregulation of tyrosine kinase activity with primary pathogenic factors depending on the tissue involved. Trismus or lockjaw in cancer patients is a common complication of oral cancers or as a result of irradiation and surgical interventions. In very rare cases, it occurs as side effect of systemic therapies. Anti-angiogenic related trismus is mostly reported with bisphosphonates, owing to their anti-osteoclastic and anti-resorptive activity. The risk increases with treatment duration, cumulative dose and is more reported with intravenous agents. Some cases have been associated with Bevacizumab exposure. TKIs are prone to induce trismus as a result of VEGFR signal blockade leading to a decrease in the vascular permeability and angiogenesis of the temporomandibular joint. Eventually, muscle atrophy and fibrosis mediated through the induction of apoptosis, can contribute to trismus. It is also possible that VEGFR blockade plays a role in the pathogenesis of trismus by affecting osteoclast differentiation and bone resorption activity.

In our case-report, the patient did not exhibit any traumatic, infectious, or dental cause that could explain the occurrence of trismus. The course of the symptoms with trismus improving after discontinuing the treatment and resuming when reintroduced confirmed our diagnosis. One case report had reported the occurrence of trismus in an elderly patient after 5 years of commencing first line Sunitinib treatment for metastatic renal cell carcinoma, that also recurred when changing to Pazopanib, and resolved completely upon pazopanib cessation [14]. A recent publication reported three cases of oral toxicities including two cases of jaw osteonecrosis and one case of gingival bleeding in patients treated with Pazopanib as monotherapy for metastatic RCC [15].

CONCLUSIONS

Pazopanib as well as other TKIs are still part of the therapeutic arsenal used every day in clinical oncology practice. Despite their promising therapeutic effects, their side effects can be very challenging. Because they are usually benign, oral side effects are often underestimated, and patients rarely undergo oral and dental check-up by a stomatologist before prescription. In most

cases, trismus requires only dose reduction. Permanent treatment discontinuation should be considered in case of severe effects at the starting dose or if symptoms do not resolve at the reduced dose. Maintaining optimal oral hygiene, reducing oral microbial load are essential to reduce its occurrence. If not given early consideration, trismus can dramatically affect the quality of life and potentially evolve to aseptic osteonecrosis of the jaw. Given the variety of possible side effects of TKI, sharing case reports is essential to help in early diagnosis, timely intervention, and planning preventive strategies.

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CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interest.

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ETHICAL APPROVAL

Approval by an ethics committee or institutional review board is not necessary.

CONSENT FOR PUBLICATION

Written informed consent is obtained from the patient for publication of this case-report. A copy is available upon request.

GUARANTOR

N. Benhima have full access to data and are responsible for its integrity. Data is available upon request.

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