Case Report

Adverse Reactions of Cabozantinib in Renal Cell Carcinoma Patient

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Abstract

Cabozantinib (CAB), a Tyrosine Kinase Inhibitor (TKI) is the first-line therapy for Metastatic Renal Cell Carcinoma (mRCC) updated recently. Reports on adverse reactions of CAB include cutaneous reactions in a RCC patient. Other TKI (Sunitinib) reported cases on drug induced acute interstitial nephritis. To illustrate this, we depict a case on CAB induced adverse reactions in a RCC patient after 1 month of therapy, causing gastric ulceration with bleeding and acute interstitial nephritis with acute renal failure. The culprit drug was terminated immediately after differential diagnosis by biopsy and corticosteroid therapy was initiated. Improvement in renal functions was witnessed and later on CAB was resumed in a low dose strategy of 20 mg a day. The study objective is to provide proper direction that will decrease the impact of adverse events and resource to maximize the utility of CAB in patients with advanced renal cell carcinoma.

Keywords: Cabozantinib; Gastric bleeding; Inflammation; Nephritis, Renal carcinoma; Tyrosine kinase inhibitors

Research in-context

- Tyrosine Kinase inhibitor, Sunitinib is indicated in the treatment of mRCC and is reported to cause drug induced interstitial nephritis.
- CAB, a newer therapy form RCC from 2016, is reported to cause cutaneous reaction.
- Are there previous cases misdiagnosed with similar conditions due to poor monitoring?
- CAB on therapy form RCC has caused interstitial nephritis and gastric ulceration with bleeding confirmed by biopsy and endoscopy.
- Wide variations in renal parameters were observed until slow tapering and termination of CAB, where they returned to normal.
- Awareness on adverse reactions of CAB would help in better diagnosis of conditions and tapering or termination of the drug.

Introduction

Cabozantinib (CAB), approved by US-FDA in 2012, was earlier used to treat medullary thyroid cancer and Renal-Cell Carcinoma (RCC) as second-line. It is a small molecule inhibitor of tyrosine kinase, cMET and VEGFR2 by inhibiting AXL and RET. Updated European association of urology guidelines on RCC suggests nonspecific TKI as the first line therapy for RCC [1]. No previous reports on adverse effects of this drug is available, except a case on cutaneous reaction secondary to CAB, due to its recent use in mRCC [2]. It is recently the first-line of choice in mRCC patients with intermediate or poor fatality advantageous with progression-free survival rate, with high rates of G3-4 toxicity [3]. Patients of phase III trial were highly benefitted when on combination with immunotherapy [4,5].

Drug-induced acute interstitial nephritis deteriorates the renal function where early detection and termination of the drug could resume normal functioning. Steroidal therapy helps in faster recovery with low hospital stay [6,7]. The present case report elucidates on the adverse reactions of CAB in a RCC patient.

Case Presentation

72-year-old male patient with a history of T2DM and hypertension for the past 15 years on regular therapy, presented with chief complaints of blood in urine x 2 episode, chills, rigors on & off for past 2 days, reduced urine output and constipation. He was recently diagnosed with Papillary Renal Cell Carcinoma on therapy with T.Cabozantinib 60mg P.O. daily since 1 month. Colonoscopy reported normal anal canal and mucosal regions; upper G1 endoscopy showed bleeding with erosion of antrum and pylorus indicating severe gastric ulcerations. His lab investigations showed anemic state, hyponatremia, bleeding with erosion of antrum and pylorus indicating severe gastric ulcerations. His lab investigations showed anemic state, hyponatremia, bleeding with erosion of antrum and pylorus indicating severe gastric ulcerations. His lab investigations showed anemic state, hyponatremia, bleeding with erosion of antrum and pylorus indicating severe gastric ulcerations. 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Foci of lymphocytes and eosinophilic tubulitis were evident. Acute interstitial nephritis resulting in tubular injury due to CAB was predicted as adverse reaction of the drug with Naranjo’s score and WHO-UMC causality showing “probable” for cabozantinib (Score 7).

He was withdrawn temporarily from CAB therapy and was on hemodialysis along with corticosteroid therapy. Within 2 weeks of therapy, there was considerable improvement in his renal function tests and gastric ulcerations. There were no other causes for the adverse reaction, immediate termination of the drug witnessed improving patient conditions. Later on initiation of therapy with same drug was done at 20 mg dose (Figures 1 and 2).

**Discussion**

The patient was on CAB therapy for 1 month. Chief complaints along with laboratorial investigations, renal biopsy and endoscopy revealed acute interstitial nephritis with gastrointestinal bleeding due to CAB.

Gastrointestinal bleeding is a black-box warning of CAB along with change in renal functions and acute renal failure being a prominent side effect of TKI. The pathogenesis of CAB involved in this reaction is not completely understood [8,9]. Factors involved in drug-induced interstitial nephritis include immunologic reaction or hypersensitivity type I, slower damage to tubules, direct nephrotoxicity [10,11].

Other possible differential diagnosis in this case include hemolytic-uremic syndrome. The biopsy of tumor is the only determining factor for its diagnosis as drug induced interstitial nephritis. Wide deviations in renal function were evident directing to acute renal failure. With termination of the drug, reversal of renal failure was observed (Figure 3). CAB includes the following tyrosine kinase receptors namely stem cell factor receptor C-kit, IMS-like tyrosine kinase-3, platelet-derived growth factor receptor, colony stimulating factor-1 [12,13].

Therapy of acute interstitial nephritis and drug-induced gastric ulcerations involve quick termination of the culprit drug along with corticosteroid therapy. After the conditions resolved, initiation of CAB at a lower dose is advised [14,15]. Both the physician and patient should be completely aware of the side effects and adverse reactions if faced again on re-administration.

This is the first case elucidating on acute interstitial nephritis and gastric ulcerations with bleeding due to CAB. Awareness and further future studies on ADR of CAB could be focused.

**Acknowledgement**

The authors are thankful to Dr. Sekar, Chief Medical Superintendent, Government Hospital, Thiruvallur for his constant support and encouragement throughout the study. We thank the patient who gave his willing consent for the publication of his case by sharing complete information needed for the study.

**Conflict of Interest**

The author declares no conflicts of interest concerning the content of this case report.

**Contribution statement:**

A.K.R and V.P.J have been throughout the patient's admission in hospital and obtained the case. N.B also accompanied throughout the case discussions. The other Co-authors helped with literature review. Write up and final approval of the paper was done by A.K.R, V.PJ, NB and others.

**Ethical consideration**

Written informed consent was obtained with permission from the patient.

**References**


