Journal of Clinical Pharmacology and Therapeutics

ISSN: 2766-8347

Case Report

Adverse Reactions of Cabozantinib in Renal Cell Carcinoma Patient

Asha K Rajan[1], Vedha pal Jeyamani S[1], Deepak Paul Denagaran[1], Franklin Jose[1], Nallabothula Manoj Kumar[1] and Narendra Babu[2]*

[1]Department of Pharmacy Practice, Jaya College of Paramedical Sciences, College of Pharmacy, India

[2]Assistant Surgeon, Government Head Quarters Hospital, India

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 ofmRCC 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 non-specific 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 × 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, with acute renal failure. Estimated Glomerular filtration rate was 35 ml/min/1.73 sq BSA, C - Reactive protein level was 47.8 mg /L, Pt levels - 12 sec (control), 21.5 sec (test), INR: 1.79.

Anti-nuclear antibody, rheumatoid factor, anti-mycloperoxidase, anti-proteinase 3, peripheral and cytoplasmic anti-neutrophilic, cytoplasmic antibodies were all negative. Renal biopsy of the patient showed a grey brown tumor measuring 6.5 cm × 6 cm × 4 cm occupying lower pole and part of mid pole, grey white to grey brown hemorrhagic. Pelvicalyceal system was involved. Malignant neoplasm was disposed in papillary configuration lined by polygonal cells with moderate eosinophilic cytoplasm and hyperchromatic nuclei with nucleoli visible at high power. Tumor infiltrating lesions were present. There was also extensive interstitial inflammation with eosinophils and edema. Cortex was more inflamed when compared to medulla.

Citation: Rajan AK, Jeyamani SV, Denagaran DP, Jose F, Manoj Kumar N, Narendra B. Adverse Reactions of Cabozantinib in Renal Cell Carcinoma Patient. J Clin Pharmacol Ther. 2020;1(1):1005.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Nov 20th, 2020

***Corresponding author:** Asha K Rajan, Department of Pharmacy Practice, Jaya College of Paramedical Sciences, College of Pharmacy, Thiruninravur, Chennai-602024, India, Tel: +918667012876, E-mail: ashapharmd523@gmail.com

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.

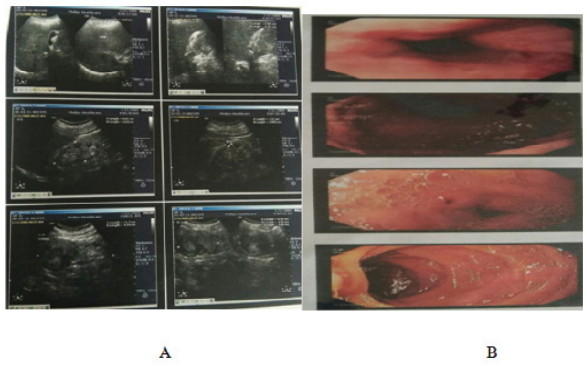

Figure 1: A) Heterogeneously hypoechoic mass lesion measuring 66 mm × 56 mm × 45 mm noted exophytically in lower pole of left kidney along with renal cortical cysts of interstitial nephritis. B) Endoscopy revealing gastric ulceration associated with bleeding.

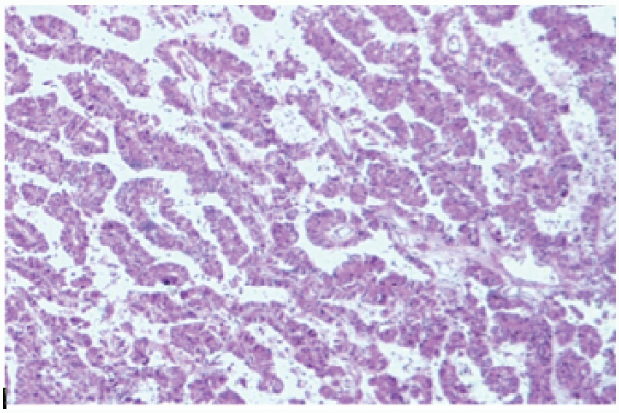

Figure 2: Malignant neoplasm disposed in papillary configuration lined by polygonal cells with moderate eosinophilic cytoplasm and hyperchromatic nuclei and tumor infiltrating lymphocytes present with interstitial inflammation with eosinophils and edema.

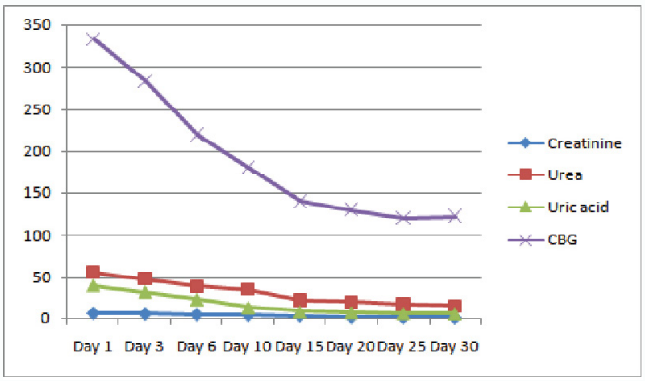

Figure 3: Renal function tests of the patient after termination of cabozantinib.

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.P.J, NB and others.

Ethical consideration

Written informed consent was obtained with permission from the patient.

References

1. Albiges L, Powles T, Stachier M, Bensalah K, Giles RH, Hora M, et al. Updated European association of urology guidelines on renal cell carcinoma: immune checkpoint inhibition is the new backbone in first-line treatment of metastatic clear

cell renal cell carcinoma. Eur Urol. 2019;76(2):151-6.

2. Growcott S, Banner A, Bray A, Hilman S. A rare cutaneous adverse effect secondary to cabozantinib therapy. Oxf Med Case Reports. 2018;2018(12):omy105.

3. Clarkson MR, Giblin L, O'Connell FP, O'Kelly P, Walshe JJ, Conlon P, et al. Acute interstitial nephritis: Clinical features and response to corticosteroid therapy. Nephrol Dial Transplant. 2004;19(11):2778-83.

4. Bersanelli M, Leonardi F, Buti S. Spotlight on CAB for previously untreated advanced renal cell carcinoma: Evidence to date. Cancer Manag Res. 2018;10:3773-80.

5. Barakat RK, Singh N, Lal R, Verani RR, Finkel KW, Foringer JR. Interstitial nephritis secondary to bevacizumab treatment in metastatic leiomyosarcoma. Ann Pharmacother. 2007;41(4):707-10.

6. Surendra M, Raju S, Chandragiri S, Uppin MS, Raju N. Steroid therapy in drug-induced acute interstitial nephritis-retrospective analysis of 83 cases. Saudi J Kidney Dis Transpl. 2019;30(1):157-65.

7. Azar I, Esfandiarifard S, Sinai P, Wazir A, Foulke L, Mehdi S. Sunitinib-induced acute interstitial nephritis in a thrombocytopenic renal cell cancer patient. Case Rep Oncol Med. 2017;2017:6328204.

8. Perazella MA, Markowitz GS. Drug-induced acute interstitial nephritis. Nat Rev Nephrol. 2010;6(8):461-70.

9. Jonasch E, Gao J, Rathmell WK. Renal cell carcinoma. BMJ. 2014;349:g4797.

10. Winn SK, Ellis S, Savage P, Sampson S, Marsh JE. Biopsy-proven acute interstitial nephritis associated with the tyrosine kinase inhibitor sunitinib: a class effect? Nephrol Dial Transplant. 2009;24(2):673-5.

11. Zuo RC, Apolo AB, DiGiovanna JJ, Parnes HL, Keen CM, Nanda S, et al. Cutaneous adverse effects associated with the tyrosine-kinase inhibitor cabozantinib. JAMA Dermatol. 2015;151(2):170-7.

12. Mizukawa Y, Yamazaki Y, Shiohara T. *In vivo* dynamics of intraepidermal CD8+ T cells and CD4+ T cells during the evolution of fixed drug eruption. Br J Dermatol. 2008;158(6):1230-8.

13. Izzedine H, Brocheriou I, Rixe O, Deray G. Interstitial nephritis in a patient taking sorafenib. Nephrol Dial Transplant. 2007;22(8):2411.

14. Khurana A. Allergic interstitial nephritis possibly related to sunitinib use. Am J Geriatr Pharmacother. 2007;5(4):341-4.

15. Lomax AJ, Hill PA, Ashley DM. Case report of interstitial nephritis induced by bevacizumab therapy for glioblastoma multiforme. J Oncol Pharm Pract. 2013;19(4):365-8.