

SINGLE DOSE REGORAFENIB-INDUCED HYPERTENSIVE CRISIS

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Gastrointestinal stromal tumors (GISTs) are uncommon tumors of the gastrointestinal (GI) tract. Regorafenib is a new multikinase inhibitor and is approved for the treatment of GISTs in patients who develop resistance to imatinib and sunitinib. The most common drug-related adverse events with regorafenib are hypertension, hand-foot skin reactions, and diarrhea. Grade IV hypertensive side effect has never been reported after a single dose. In this report, we present a case of Grade IV hypertensive side effect (hypertensive crisis and seizure) after a single dose of regorafenib. A 54-year-old male normotensive GIST patient was admitted to the emergency department with seizure and encephalopathy after the first dosage of regorafenib. His blood pressure was 240/140 mmHg upon admission. After intensive treatment with nitrate and nitroprusside, his blood pressure returned to normal levels in five days. Regorafenib was discontinued, and he did not experience hypertension again. This paper reports the first case of Grade IV hypertension after the first dosage of regorafenib. We can suggest that hypertension is an idiosyncratic side effect unrelated to the dosage. **Key Words:** hypertension, regorafenib, gastrointestinal stromal tumor.

Gastrointestinal stromal tumors (GISTs) are uncommon tumors of the gastrointestinal (GI) tract. These tumors originate in very early forms of cells found in the wall of the GI tract called interstitial cells of Cajal [1]. GISTs usually have mutations in proto-oncogenic genes encoding the receptor tyrosine kinase (RTK) stem cell factor receptor (KIT) or platelet-derived growth factor receptor alpha (PDGFR- α) [2–4]. The development of tyrosine kinase inhibitors that target the changes in these genes has improved the prognosis of GISTs. Imatinib and sunitinib inhibit multiple RTKs, including KIT and PDGFR- α , and are indicated for first- and second-line targeted therapy, respectively, in patients with GISTs [2].

Almost all patients develop resistance to these multikinase inhibitors [2]. Regorafenib is a new multikinase inhibitor and is approved for the treatment of GISTs in patients who develop resistance to imatinib and sunitinib and for metastatic colorectal cancer. This is a novel broad-spectrum kinase inhibitor, with activity against multiple targets, including vascular endothelial growth factor receptor (VEGF) 1, 2, 3, fibroblast growth factor receptor (FGFR) 1, PDGFR β , tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2 (TIE2) and the mutant oncogenic kinases KIT, RET, B-RAF [5]. The most common drug-related adverse events with regorafenib are hypertension, hand-foot skin reactions, and diarrhea [6]. Grade IV hypertensive side effect has never been reported after a single dose.

In this report, we present a case of Grade IV hypertensive side effect (hypertensive crisis and seizure) after a single dose of regorafenib.

Case report. A 54-year-old male was diagnosed with a 17×8 cm gastric mass by a CT scan. The patient underwent partial gastric resection and removal of the mass. Immunohistochemical analysis revealed that the tumor was positive for CD117 and CD34 but negative for S100, and the patient was diagnosed with GIST. The CT scan showed hepatic and splenic metastasis 10 months after the surgery. The patient received imatinib treatment at 400 mg/day and was examined every three months. A CT scan at the 15th month of imatinib treatment showed progression in the size of the metastasis and new lymph nodes. We discontinued imatinib and prescribed sunitinib 50 mg/day (28 days on, 14 days off). A CT scan at the 28th month of sunitinib treatment showed tumor progression. Therefore, sunitinib treatment was changed to oral regorafenib 160 mg/day.

The patient was normotensive and had no previous history of high blood pressure. He was not receiving any medication except imatinib and sunitinib. The patient had routinely taken his blood pressure since commencing the tyrosine kinase inhibitor treatment. Eight hours after the first dosage of regorafenib, the patient was admitted to the emergency department with seizure and encephalopathy. His blood pressure was 240/140 mmHg upon admission. A cranial CT scan was performed and excluded metastasis. All blood workup was normal, including liver, kidney, and thyroid function. Echocardiography was normal.

After intensive treatment with nitrate and nitroprusside, his blood pressure returned to normal levels in five days. Regorafenib was discontinued, and he did not experience hypertension again. After all work-up, the case suggests that hypertensive crisis was related to the single dose of regorafenib treatment.

Regorafenib is a novel oral multikinase inhibitor that regulates tumor angiogenesis. In common with other antiangiogenic drugs targeting the VEGF/VEGFR pathway, one of the dose-limiting side effects of regorafenib is hypertension [6]. A number of mechanisms have been suggested for VEGF signaling pathway inhibitor associated hypertension. According to one study,

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Abbreviations used: GI tract – gastrointestinal tract; GISTs – gastrointestinal stromal tumors; KIT – stem cell factor receptor; PDGFR- α – platelet-derived growth factor receptor alpha; RTK – receptor tyrosine kinase.

VEGFR pathway inhibitors decrease NO synthesis and lead to a loss of parallel capillary circulation in normal, nontumor tissue, a process called rarefaction. Other studies suggested a role for endothelial dysfunction, leading to an increase in endothelin-1 (ET-1) and aortic stiffness [7–10]. De Jesus-Gonzalez et al. [11] showed that regorafenib induces coordinated and reversible suppression of NO and stimulation of ET-1.

Two phase III studies of regorafenib have been performed. In the CORRECT study, which included patients with metastatic colorectal cancer, 36.7% of 500 patients in the regorafenib group had hypertension [12]. Treatment-related Grade III hypertension occurred in only 7% of cases. Grade IV hypertension was not reported in this study. In the second randomized, placebo-controlled, phase III trial of patients with advanced GISTs, regorafenib-induced hypertension was seen in 49% of 132 patients [6]. Among these, 23% had Grade III hypertension, and only one patient had Grade IV hypertension. The study contained no data on the patient's dosage or the duration of regorafenib treatment.

George et al. [13] and Bruix et al. [14] reported regorafenib-induced hypertension in 36% of patients in two phase II studies ($n = 33$ and $n = 36$, respectively). All the patients in George et al. [13] study had Grade III hypertension. Bruix [14] reported a patient with Grade \geq III hypertension, but the actual grade was not reported whether grade III or IV in the study. Eisen et al. [15] showed that only 3 of 49 patients had Grade \leq IV hypertension during regorafenib usage in their phase II clinical trial.

In conclusion, this paper reports the first case of Grade IV hypertension after a single dose of regorafenib. Grade IV hypertension is an unexpected adverse effect of regorafenib therapy according to the aforementioned five clinical trials. These studies included 750 patients, and only one case of Grade IV hypertension was reported. Our patient experienced Grade IV hypertension after a single dose of regorafenib treatment, and the hypertension ceased after discontinuation of the drug. Our findings suggest that hypertension is an idiosyncratic side effect unrelated to the dosage.

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