LETTER to the EDITOR

Are Rogerofenib and Nilotinib Effective for Advanced Gastrointestinal Stromal Tumor (GIST) Patients who have Already been Given Main Treatments?

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Dear Editor

Patients with GISTs most commonly have KIT and PDGFRA mutations. The therapeutic agents are determined based on these sites of mutation. Imatinib and sunitinib are proven to be effective against GIST, and these agents are now the standard treatment options for GISTs. Moreover, several novel molecular-targeted agents are under development, particularly regorafenib and nilotinib which have phase III trials. In these trials, it has been shown to contribute of survival with regorafenib but longer survival has not obtained with nilotinib. We have two cases who were responder with regorafenib and nilotinib in the fifth-line therapy.

First case, a 45-year-old male patient who had GIST in small intestine with multipl liver metastases. C-KIT gene mutation analysis was performed on the pathology preparation which has indicated an exon 11 deletion. In the immunohistochemical evaluations, it was found that there was positive staining for CD34 and SMA. Imatinib 400 mg/day had been initiated and it had been used for 7 years. After progression imatinib dose was increased to 800 mg/day, then the patient was shifted to treatment with sunitinib, then treated with sorafenib for 14 months, 2 months, 1 month, respectively. An ileus had occured after a month of sorafenib treatment. This was considered as clinical progression and then the patient was shifted to treatment of regorafenib (160 mg/day). The ileus symptoms markedly regressed on the 7th day of regorafenib treatment and completely resolved on the 14th day (Figure 1). The patient died at the 10th month of treatment with regorafenib due to liver failure.

Second case, a 40-year-old female patient who had GIST in stomach with multipl liver metastases. C-KIT and PDGRFA gene mutation analysis was performed on the pathology preparation which has indicated no mutation anywhere. In the immunohistochemical evaluations, it was found that there was positive staining for CD34 and negative staining for SMA. Progression occured at the first evaluation which was performed in 3rd month during first and second-line imatinib therapies (400 mg/day and 800 mg/day). Then the patient was shifted to treatment with sunitinib, then treated with regorafenib for 5 months and 3 months, respectively. During treatment with imatinib, sunitinib and regorafenib progression occured in a short time. Therefore, nilotinib (800 mg/day) have been initiated and now she is going stable disease with nilotinib for 12 months.

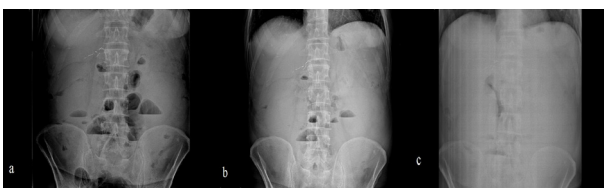

Figure 1. Ileus had Completely Resolved for 14 Days with Regorafenib Treatment in X-RAY Scanning. A) before regorafenib treatment **B)** on the 7th day of regorafenib treatment **C)** on the 14th day of regorafenib treatment

In the recently reported phase III randomized controlled double blind placebo controlled GRID trial of regorafenib in patients with GIST tumors resistant to both imatinib and sunitinib, the median PFS of patients on the regorafenib arm was 4.8 months and 0.9 months for those on placebo with a HR 0.27 (95% CI, 0.18-0.39), P<0.0001 (Demetri et al., 2013). The phase III study of nilotinib versus best supportive care (BSC) in third-line therapy, did not demonstrate an improvement in PFS on central review with a median of 109 days in the nilotinib arm versus 111 days in the control arm (Reichardt et al., 2012). However in phase II trials and retrospective studies of nilotinib, response was ranged from partial regression (PR) 10-12%, with stable disease (SD) of 37-59% (Vadakara and von Mehren, 2013). Three randomized controlled trials were selected for meta-analysis. The patients who were resistant or intolerant to both imatinib and sunitinib, nilotinib or regorafenib improved progression-free survival (HR 0.40; 95% CI 0.19-0.84; P=0.02) but not overall survival (HR 0.83; 95% CI 0.63-1.08; P=0.17) (Wu et al., 2014).

Imatinib exhibits inhibitory activity against ABL kinase, as well as KIT and PDGFRA receptor. Sunitinib inhibits VEGFR-1,2,3, PDGFRA, PDGFRB, KIT, Flt3, RET and CSF1R. Regorafenib inhibits VEGFR-1,2,3, PDGFRB, FGFR1, KIT, RET and BRAF. Nilotinib inhibits ARG, KIT, PDGFRA and PDGFRB (Serrano and George, 2014). All tyrosine kinase inhibitors which are used for GISTs, have partly different targets so, a non-responder patient with a certain agent may become "*responder*" with another. In a study of Demir et al. (2013) it was showed that, SMA negative and CD 34 positive cases of GIST, had poor prognosis (Demir et al., 2013). Our second case was in same immunohistochemical features so that it may be the reason of unresponsiveness

to tyrosine kinase inhibitors which were given at previous-lines therapies.

In clinical studies, new generation tyrosine kinase inhibitors such as rogerofenib and nilotinib which are used in later periods of disease, shows limited improvements. However, in some patients, long-term disease control or improvement in symptoms can be achieved with these agents. As in these two cases, in later even in final periods of disesase, we suggest that these agents should be tried as a chance.

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