Regorafenib third-lined therapy in advanced GISTs--- A single center analysis based on different genotypes

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Objective

The relationship between primary and secondary mutational status and efficacy of regorafenib in third-line therapy on GISTs is yet clear.

Methods

From Jun 2017 to Dec 2021, a total of 62 patients with advanced GIST refractory to imatinib and/or sunitinib were enrolled in this study from the First Affiliated Hospital, Sun Yat-sen University.

Results

Primary mutational was most common in KIT exon 11(40/62, 64.5%) , followed by exon 9 (19.4%), exon 17 (4.8%). Six cases (9.7%) belonged to SDH deficiency and one case (1.6%) was NF1-associated GISTs. Before receiving treatment of regorafenib, specimens obtaining for secondary mutations were as follows: 39 cases from surgery，12 from core-needle biopsy; ctDNA alone was performed in 9 cases and 2 patients refused to secondary mutational test. Excluding 6 patients with SDH deficiency, 14 patients (25.8%) had mutations in exon 11+13, 15 (27.7%) in exon 11+17, 7 (13.0%) in exon 9+17, 4 (7.4%) in exon 11+13+17. Exon 11 + 18, exon 11 + 13 + 18, exon 11 + 13 + 17 + 18, exon 9 + 16, exon 11 + 17 + 18 and NF-1 were found in 1 case, respectively (1.9%). Eight (14.7%) patients with primary KIT mutation were not detected any secondary mutation （2nd-not-detected）. There was no complete response, 4 of partial response (4/54, 7.4%), 27 of stable disease (50.0%). Progression disease was seen in 23 patients (42.6%) and 8 were not applicable (no assessable lesion) to imaging response assessment due to R0/1 surgery before using regorafenib. The median follow-up time was 19.0 months. The median progression-free survival (mPFS) was 5.4 months (0.2-29.1 months) and the median overall survival (mOS) was 20.3 months (0.2-37.0 months). For primary mutation analysis, it was found that SDH-deficient patients had longer mPFS (29.1 months) than those with mutations in exon 9 or exon 11 (5.4 and 4.8 months, respectively; P=0.013). In terms of secondary mutations, patients with activation loop mutations (exon 17+18) showed both longer mPFS (7.3 months vs 1.9 months, P=0.001) and longer mOS (20.3 months vs 7.7 months, P=0.059) than those patients with non-activation loop mutations. Not any specific or new adverse reaction was found in all patients. By Cox-regression analysis，response to regorafenib and mutational status were independent predictors of PFS，response to regorafenib was also an independent predictor of OS.

Conclusion

Regorafenib seems to have better treatment efficacy in GIST patients with SDH deficiency compared to those with primary KIT mutations, and better with secondary mutations in activation loop than those with non-activation loop mutations. It is necessary to carry out clinical research for later-line treatment choice based on different genotypes for imatinib-resistant GISTs.
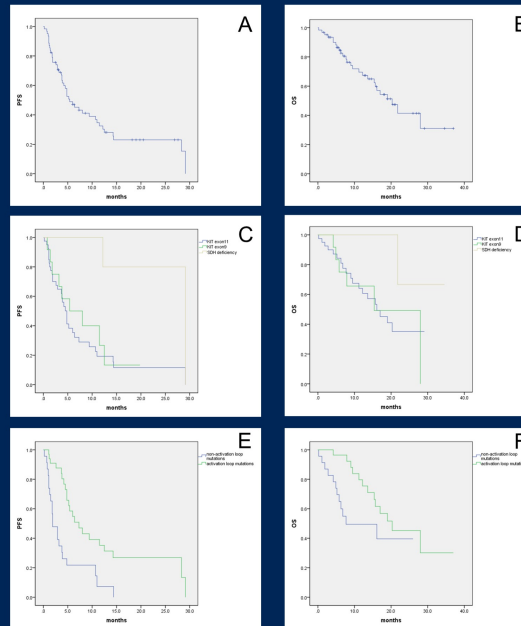
Figure 1. Progression-free survival and overall survival

A. Progression-free survival of all patients
B. Overall survival of all patients
C. **Progression-free survival of patients based on different primary mutation**
D. Overall survival of **patients based on different primary mutation**
E. **Progression-free survival of patients with** activation loop mutations or not
F. Overall survival of **patients with** activation loop mutations or not

Table 1. Clinical Characteristics of Patients Enrolled

Characteristic	No(%)
Gender	
Male (%)	35(58.1)
Female (%)	26(41.9)
Primary site	
Stomach (%)	16(25.8)
Duodenum (%)	7(11.3)
Small bowels (%)	37(59.7)
Rectum (%)	1(1.6)
Others (%)	1(1.6)
Primary mutation	
Kit exon 11 (%)	40(64.5)
Kit exon 9 (%)	12(19.4)
Kit exon 17 (%)	3(4.8)
SDH deficiency (%)	6(9.7)
NF1-associated (%)	1(1.6)
Specimens obtaining	
Surgery (%)	39(62.9)
core-needle biopsy (%)	12(19.4)
ctDNA (%)	9(14.5)
None(%)	2(3.2)
Secondary mutation	
Kit exon 11 +13 (%)	14(25.8)
Kit exon 11 +17 (%)	15(27.7)
Kit exon 9 +17 (%)	7(13.0)
Kit exon 11 +13+17 (%)	4(7.4)
Kit exon 11 +18 (%)	1(1.9)
Kit exon 11 +13+18 (%)	1(1.9)
Kit exon 11 +13 +17+18(%)	1(1.9)
Kit exon 9 +16 (%)	1(1.9)
Kit exon 11 +17+18 (%)	1(1.9)
NF1-associated (%)	1(1.9)
No secondary mutation(%)	8(14.7)

Table 2. Pathological type

Pathological type	No(%)
Spindle cell (%)	49(79.0)
Epithelioid cell (%)	5(8.1)
mixed type(%)	2(3.2)
Unkonwn(%)	6(9.7)

Table 3. Dose

Dose	No(%)
160mg (%)	25(40.3)
120mg (%)	35(56.5)
80mg(%)	2(3.2)

Table 4. Best judgment

Best judgment	No(%)
PR (%)	4(7.4)
SD (%)	27(50.0)
PD(%)	23(42.6)
NA(%)	8

Table 5. Adverse events*

Adverse events	No (%) Grade 0	No (%) Grade 1/2	No (%) Grade 3/4
Hand-foot syndrome	13(26)	19(38)	18(36)
Hypertension	41(82)	5(10)	4(8)
Anemia	12(20.7)	34(58.6)	12(20.7)
Leukopenia	33(56.9)	25(43.1)	0(0)
Neutropenia	43(74.1)	14(24.1)	1(1.8)
Impaired liver function	32(55.2)	15(25.9)	11(18.9)
Impaired renal function	48(82.8)	10(17.2)	0(0)

*It was a rare serious adverse event that there was perforation of the digestive tract because of rupture of the metastatic tumor after receiving regorafenib. The reason is not clear.

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