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ORIGINAL ARTICLE

Toxicity Management and Effectiveness of Regorafenib in Advance GIST Patients: A Real-world Study

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OBJECTIVE

Regorafenib, a multikinase inhibitor, is an approved third-line therapy for advanced gastrointestinal stromal tumors (GISTs). However, its routine clinical application is difficult due to the associated adverse events (AEs) reported by patients in the 1st month, which leads to early discontinuation. In this study, we presented our experiences in toxicities management and the effectiveness of regorafenib in our institutional cancer center.

METHODS

Twenty-two patients treated with regorafenib as a third-line therapy for advanced GISTs were retrospectively evaluated who had progressive disease after imatinib and sunitinib treatments. All patients received a full dose of 160 mg/day of regorafenib.

RESULTS

The average age of the patients was 49 years (range: 25-61 years), with a male preponderance (63.6%). The average follow-up time for the subjects was 114.2 months (16.2-210.3), while the median time of regorafenib using time was 7.7 months (1.9-29.1). The median overall survival (OS) of the patients was found as 10 months, while the 1-year OS rate was 38.3%. The median progression-free survival was found as 7.1 months. Regorafenib-related partial response was observed in 5 patients (22.7%), stable disease in 9 (40.9%), and progressive disease in 8 (36.4%). The disease control rate was 63.7%. Treatment-related grade 3/4 AEs were seen in ten (45.4%) patients. The most common AE was hand-foot skin reaction (5; 18.2%), followed by fatigue (3; 13.6%) and hypertension (2; 9.1%). Dose reductions were required in 7 patients (31.8%). The treatment was discontinued in a patient due to stroke.

CONCLUSION

Our results demonstrate promising activity and manageable side effects of regorafenib as third-line therapy of GIST in daily clinical practice in the Turkish population.

Keywords: Advanced disease; adverse events; gastrointestinal stromal tumors; regorafenib.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most seen mesenchymal tumor of the gastrointestinal tract (GIT) that originate from intestinal Cajal cells.[1,2] It accounts for 1-2% of all GIT cancers.[2] The average age of diagnosis is usually >60 years.[3] GISTs affect any region along the GIT (from the upper esophagus

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to the anus) and are most commonly detected in the gastric (50-60%), followed by the small intestine (30-40%), colon (5-10%), and esophagus (1-2%).[1,4] The clinical presentation of GISTs varies with the primary tumor site and includes gastrointestinal bleeding, bowel obstruction, and dysphagia, although 15-20% of all patients are asymptomatic.[1,4] Approximately more than 90% of GISTs express KIT or PDGFR driver mutations.[5,6] The remaining 5-10% of GISTs express no KIT or PDGFR mutations and are known as wild-type GISTs and include a variable molecular group. However, recently, approximately 4% of GISTs have been reported to have a BRAF mutation.[7-9] Imatinib - an active agent against PDGFRA and KIT - was first reported to be effective in the treatment for advanced GISTs 20 years ago and has remained the first-line standard treatment until date.[10,11] However, it may develop imatinib resistance in the majority of patients who have advanced GISTs disease. Sunitinib - another tyrosine kinase inhibitor of PDGFRA and KIT - has been used as second-line therapy after the progression on imatinib treatment, with clinically meaningful efficacy outcomes in randomized trials.[12,13] Nevertheless, sunitinib treatment may develop resistance generally in the first year. Regorafenib - an oral multikinase inhibitor with angiogenic (VEGF receptors), stromal (FGFR and PDGFR receptors), and oncogenic (KIT, BRAF, and RET) effects - was applied in randomized clinical studies and reported significant efficacy for the third-line therapy for advance GISTs.[14-16] In the GRID trial, regorafenib increased progression-free survival (PFS) in patients who had advanced GISTs disease after treatment failure with imatinib and sunitinib.[16]

Randomized and clinical researches are insufficient to explain the effectiveness of the treatments for various patients in clinical practice because of the patient selection criteria. Real-life experience is important to validate Phase III, randomized, and clinical trials as well as to identify and determine relevant risk groups. The clinical data on regorafenib treatment of advanced GISTs in the Turkish population are scarce. We purpose to present the safety and effectiveness of regorafenib as a third-line therapy against advance GISTs at our tertiary cancer center.

MATERIALS AND METHODS

In this cross-sectional retrospective study, we analyzed 197 patients clinical data who were diagnosed with GISTs between January 2010 and January 2021 at a single cancer center. Based on the patient records, 25 patients had received regorafenib as the third-line therapy for advance GISTs, which had progressed despite imatinib and sunitinib treatments. The clinical data of three patients were insufficient and hence not included in the study; finally, 22 patients were evaluated. The tumor biopsy specimen was assessed by a soft-tissue expert pathologist for all patients. The baseline clinicopathological and laboratory data were retrieved from the institutional registries, and details of the patient's characteristics were recorded, such as the age, gender, treatment history, tumor size, tumor location, previous treatments data, and The Eastern Cooperative Oncology Group (ECOG) performance status.

The dose of regorafenib was started at 160 mg/day (every 4 weeks on a schedule of 3 weeks on and 1 week off) through the oral route. When the patient could not tolerate the drug due to the ensuing side effects, the dose was first reduced to 120 mg and then to 80 mg, and ultimately, to 60 mg, if necessary. Based on the age of the patients, they were assigned to two subgroups: <60 years and ≥60 years. Primary tumor location, primary tumor diameter, and metastatic sites were recorded based on the images before regorafenib treatment. Clinical staging was performed with reference to the AJCC stage classification 8th edition for GIST tumors. The Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 was applied to evaluate the disease progression. The time until the development of resistance to imatinib, which served as a risk factor, was divided into two subgroups: ≤24 months and >24 months. The responses to regorafenib treatment were evaluated into four subgroups according to the RECIST 1.1. The disease control rate (DCR) was evaluated as the sum of complete response, partial response (PR), and stable response (SD). The severity of adverse events (AEs) was graded using the Common Terminology Criteria for AEs (version 5.0) scale. Overall survival (OS) was primarily targeted in the survival analysis. Furthermore, PFS was evaluated. OS was considered as the time from the onset of regorafenib to disease-related death. PFS was considered as the time from the beginning of sunitinib to the first radiological tumor progression.

Statistical Analysis

Descriptive statistical analyses were conducted on all data collected in this study. The curves were compared by the log-rank test, and survival was evaluated using a 95% confidence interval for each median time reported. Kaplan-Meier analysis was used for the estimation of the OS and PFS. SPSS Version 25.0 was used for all statistical analyses, and for statistical significance was

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considered as p<0.05. Univariate and multivariate Cox regression models were applied to explore the potential prognostic risk factors in each subgroup on OS and PFS.

RESULTS

Demographic and Clinicopathological Characteristics

We evaluated 22 patients receiving regorafenib as the third-line therapy for advance GISTs. The average age of the patients was 49 years (range: 25-61years), with a male preponderance (63.6%). Table 1 presents detailed clinical and treatment features of the patient. Except for five patients with an ECOG-PS of 2, all patients' ECOG-PS was 0 or 1. The most common primary tumor location was the small bowel (n=12; 54.5%), followed by the gastric (n=8; 36.4%) and colonic (n=2; 9.1%) regions. The median primary tumor diameter was 10 cm (range: 2-18). There were 16 (72.7%) cases of local disease and 6 (27.3%) of advanced disease at the time of diagnosis. Metastasis occurred most frequently in both the abdomen and the liver (72.7%), followed by that in the abdominal only (22.7%) or liver only (4.5%).

The median follow-up time of the patients after advanced GISTs diagnosis was 114.2 months (range; 16.2-210.3). The duration of systemic treatments and the follow-up times is summarized in Table 2. The median time of imatinib use for advanced GISTs was 37.9 months (range; 6.2-123.9). Eight (36.4%) patients developed resistance to imatinib treatment within the first 2 years of treatment. The median duration of sunitinib usage after imatinib treatment was 19.3 months (range; 2.7-53.1). The median duration of regorafenib usage was 7.7 months (1.9-29.1). In our study, the median OS was 10.1 months (range; 2.2-18), (Fig. 1) and the median PFS was 6.5 months (1.9-13.1) from to start of regorafenib treatment. In terms of the response to regorafenib treatment, 5 (22.7%) patients showed a PR, 9 (40.9%) showed SD, and 8 (36.4%) showed PD. The DCR was 63.6%. Univariate analysis of risk factors revealed that the best response to regorafenib (SD or PD) (p=0.017) and ECOG-PS:2 (p=0.022) was related with poor survival outcomes. However, we found that the female gender had a positive impact on OS (p=0.021).

In this cohort, 10 (45.4%) patients experienced regorafenib-related grade 3 or 4 AEs. The most common AE was hand-foot skin reaction in five (18.2%) patients, fatigue in 3 (13.6%) patients, and hypertension in 2 (9.1%) patients. Dose reductions done in 7 patients (31.8%), of which 6 (27.2%) required a reduction to 120 mg and 1 patient (4.5%) to 80 mg. In addition, the treatment was discontinued in one patient due to stroke.

Table 1 Basic clinical characteristics and treatment outcomes

Characteristics	n=22	%
Gender		
Male	14	63.6
Female	8	36.4
Age at diagnosis	49±11	25-61
<60 years	19	86.4
≥60 years	3	13.6
ECOG-PS		
0	4	19.0
1	12	57.2
2	5	23.8
Primary tumor location		
Gastric	8	36.4
Small bowel	12	54.5
Colon	2	9.1
Primary tumor diameter (cm)	10±4.6	2-18
Stage at diagnosis		
Local	16	72.7
Metastatic	6	27.3
Metastasis location		
Abdomen	5	22.7
Liver	1	4.6
Abdomen and liver	16	72.7
Time to imatinib resistance		
≤24 month	8	36.4
>24 month	14	63.6
Response type to regorafenib		
Complete response	0	0.0
Partial response	5	22.7
Stable disease	9	40.9
Progressive disease	8	36.4
Grade 3 or 4 toxicity		
None	12	54.6
Hand-foot skin reaction	5	22.7
Fatigue	3	13.6
Hypertension	2	9.1
Diarrhea	1	4.5
Stroke	1	4.5
Outcomes		
Death	15	31.8
Alive	7	68.2

ECOG-PS: The Eastern Cooperative Oncology Group Performance Status

DISCUSSION

In this real-world study, for the first time, we evaluated the safety and efficacy of regorafenib in advanced GISTs

Table 2 Duration of systemic treatments and follow-up times

Systemic therapies	Mean±SD	Min-max
Duration of imatinib treatment (month)	37.9±29.8	6.2-123.9
Duration of sunitinib treatment (month)	19.3±15.2	2.7-53.19
Duration of regorafenib treatment (month)	7.7±5.6	1.9-29.1
Follow-up time	114.2±47.7	16.2-210.4

SD: Standard deviation; Min: Minimum; Max: Maximum

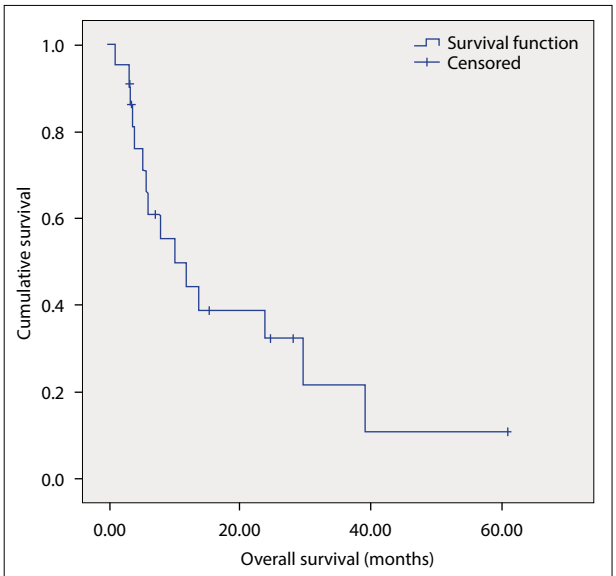

Fig. 1. The median overall survival (OS) was 10.1±4.0 months (2.2-18.0) for all cohort. The 1-, 2-, and 3-year survival rates for OS were 38.3%, 21.5%, and 10.7%, respectively.

patients in a Turkish population. According to our results, the ORR was observed in 22.7% of the patients. The median time PFS and OS was 6.5 and 10.1 months, respectively, while the rate for 1-year survival was 38.3%.

Regorafenib is an angiogenic (VEGF receptors), stromal (FGFR and PDGFR receptors), and oncogenic (KIT, BRAF, and RET) receptor tyrosine kinases inhibitor. Concerning GISTs, regorafenib could significantly improve the PFS in patients with advanced disease progression after the treatment failure of at least imatinib and sunitinib in Phases II and III (GRID) trials.[15,16] As per the recent guidelines, regorafenib is the standard third-line therapy for advance GISTs.[3,7]

In the GRID trial, the median PFS was found as 4.8 months for patients in the regorafenib arm, compared with 0.9 months for the placebo arm (HR 0.27; p<0.0001). Furthermore, the DCR was 52.5% and 9.1% in the regorafenib and placebo arms, respectively. In addition, no statistically significant difference between the two arms was noted in OS because cross-over was allowed.[16]

In our study, the median PFS and OS were 6.5 and 10.1 months, respectively. PFS was slightly higher than GRID trial (6.5 vs. 4.8 months. This may be related to the retrospective nature of our study and the fact that we followed side effects very closely and increased drug compliance. In addition, there was no significant difference for PFS when we compared the patients with whom we had dose reduction with did not (p=0.487). This result was consistent with other retrospective studies.[17-19] The PR rate was 22.7%, and similar with those reported in the GRID trial. However, the DRR was 63.6%, which is slightly greater than that recorded in the Phase III trial (DRR: 52.6%). Moreover, the median time of regorafenib treatment was longer in our study when compared with that in the GRID population (7.7 months vs. 5.7 months).[16] In our study, we achieved long-term disease control in two cases. When we look at the literature, it is reported that long-term disease control is achieved in a small patient population in the GRID study and other retrospective studies.[16-19] This may be related to genetic mutations (KIT, PDGFR, KRAS, and BRAF) and detailed mutation analysis may be useful in predicting treatment response.[20]

The standard schedule of regorafenib is 160 mg/day, once daily, for 3 weeks, followed by a 1-week off therapy. Despite showing effectiveness on survival, regorafenib has been associated with severe grades 3-4 side effects, including skin reactions, fatigue, stomatitis, diarrhea, and hypertension. Due to these side effects, dose interruption or dose reduction may be required in the routine application of this drug. Thus, the tolerated of regorafenib is difficult in daily clinical practice. Recent years have observed the adoption of different schedules by clinicians across the world so as to improve patient adherence.[8,17-19]

In our study, 10 (45.4%) patients experienced grades 3 or 4 AEs. The most seen seriously grades 3-4 side effects were the hand-foot reaction of the skin in 5 (18.2%) patients, fatigue in three (13.6%), and hypertension in 2 (9.1%) patients. Our results demonstrated that the safety profile of regorafenib is manageable, with AEs that can be sustained through dose modifications and supportive care. In this cohort, only one patient discontinued regorafenib due to stroke. Dose reductions were done in 7 patients (31.8%), of which 6 (27.2%) required a dose

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reduction to 120 mg and 1 patient (4.5%) to 80 mg. We observed that grades 3-4 side effects were usually observed in the 1 week of treatment. Based on our experience with the treatment of colon cancer, regorafenib was started at a total dose (160 mg/day), after which the patients were very closely monitored for any side effects for the first 2 months, which allowed us to recognize the side effects earlier and manage them better.

Across the world, the routine clinical application of regorafenib is reportedly difficult to tolerate due to the associated side effects.[8,17-19] In this study, we have presented our experiences on the safety and efficacy of regorafenib based on the results of evaluating the data of our high-volume sarcoma center. We recommend that treatment compliance can be increased with close follow-up, supportive treatment, and patient education.

This study contains a number of limitations. First, its retrospective design may have led to biases in patient and treatment choices. However, it is essential to note that all patients were evaluated by the same physicians. Second, this retrospective clinical study was conducted on a heterogeneous patient population. Unlike randomized trials with strict inclusion criteria, our findings may be more representative of patients observed in routine clinical practice. Our clinical assessment was also limited due to the lack of data on the detailed analysis of the genetic mutations relevant to TKİ resistance (for KIT, PDGFRA, BRAF, RET, and RAF-1), as detailed genetic analyses were not covered by our patients' insurance.

Herein, we have presented real-life data on regorafenib as the third-line therapy for advance GISTs from a single institutional center. Based on the study findings, we recommend regorafenib as an effective therapy with an acceptable safety profile for advanced GISTs patients.

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Ethics Committee Approval: The study was approved by the İstanbul University İstanbul Faculty of Medicine Clinical Research Ethics Committee (no: 11, date: 28/05/2021).

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