Treatment of gastrointestinal stromal tumors: A single-center experience

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ABSTRACT

OBJECTIVE: Gastrointestinal stromal tumors are the most common mesenchymal tumors of the gastrointestinal tract. We aimed to examine the clinical characteristics and treatment outcomes of patients diagnosed with gastrointestinal stromal tumor (GIST) who were followed up and treated in our center.

METHODS: This study retrospectively evaluated the clinical characteristics, disease stages, administered treatments, and treatment responses of 67 patients diagnosed with GIST who presented to our center between 2007 and 2015.

RESULTS: Of the 67 patients included in our study, 24 (35.8%) were female and 43 (64.2%) were male. Median age at diagnosis was 54 years (23–86). Primary tumor localization was the stomach in 38.8% (n=26), small intestine in 46.2% (n=31), colorectal in 6% (n=4), and extra-gastrointestinal in 9% (n=6) of the patients. At diagnosis, 19 patients (28.4%) were at a metastatic stage. Fifty-seven patients (85.1%) underwent surgery. Thirty-three patients received one line, 20 patients received two lines, and 12 patients received three lines of treatment. The first-line treatment resulted in complete response in 12 patients (36.4%), partial response in 15 patients (45.5%), stable disease in 5 patients (15.2%), and progression in 1 patient (3%). Progression-free survival (PFS) was 36 months for the first-line treatment. The second-line treatment resulted in partial response in 7 patients (35%), stable disease in 12 patients (60%), and progression in 1 patient (5%). PFS was 12 months for the second-line treatment. The third-line treatment resulted in complete response in 1 patient (8.3%), partial response in 3 patients (25%), stable disease in 5 patients (41.7%), and progression in 3 patients (25%). PFS was 9 months for the third-line treatment. The fourth-line treatment resulted in stable disease in 4 patients (80%) and progression in 1 patient (20%). PFS was 4 months for the fourth-line treatment. Overall survival was 90 months for all patients.

CONCLUSION: The use of tyrosine kinase inhibitors such as imatinib has a significant favorable effect on the prognosis in the treatment of GISTs, both in adjuvant therapy and in advanced stage disease.

Keywords: Gastrointestinal stromal tumors; imatinib; tyrosine kinase inhibitors.

Subepithelial mesenchymal tumors comprise approximately 1% of all gastrointestinal tract (GIT) tumors [1]. Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the GIT and constitute 90% of gastrointestinal sarcomas [1]. Although they occur more frequently in the stomach and segments of the small intestine, they can also be encountered in any localization in the GIT, the peritoneum, omentum, and mesentery [2]. According to the 2001–2011 SEER data, the incidence of GIST was reported as 0.68/100.000. The mean age of occurrence of GISTs, the prevalence of which increases in middle and advanced ages, is 64 years, and it is rarely encountered below the age of 40 years [3]. About 5% of GISTs, the

majority of which occur sporadically, present as primary familial GIST, neurofibromatosis, or a component of Stratakis syndrome [4]. Although various indices are utilized in predicting the prognosis, the localization of the primary tumor, tumor size, and mitotic rate is important factors that influence the prognosis [5]. Meanwhile, a KIT mutation is present in 80% of GISTs [6]. Patients at non-metastatic stages with a tumor size ≥2 cm must undergo a gross total resection with negative surgical margins [7, 8]. Since lymph node metastasis is rarely seen in GISTs, lymphadenectomy is not recommended as a routine procedure for these patients [7–9]. For patients in the high-risk group who underwent complete surgical resection, the National Comprehensive Cancer Network guidelines recommend a 36-month adjuvant imatinib treatment. Since there is relative resistance to cytotoxic chemotherapy, tyrosine kinase inhibitors are used in patients with GISTs at a metastatic stage [10]. This study evaluates the clinical characteristics and treatment outcomes of patients diagnosed with GIST who were followed up and treated in our center.

MATERIALS AND METHODS

Hospital archives were retrospectively reviewed for files of patients diagnosed with GIST who presented to our center between 2007 and 2015. Data of a total of 67 patients were retrieved. The patients' clinical characteristics, disease stages, administered treatments, and treatment responses were retrospectively evaluated.

Statistical Analysis

SPSS 18.0 program package was used in the statistical analysis of the data. Patient characteristics and frequencies of the parameters were analyzed using descriptive statistics, quantitative variables with a normal distribution using Student's t-test, and variables without a normal distribution and non-parametric variables using the Mann–Whitney U-test. A confidence interval of 95% and $p < 0.05$ were adopted. Kaplan–Meier and Cox regression analyses were used for survival analyses.

Ethics Consent

The study was approved by the research ethics committee of Dicle University, Faculty of Medicine (date/reference number: September 03, 2020/285). All analyses were performed in accordance with the principles of the Declaration of Helsinki.

Highlight key points

- In this study, high tumor mitosis rate and metastatic disease were closely related with the risk of death
- High response rates were observed with imatinib in the first-line treatment in metastatic GISTs
- A 15-month PFS was achieved with the use of sunitinib in the second-line treatment of metastatic GISTs
- Gastric and intestinal localized GISTs had better overall survival than extra-gastrointestinal locations.

RESULTS

This study included 67 patients diagnosed with GIST, the data of whom could be accessed. Of our patients, 24 (35.8%) were female and 43 (64.2%) were male. Median age at diagnosis was 54 years [23–86]. The presenting complaint was abdominal pain at a rate of 49.3% (n=33), GIT bleeding at a rate of 19.4% (n=13), abdominal mass at a rate of 14.9% (n=10), an acute abdomen at a rate of 6% (n=4), and the patients were asymptomatic or had non-specific complaints at a rate of 10.4% (n=7). The primary tumor localization was the stomach in 38.8% (n=26), duodenum in 25.4% (n=17), jejunum in 4.5% (n=3), ileum in 4.5% (n=3), jejunum+ileum in 11.8% (n=8), colon in 4.5% (n=3), rectum in 1.5% (n=1), and extra-gastrointestinal in 9% (n=6) of the patients. Spindle histology was present in 47 patients (70.1%) and epithelioid or mixed histology was present in 20 patients (29.9%). Detailed information is provided in Table 1. At diagnosis, 46 patients (68.6%) were at a non-metastatic stage, 2 patients (3%) at a locally advanced inoperable stage, and 19 patients (28.4%) at a metastatic stage. Thirteen patients (68.4%) at the metastatic stage had liver metastasis.

In total, 57 patients (85.1%) underwent surgery. Surgical procedures were performed for palliative purposes in 6 patients (9%); of the remaining patients, 46 (68.7%) underwent R0 resection, 1 (1.5%) underwent R1 resection, and 4 (6%) underwent R2 resection. According to the Armed Forces Institute of Pathology (AFIP) classification, of the 47 patients in whom R0 or R1 was achieved, 10 (21.3%) were in the very low-risk group, 7 (14.9%) in the low-risk group, 18 (38.3%) in the moderate-risk group, and 12 (25.5%) in the high-risk group. Neoadjuvant therapy was administered to 3 patients (4.5%) and adjuvant therapy to 12 (17.9%) patients. One patient showed progression during neoadjuvant therapy and another patient showed recurrence

TABLE 1. General characteristics of the patients (n=67)

Parameters	(%)	Parameters	(%)
Gender		Epithelioid or mixed	29.9
Female	35.8	Mitotic rate (per 50 HPF)	
Male	64.2	≤5	59.7
Age (years, median)	54 (23–86)	6–10	19.4
Initial complaint		>10	20.9
Abdominal pain	49.3	AFIP risk score	
Gastrointestinal bleeding	19.4	Very low	21.3
Abdominal mass	14.9	Low	14.9
Acute abdomen	6	Intermediate	38.3
Asymptomatic	10.4	High	25.5
Localization		Disease stage at diagnosis	
Gastric	38.8	Non-metastatic	68.6
Duodenum	25.4	Locally advanced inoperable	3
Jejunum	4.5	Metastatic	28.4
Ileum	4.5	Surgical situation	85.1
Jejunum+ileum	11.8	R0	68.7
Colon	4.5	R1	1.5
Rectum	1.5	R2	6
Extra-gastrointestinal	9	Palliative	9
Tumor size (cm)		Treatment status	
≤2	3	Neoadjuvant	4.5
2.1–5	23.9	Adjuvant	17.9
5.1–10	34.3	First line	49.3
>10	38.8	Second line	29.9
Histological type		Third line	17.9
Spindle	70.1	Fourth line	7.5

HPF: High-power fields; AFIP: Armed Forces Institute of Pathology; cm: Centimeter.

during adjuvant therapy. These two patients were administered sunitinib therapy as second-line treatment.

A total of 33 patients (49.3%), including 20 patients (29.8%) with advanced stage presentation and 13 patients (19.4%) who showed recurrence after curative treatment, were given 400 mg/day imatinib as first-line treatment. The first-line treatment achieved complete response in 12 patients (36.4%), partial response in 15 patients (45.5%), and stable disease in 5 patients (15.2%), while 1 patient (3%) showed progression. A total of 20 patients (29.9%) including two patients who showed progression during adjuvant and neoadjuvant therapy and 18 patients who showed progression with first-line 400 mg imatinib therapy were advanced to second-line treatment. As second-line treatment, 9 patients (45%) used 600–800 mg/day imatinib and 11 patients (55%) used sunitinib. The second-line treatment resulted in partial response in 7 patients (35%), stable disease in 12 patients (60%), and progression in 1 patient (5%). Twelve patients (17.9%) were advanced to third-line treatment. As third-line treatment, 5 patients (41.7%) used sunitinib, 2 patients (16.7%) used nilotinib, 4 patients (33.3%) used regorafenib, and 1 patient (8.3%) used sorafenib. The third-line treatment resulted in complete response in 1 patient (8.3%), partial response in 3 patients (25%), stable disease in 5 patients (41.7%), and progression in 3 patients (25%). Five patients (7.5%) could receive a fourth line of treatment. Of these patients, 3 (60%) used sorafenib and 2 (40%) used regorafenib. The fourth-line treatment resulted in stable disease in 4 patients (80%) and progression in 1 patient (20%) (Table 2).

TABLE 2. Treatments patients have received and treatments response rates

Treatment received	The line where the treatment is used				
	Adjuvant	1st line	2nd line	3rd line	4th line
Imatinib 400 mg	12	33	–	–	–
Imatinib 600–800 mg	–	–	9	–	–
Sunitinib	–	–	11	5	–
Sorafenib	–	–	–	1	3
Nilotinib	–	–	–	2	–
Regorafenib	–	–	–	4	2
Total	12	33	20	12	5
Response					
Complete response n (%)	–	12 (36.4)	0 (0)	1 (8.3)	0 (0)
Partial response n (%)	–	15 (45.5)	7 (35)	3 (25)	0 (0)
Stable disease n (%)	–	5 (15.2)	12 (60)	5 (41.7)	4 (80)
Progression n (%)	–	1 (3)	1 (5)	3 (25)	1 (20)
PFS (months)	–	36	12	9	4

PFS: Progression-free survival.

For the first-line treatment, the median progression-free survival (PFS) with 400 mg/day imatinib was 36 months. For the second-line treatment, PFS for the entire group was 12 months. PFS was 8 months for those who used 600–800 mg/day imatinib and 15 months for those who used sunitinib as second-line treatment. There was no statistically significant difference between these two groups [HR: 0.36, (95% CI 1.21–1.09), p=0.072]. For the third-line treatment, a PFS of 9 months was achieved for the entire group. PFS times obtained with sunitinib, nilotinib, sorafenib and regorafenib were 12 months, 9 months, 5 months, and 7 months, respectively. In comparison to sunitinib, nilotinib was associated with (HR: 1.17 [95% CI 0.12–11.56], p=0.88), sorafenib with (HR: 3.56 [95% CI 0.32–39.26], p=0.29), and regorafenib with (HR: 1.12 [95% CI 0.29–4.24], p=0.87). There were no statistically significant differences between the groups in terms of PFS (log rank p=0.70). The fourth-line treatment achieved a 4-month PFS with both sorafenib and regorafenib. There was no statistically significant difference between these two groups (p=0.38).

Regarding drug-related side effects of any grade, imatinib use resulted in fatigue in 15 patients (35.7%), nausea in 7 patients (16.7%), edema in 3 patients (7.1%), and thrombocytopenia in 1 patient (2.4%). Sunitinib therapy resulted in fatigue in 5 patients (25%), loss of appetite in 3 patients (15%), hypertension in 1 patient (5%), hand-foot syndrome in 1 patient (5%), and thrombocytopenia in 1 patient (5%). Sorafenib use resulted in hand-foot syndrome in 1 patient (25%) and fatigue in 2 patients (50%). Regorafenib resulted in diarrhea in 1 patient (16.7%) and edema and fatigue in 2 patients (33.3%).

Overall survival (OS) for the entire group was 90 months. OS was 54 months for patients who showed recurrence following curative therapy and 63 months for patients who were metastatic at presentation. There was no statistically significant difference between these two groups in terms of overall survival (HR: 0.94 [95% CI 0.43–2.08], p=0.89). When categorized according to the primary tumor localization, OS was 93 months for a gastric localization, 122 months for an intestinal localization, and 37 months for an extra-gastrointestinal localization. An extra-gastrointestinal localization was associated with a shorter OS, with statistical significance (HR: 3.80 [95% CI 1.31–11.03], p=0.014) (Fig. 1).

DISCUSSION

GISTs can occur in any localization in the GIT, with a predisposition to mainly localize in the proximal regions of the tract [2]. CD117 is negative in the leiomyomas, leiomyosarcomas, and other fusiform cell tumors of the
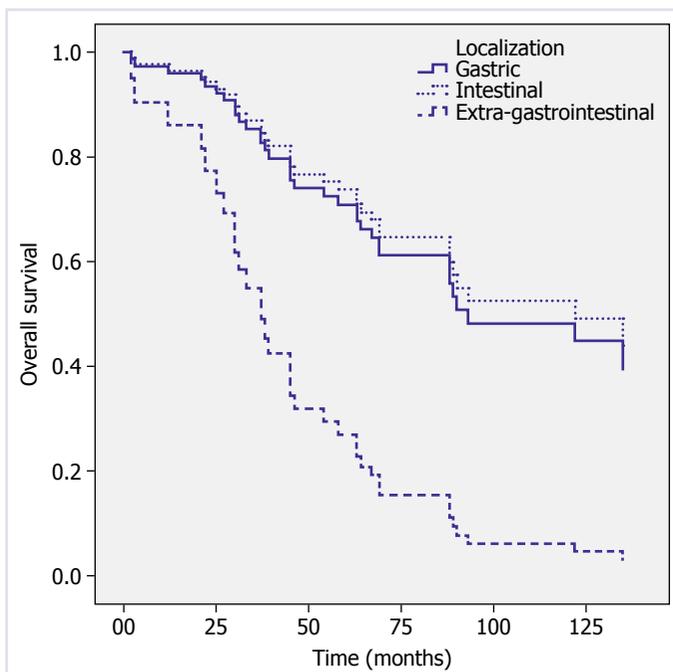
FIGURE 1. Overall survival according to the primary tumor localization.

GIT, while CD117 positivity is seen in almost all GISTs [11]. GISTs, which are encountered most commonly in the stomach, are also encountered in the jejunum, ileum, and duodenum in the small intestine, in descending order of prevalence. They are less common in the esophagus, colon, and the appendix [12–14]. Since GISTs of intestinal origin manifest a more aggressive course, grading and risk stratification consider the primary tumor localization as well as mitosis and tumor diameter [12, 15]. In the present study, 38.8% of the cases were localized in the stomach, 25.4% in the duodenum, 20.8% in the jejunum and/or ileum, 6% in a colorectal localization, and 9% in an extra-gastrointestinal localization. In this study, there was no statistically significant difference between gastric and non-gastric GIT localizations with regard to overall survival (p=0.74). The presenting complaints associated with GIST include GIT bleeding at a rate of 28–50%, incidental at a rate of 13.18%, abdominal pain at a rate of 8–17%, acute abdomen at a rate of 2–14%, and an asymptomatic abdominal mass at a rate of 5% [12, 15]. In the present study, 49.3% of our patients showed abdominal pain, 14.9% showed GIT bleeding, and 6% showed an acute abdomen at admission. GISTs were detected incidentally in 7 patients (10.4%).

Regarding the treatment approaches, surgery constitutes one of the most important options. Curative

surgery must be aimed for non-metastatic patients [7]. For patients inoperable at presentation, surgery following neoadjuvant therapy, with metastasectomy in appropriate cases, may be considered [5, 16]. Proceeding with adjuvant imatinib following metastasectomy was shown to improve survival [17]. However, certain patients may require palliative surgery. In the present study, 57 patients (85.1%) underwent surgery. Forty-six patients (68.6%) underwent R0 resection, 1 patient (1.5%) R1 resection, 4 patients (6%) R2 resection, and 6 patients (9%) palliative surgery. Three patients underwent surgery following neoadjuvant therapy. One of these patients was operated due to showing progression under neoadjuvant therapy, and second-line treatment was initiated due to incomplete resection. Since one of the patients who were administered neoadjuvant therapy was metastatic at presentation, curative surgery and metastasectomy targeting the metastasis in the liver were performed. A PFS of 60 months was achieved in this patient, and the patient died due to another cause while in remission. Furthermore, as another patient who was metastatic at presentation showed regression after two lines of treatment, curative surgery and metastasectomy were performed, and the treatment was subsequently continued with adjuvant therapy with imatinib. This patient achieved a PFS of 20 months and was under follow-up in remission.

In non-metastatic GISTs, the prognosis is strongly associated with tumor size, mitotic rate, and the tumor localization. At present, various scoring systems such as the NIH and modified NIH scoring systems are used in predicting the prognosis and deciding whether to start adjuvant therapy [18]. According to the modified NIH criteria, disease-specific survival rates of patients with risk levels I-IV are 100%, 96%, 67%, and 25%, respectively [19]. In the present study, we found that an increase in the mitotic rate (p=0.025) and metastatic stage disease at diagnosis (p=0.001) significantly increased the risk of mortality, while gender (p=0.869), tumor size (p=0.14), tumor localization (p=0.593), and histological subtype of the tumor (p=0.47) were not found to have a statistically significant relationship with OS. We reason that this could be due to the heterogeneous nature of our patient population and that they underwent variable lines of treatment. For patients who used adjuvant imatinib, the 5-year recurrence-free survival rate was 66% and the overall survival rate was 92% [20]. In the present study, 12 patients were given adjuvant imatinib therapy in the post-operative period

for adjuvant purposes due to being high risk according to the AFIP criteria. Second-line treatment was initiated due to the occurrence of recurrence in one patient during adjuvant therapy. For the remaining 11 patients who used adjuvant imatinib, the 5-year survival rate was 91%. Meanwhile, active surveillance was conducted for 35 patients who underwent complete surgical resection and were not in the high-risk group (very low risk 21.3% [n=10], low risk 14.9% [n=7], and moderate risk 38.3% [n=18]). In total, 33 patients, including 20 patients who had advanced stage disease at admission and 13 patients who showed recurrence after curative treatment, were administered palliative treatment options. In GISTs, the most common site of metastasis is the liver, with a rate of 67% [21]. In the present study, liver metastasis was present in 13 patients (68%).

Imatinib is among the first-line treatment options for recurrent or metastatic GIST patients. In a Phase-III study by Blanke et al. [22] on metastatic GIST patients, 400 mg/day imatinib resulted in partial response at a rate of 43% and stable disease at a rate of 32% with an 18-month PFS during a 54-month follow-up period. In the present study, 33 patients were started on 400 mg/day imatinib as first-line treatment for recurrent or advanced stage disease. In this study, complete response was achieved in 12 cases (36%), partial response in 15 cases (45.5%), and stable disease in 5 cases (15.2%). Meanwhile, 1 patient (3%) showed progression. A PFS time of 36 months was achieved with 400 mg imatinib as first-line treatment. The side effects of imatinib include anemia, periorbital edema, rash, fatigue, vomiting, neutropenia, and diarrhea. Most side effects show a moderate or mild course [23]. In our study, the most common side effects associated with imatinib as a first-line treatment were fatigue and nausea.

In cases where KIT exon 9 mutations cannot be analyzed in patients who show progression with the first-line treatment, high-dose imatinib (800 mg) can be used or other treatment options such as sunitinib can be initiated [24]. A PFS of 27 weeks was reported with sunitinib for patients who showed progression with imatinib as first-line treatment [25]. In our study, 9 patients (45%) were administered high-dose imatinib due to progression. Meanwhile, 11 (55%) patients were given sunitinib as second-line treatment. In the second-line treatment, there was partial response in 7 (35%), stable disease in 12 (60%), and progression in

1 (5%) of the 20 patients. The PFS time was 8 months with high-dose imatinib and 15 months in patients who used sunitinib. For the second-line treatment, the PFS time for the entire group was 12 months. These two medications were not significantly different with regard to PFS (p=0.072). Sunitinib is a well-tolerated medication, and its most common side effects were reported to be fatigue, diarrhea, skin discoloration, and nausea-vomiting [25]. In the present study, the most common side effects observed in association with sunitinib were fatigue, loss of appetite, hand-foot syndrome, and hypertension.

In metastatic GISTs, patients who show progression after the second-line treatment may be given tyrosine kinase inhibitors that were not used before. Among these are agents such as nilotinib, dasatinib, sorafenib, and regorafenib. In patients who show progression after sunitinib, regorafenib, sorafenib, and nilotinib were associated with PFS times of 4.8 months, 5.2 months, and 3 months, respectively [26, 27]. In the present study, 12 patients received third-line treatment. Sunitinib was used after nilotinib in 2 patients (16.7%), sorafenib in 1 patient (8.3%), regorafenib in 4 patients (33.3%), and high-dose imatinib in 5 patients (41.7%). The outcome was complete response in 1 patient (8.3%), partial response in 3 patients (25%), stable disease in 5 patients (41.7%), and progression in 3 patients (25%). The third-line treatment achieved a PFS time of 9 months. PFS times associated with sunitinib, nilotinib, sorafenib, and regorafenib were 12 months, 9 months, 5 months, and 7 months, respectively. In comparison to sunitinib, hazard ratios (HR) regarding the risk of progression were 1.17 ([95% CI 0.12–11.56], p=0.88], 3.56 ([95% CI 0.32–39.26], p=0.29), and 1.12 ([95% CI 0.29–4.24], p=0.87) for nilotinib, sorafenib, and regorafenib, respectively. There were no statistically significant differences between the groups in terms of PFS (log rank p=0.70).

We had five patients who received fourth-line treatment. Two patients (40%) used regorafenib and 3 (60%) used sorafenib. The outcome was stable disease in 4 patients (80%) and progression in 1 patient (20%). In the fourth-line treatment, both medications were associated with a PFS of 4 months. The most widely reported side effects of regorafenib are hypertension, hand-foot syndrome, and diarrhea [26]. Meanwhile, the most widely reported side effects of sorafenib are hand-foot syndrome and hypertension. In our study, the most common side effects were diarrhea and fatigue

in patients on regorafenib, and hand-foot syndrome and fatigue in patients on sorafenib.

The use of imatinib in adjuvant and neoadjuvant therapy has a favorable influence on the prognosis of GISTs. Gastric and small intestine GISTs were associated with 5-year survival rates of 83.3% and 82.2%, respectively [9]. When categorized according to the disease localization, OS was 93 months for patients with GIST of gastric origin and 122 months for non-gastric GIT localizations. Meanwhile, the OS was 37 months for an extra-gastrointestinal localization. Based on the literature, GISTs of intestinal origin show a more aggressive course than those of gastric origin [12]. In the present study, there was no statistically significant difference between GISTs of gastric and non-gastric GIT localizations in terms of OS. The OS was numerically better for non-gastric localizations. On the other hand, the OS time associated with extra-gastrointestinal localizations was lower compared with GIT localizations, with statistical significance (p=0.014, HR: 3.80 [95% CI 1.31–11.03]) (Fig. 1). When all patients were included in the analysis, the overall survival time was 90 months.

Conclusion

In GISTs, a surgical approach in non-metastatic cases and adjuvant imatinib therapy in high-risk patients was determined to have a favorable influence on the prognosis. If primarily a neoadjuvant imatinib treatment is to be planned, close surveillance of the patient is required due to the risk of progression. In metastatic cases, imatinib is associated with favorable outcomes as first-line treatment and sunitinib as second-line treatment. Patients who were inoperable at admission must be reevaluated with regard to operability at each line of treatment – due to the positive effects of curative surgery and metastasectomy on the prognosis.

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