EJMI

DOI: 10.14744/ejmi.2022.14970
EJMI 2022;6(3):292–298

Research Article

Identifying Risk Factors Associated with Survival and Drug-Related Toxicities in Imatinib-Resistant Gastrointestinal Stromal Tumor (GIST) Patients Treated with Sunitinib

Ferhat Ferhatoglu,[1] Senem Karabulut,[2] Nail Paksoy,[2] Didem Tastekin[2]

[1]Department of Medical Oncology, Basaksehir Cam and Sakura City Hospital, Istanbul, Türkiye
[2]Department of Medical Oncology, Istanbul University Institute of Oncology, Istanbul, Türkiye

Abstract

Objectives: Sunitinib is the preferred second-line treatment option to imatinib escalation in patients with imatinib-resistant advanced gastrointestinal stromal tumors. In this study, we aimed to determine the risk factors affecting survival and sunitinib-related toxicities in imatinib-resistance GIST patients.

Methods: Clinical characteristics of 40 imatinib-resistant GIST patients who received second-line sunitinib were evaluated. Statistical analysis was performed to determine risk factors associated with survival and sunitinib-related toxicities.

Results: The median age was 53 and the male to female ratio was 24/16. The most common of the primary tumor location was small bowel (25; 62.5%). There were 17 (42.5%) patients who developed resistance to imatinib within the first 24 months. Median overall survival (OS) and progression-free survival were 31.6 months and 19.6 months, respectively. Among many risk factors, best response to sunitinib (Hazard ratio [HR]: 2.34) and imatinib resistance (HR: 0.43 were independent prognostics for OS. The only risk factor for sunitinib-related grade 3 or 4 toxicity was advanced age (Odds ratio: 1.90).

Conclusion: Long-term use of imatinib and best response to sunitinib are the most important clinical parameters to evaluate the efficacy of sunitinib. Sunitinib-related toxicity is frequently observed and has a high potential for toxicity in elderly patients.

Keywords: Adrenal, adrenalectomy, laterality, lung cancer, survival

Cite This Article: *Ferhatoglu F, Karabulut S, Paksoy N, Tastekin D. Identifying Risk Factors Associated with Survival and Drug-Related Toxicities in Imatinib-Resistant Gastrointestinal Stromal Tumor (GIST) Patients Treated with Sunitinib. EJMI 2022;6(3):292–298.*

Gastrointestinal stromal tumor (GIST), a member of soft tissue tumors, is the most common sarcoma of the gastrointestinal tract (Gut).[1] It constitutes 1-2% of all gastrointestinal tract cancers.[2] The average age of incidence is 67.[3] Ligand-independent auto-activation is observed in the c-kit proto-oncogene in 85-90% of GISTs, which are generally considered to originate from intestinal Cajal cells. The second most common mutation is observed in the platelet-derived growth factor receptor alpha (PDGFRA) gene, around 5%. Approximately 10% of GIST patients are found to have no specific driver mutant gene (wild-type GIST); however, recently approximately 4% of this population have been found, in fact, to have a BRAF mutation.[4,5] Pathological diagnosis can be made

Address for correspondence: Ferhat Ferhatoglu, MD. Basaksehir Cam ve Sakura Sehir Hastanesi Tibbi Onkoloji Anabilim Dali, Istanbul, Türkiye
Phone: +90 532 130 09 19 **E-mail:** drferhatoglu@gmail.com

Submitted Date: March 02, 2022 **Accepted Date:** May 26, 2022 **Available Online Date:** July 21, 2022

histologically and it can also be demonstrated with the presence of the c-kit mutation (CD117) and DOG-1 staining.[6] The primary tumor can be observed anywhere in the gastrointestinal tract from esophagus to anal canal; the stomach (40-60%) is the area where it is observed most frequently and it is followed by the small intestine (20-30%).[7,8] Approximately 1 in 10 patients present with multiple primary GIST foci.[9]

Imatinib mesylate is an oral multikinase inhibitor targeting certain proteins, especially bcr-abl, c-kit, PDGFR. In the SWOG S0033 study comparing conventional-dose imatinib with high-dose imatinib, conventional-dose imatinib has become the standard first-line therapy in the patients with metastatic/unresectable GIST, as the median overall survival (OS) (55 months versus 51 months, respectively) and progression-free survival (PFS) (18 months versus 20 months, respectively) were comparable in both arms.[10] Despite the success of imatinib, 10% of the patients show primary resistance to this drug.[11] Also, although disease control is maintained with imatinib, secondary drug resistance usually develops within the second year of treatment.[9,12,13] Mechanisms responsible for primary resistance are most commonly due to the c-kit exon 9 mutation and wild-type GISTs (lack of activating mutations in the c-KIT or PDGFRA).Whereas secondary resistance is usually derived from the new clones that develop secondary KIT mutations under imatinib suppression.[14]

Similar to imatinib, sunitinib has antiangiogenic activity by inhibiting VEGFRs as well as inhibiting tyrosine kinase activity through c-kit and PDGFR. Phase 3 studies have revealed the OS and PFS advantage of sunitinib over placebo in the patients who progressed with the imatinib treatment. However, at least one drug related toxicity has been observed in 83% of patients.[15] Randomized clinical trials have become insufficient to explain the efficacy of treatments for various patients in clinical practice because of the patient selection criteria. Real-life experience is important to validate phase 3 randomized clinical trials and to identify determine risk groups. For this purpose, we considered it appropriate to assess the efficacy and tolerability of sunitinib in the patients with imatinib refractory GIST in our center.

Methods

In this cross-sectional study, we retrospectively obtained clinical data of 197 Turkish-Caucasian patients diagnosed with GIST between June 2000 and June 2015 in our oncology department. Of these, the ratio of patients receiving sunitinib therapy to all advanced GIST patients was 40/94 (42.5%). Data regarding age, gender, smoking status and Eastern Cooperative Oncology Group performance status (ECOG-PS) were extracted from medical records of the patients treated with sunitinib. The age of the patients at the time of diagnosis was evaluated in 2 subgroups as <60 years and ≥60 years. Primary tumor location, primary tumor diameter, metastatic sites of the tumor were recorded based on the images before sunitinib treatment. Clinical staging was performed according to the 8th edition AJCC stage classification for GIST tumor. The Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 was used to evaluate progression16. Time to resistance to imatinib as a risk factor was divided into two subgroups as ≤24 months and >24 months. The best responses to sunitinib treatment were divided into 4 subgroups according to RECIST 1.1 as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Severity of adverse events was recorded by use of the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.[17]

OS was primarily targeted in the survival analysis. Secondary endpoint was PFS. OS was considered as the time from onset of sunitinib to the disease-related death. PFS was considered as the time from onset of sunitinib to first radiological tumor progression.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (SPSS Inc, Chicago, Ill). For descriptive statistics, categorical variables are presented as count and percent. Numerical variables are presented as mean, standard deviation and minimum and maximum values. OS and PFS were assessed using Kaplan-Meier methods. Univariate and multivariate Cox regression models were used to explore the potential prognostic risk factors in each subgroups on OS and PFS. The log-rank test performed for all independent prognostic variables. Stratified logistic regression analysis was performed for subgroups to identify grade 3 or 4 treatment-related risk factors. The statistical significance level of alpha was accepted as $p<0.05$.

Results

Demographic and Clinicopathological Characteristics

Forty advanced GIST patients receiving sunitinib after imatinib failure were enrolled to the study. The median age was 53 years (25-72 years) and there was male preponderance (24 men; 60.0%) in the study population. Except for 4 patients with an ECOG - PS of 2, all patients' ECOG-PS was 0 or 1. The most common of the primary tumor location was small bowel (25; 62.5%) followed by stomach ((10; 25.0%) and colon (5; 12.5%). Median primary tumor

diameter was measured 10.6 cm (2–18 cm). According to the TNM 8th edition, there were 23 local disease (T1 – T4) and 17 metastatic (N or M positive) disease at diagnosis. Metastatic disease occurred in all patients after imatinib failure. Metastases occurring in both the abdomen and the liver was the most common finding (25; 62.5%), followed by abdominal metastases only (13; 32.5%) and liver metastases only (2; 5%).

The median follow-up time of the patients after having advanced GIST diagnosis was 92.5 months (4.9–210.5 mo). The median duration of imatinib administered for advanced GIST was 42.5 months (3.3–152.9 mo). Seventeen (42.5%) patients developed resistance to imatinib treatment within the first 24 months. In terms of the best response to sunitinib treatment, 1 (2.5%) patient had a complete response. Nineteen (47.5%) and 12 (30.0%) patients had partial and stable response, respectively. Eight (20.0%) patients had progression under sunitinib treatment. The median sunitinib treatment period was 21.7 months (1.3–88.5 mo). Eleven (30%) patients with treatment-related grade 3 or 4 toxicities were determined. The most common toxicity was that 7 (17.5%) patients had hypertension and 3 (7.5%) patients with hypothyroidism and 1 (2.5%) patient with skin reaction and deep vein thrombosis followed them. Detailed clinic and treatment features of patients were summarized in Table 1 and Table 2.

Table 1. Basic clinical characteristics and treatment outcomes

	N=40	%
Gender		
Male	24	60.0%
Female	16	40.0%
Age at diagnosis*	53±11	25-72
< 60 years	31	77.5
≥ 60 years	9	22.5
ECOG – PS		
0	16	41.0%
1	19	48.7%
2	4	10.3%
Primary tumor location		
Gastric	10	25.0%
Small bowel	25	62.5%
Colon	5	12.5%
Primary tumor diameter (cm)*	10.6±4.7	2.0-18.0
Stage at diagnosis		
Local	23	57.5%
Regional	0	0.0%
Metastatic	17	42.5%
Metastasis location		
Abdomen	13	32.5%
Liver	2	5.0%
Abdomen and liver	25	62.5%
Time to imatinib resistance		
≤ 24 month	17	42.5%
> 24 month	23	57.5%
Best response to sunitinib		
Complete response	1	2.5%
Partial response	19	47.5%
Stable disease	12	30.0%
Progressive disease	8	20.0%
Grade 3 or 4 toxicity		
None	28	70.0%
Hypertension	7	17.5%
Skin reaction	1	2.5%
Deep vein thrombosis	1	2.5%
Hypothyroidism	3	7.5%
Outcomes		
Alive	14	35%
Exitus	26	65%

ECOG – PS: Eastern Cooperative Oncology Group performance status; *Median ± standard deviation is used instead of N, minimum – maximum is used instead of %.

Survival and Risk Factors

In the cohort, median OS was 31.6 months (23.4-39.9 mo). The 1-, 2- and 5-years survival rates for OS were 82.3%, 65.2% and 36.5%, respectively (Fig. 1). Median PFS was 19.6 months (8.0 – 31.3 mo). The 1-, 2- and 5-years survival rates for PFS were 64.9%, 45.7% and 12.2%, respectively.

We applied univariate analysis to determine risk factors affecting OS (Table 3). Stage at diagnosis (Hazard ratio [HR]. 1.76; 95% Confidence Interval [CI]: 1,16–2.66; p=0.007), best response to sunitinib (HR: 2.25; 95% CI: 1.38–3.66; p=0.001), primary tumor diameter (HR: 1.10; 95% CI: 1.00–1.20; p=0.031) and ECOG-PS (HR: 1.90; 95% CI: 1.10–3.29; p=0.021) were associated with poor survival outcomes. However, we found that time to resistance to imatinib had a positive impact on OS (HR: 0.45; 95% CI: 0.20–0.98; p=0.044). We determined in multivariate analysis that best response to sunitinib (HR: 2.34; 95% CI: 1.41–3.90; p=0.001) and time to imatinib (HR: 0.43; 95% CI: 0.19–0.99; p=0.047) resistance were independent prognostic risk factors (Table 3). Best response to sunitinib (HR: 1.90; 95% CI: 1.27–2.84; p=0.002) was the only risk factor with an effect on PFS (Table 4).

Median OS data of best response to sunitinib, one of the independent prognostic factors, could not be obtained in the subgroups. Only one patient, who achieved a PFS of 51.2 months and an OS of 81.3 months, had a CR. One-year and 3-year percentages of OS were 94.1% and 74.7% in patients with PR, 83.3% and 27.5% in patients with SD,

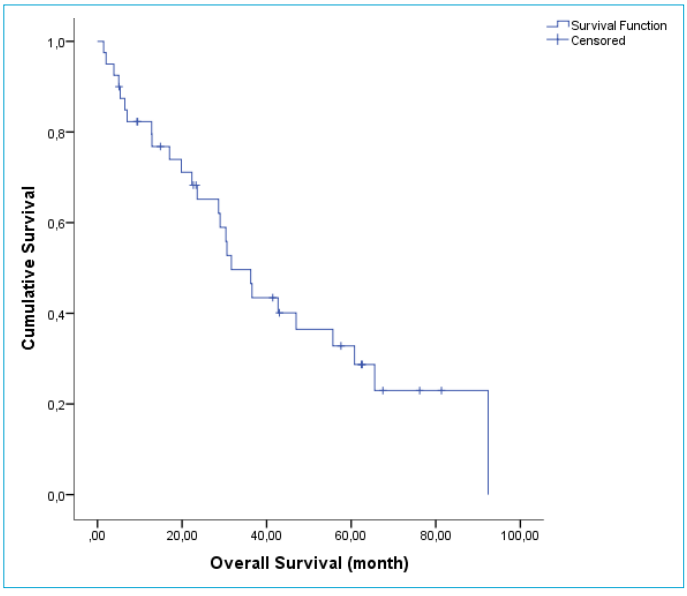

Figure 1. The median overall survival was 31.6 months (23.4-39.9 mo) in all cohort. The one-, 2- and 5-years survival rates for OS were 82.3%, 65.2% and 36.5%, respectively.

Table 2. Duration of systemic treatments and follow-up times

	Median±SD	Min.–Max.
Duration of imatinib treatment (month)	30.3±35.7	3.3-152.9
Duration of sunitinib treatment (month)	15.1±19.7	1.3-88.5
Follow-up time	101.6±55.2	4.9–210.5

SD: Standard deviation.

and 37.5% and 18.8% in patients with PD (Fig. 2). For time to imatinib resistance, the median OSs of patients who developed imatinib resistance ≤24 months and >24 months were 32 months (18.5–45.5 mo) and 49 months (36.6–62.5 mo), respectively (Fig. 3).

Over 60 years of age was the only risk factor for grade 3 or 4 toxicity (Odds ratio: 4.2; 95% CI: 1.24–20.4; p=0.043) (Table 5).

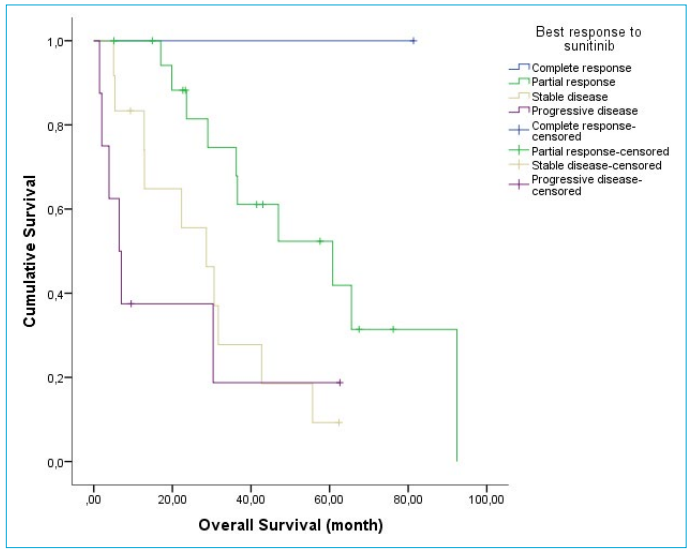

Figure 2. Survival analysis according to best response to sunitinib; complete response was ob-served in only one patient. The 1- and 3-years survival rates for OS were 94.1% and 74.7% in pa-tients with partial response, 83.3% and 27.5% in patients with stable response, and 37.5% and 18.8% in patients with progressive disease (p=0.009).

Discussion

In this study, we aimed to determine the survival and risk factors related to treatment in GIST patients who had treated with sunitinib because of the development of imatinib resistance. As a retrospective real-life study in a tertiary centre, we identified specific risk factors related to treatment.

We observed that the median age and male-to-female ratio, among baseline demographic data, were quite similar to most studies evaluating GIST patients refractory to imatinib.[15,18,19] Although it is known that the primary tumor location originates from the stomach at a ratio of 40-60%[7,8], 62.5% originated from the small intestine in our study. Similarly, other studies assessing the efficacy of sunitinib demonstrated that the most common primary localization was the small intestine.[15,18] It seems that the high progression potential of GISTs observed in the small intestine causes the small intestine to be the most common primary tumor

Table 3. Univariate and multivariate analysis for overall survival

	Univariate analysis			Multivariate analysis		
Risk factors	**P**	**HR**	**%95 CI**	**P**	**HR**	**%95 CI**
Stage at diagnosis	0.007	1,76	1,16 – 2.66	-	-	-
Best response to sunitinib	0.001	2.25	1.38 – 3.66	0.001	2.34	1.41 – 3.9
Primary tumor diameter (cm)	0.031	1.1	1.00 – 1.20	-	-	-
ECOG – PS	0.021	1.90	1.10 – 3.29	-	-	-
Time to imatinib resistance	0.044	0.45	0.20 – 0.98	0.047	0.43	0.19 – 0.99

CI: Confidence interval; ECOG – PS: Eastern Cooperative Oncology Group performance status; HR: Hazard ratio.

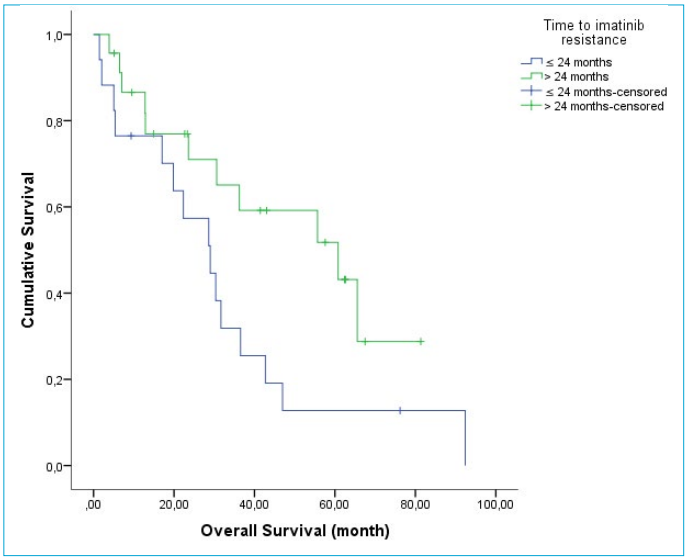

Figure 3. The median Overall survivals of patients who developed imatinib resistance ≤24 months and >24 months were 32 months (18.5–45.5 mo) and 49 months (36.6–62.5 mo), respectively (p=0.048).

Table 4. Univariate analysis for progression-free survival

Risk factors	P	HR	%95 CI
Best response to sunitinib	0.002	1.90	1.27 – 2.84

CI: Confidence interval; HR: Hazard ratio.

Table 5. Risk feature in determining grade 3 or 4 toxicities

Age at diagnosis	P	OR	%95 CI
≥ 60 years	0,043	4.2	1.24 – 20.4

CI: Confidence interval; OR: Odds ratio.

site in GIST patients who candidate for second-line therapy.

The median OS and PFS were 31.6 months and 19.6 months in our study, respectively. The median OS and PFS durations were found to be 18.5 months and 6.5 months, in a phase 3, randomized, prospective study in which Demetri et al. compared the efficacy of sunitinib with placebo in GIST patients, respectively.[15] When we compared the best response rates of the same study with ours, complete response, partial response, and stable response were 1% vs 2.5%, 34.3% vs 47.5%, and 34.3% vs 47.5%, respectively. This discordance in OS and PFS may be related to the higher partial and complete response rates of our patients and the patients' choice of treatment after sunitinib. Of note, while there was no standard treatment option after sunitinib progression during the study of Demetri et al., regorafenib was the standard third-line treatment option in our study. The longer expected survival in patients treated with sorafenib may be another reason for the longer survival in our cohort. Although it is known that there were patients included after imatinib escalation in the study of Demetri et al., we could not reach the information about the percentage of the patients in this group. Another study that we considered to be more consistent with our survival outcomes is the retrospective study of Hsu C-C et al. in which they assessed the efficacy of sunitinib versus 800 mg imatinib. The median OS and PFS rates obtained with the sunitinib treatment in this study were 35.5 months and 9.9 months, respectively.[19] The median PFS was determined to be 14.3 months in the patients with the exception of the primary exon 9 KIT mutation. On the contrary, in another study in which Henrich CM et al. assessed the efficacy of sunitinib after imatinib failure, OS and PFS were 27 months and 19.4 months in the exon 9 mutant patients, and it was 12.3 months and 5.1 months in the Exon 11 mutant patients, respectively20. The conflicting results of the other studies make it difficult to explain the results of our study. Our patients were more sensitive to systemic treatment, and this may be the reason for their long OS and PFS rates. For this, primary KIT mutation data assessment is required. However, we could not evaluate the mutation status of our patients, since primary KIT mutations were unable to study in our center.

We determined among many risk factors that the best response to sunitinib and time to imatinib resistance were independent prognostics for OS by multivariate analysis. It seems that the efficacy of sunitinib improved as the time to imatinib resistance delayed. In the study of Den Hollander D et al., a positive correlation was also determined between the period of imatinib use and PFS after sunitinib initiation. Progression to imatinib within the first 6 months of treatment was determined to be a significant predictive factor for progression-free survival in the same study.[18] Progressions observed in the first 3 to 6 months of imatinib treatment are associated with primary resistance, which are also associated with unresponsiveness to sunitinib treatment and composed 12% of all GISTs.[13,21] In our study, we could not include it in the statistical assessment as a risk factor because only two patients developed progression in less than 6 months. Other more common mutations usually develop after a median of 2 years of imatinib treatment.[12] The acquired secondary KIT mutations are the most common causes for these secondary resistances20,24. These secondary mutations are mostly occur in exons 13/14 (the cytoplasmic ATP-binding domain) or exons 17/18 (the activation loop). In addition to its antiangiogenesis effect, sunitinib can have an effect on secondary mutations by possibly binding to the receptor from different regions.

In our study, the rate of the patients with grade 3 or 4 toxic-

ity was 30%. We found in the univariate analysis that >60 years of age was prognostic. In the study of Demetri et al., the incidence of serious toxicities was determined to be 20% in the study population.[15] In a phase3, randomized study in which the efficacy and tolerability of sunitinib as first-line therapy in renal cell carcinoma was assessed, grade 3-4 toxicity was found to be 48%.[25] When considered together with existing studies, sunitinib has a high risk of toxicity. Also, it has been demonstrated in the other clinical studies that there is a significantly higher risk of sunitinib toxicity in elderly patients.[18,26]

The retrospective nature and cross-sectional design of our study, the low number of primary-resistant patients and inability to study primary KIT mutations causing kinase activation are important limitations. In addition, certain risk factors related to survival and drug toxicity may not have statistical significance due to the low number of patients. As a result, we revealed specific subgroups that may predict sunitinib efficacy and tolerability in patients with imatinib-resistant GIST. We believe that our findings may facilitate the management of patients in clinical practice.

Disclosures

Ethics Committee Approval: Retrospective analyses of clinical data were approved by the Academic Committee of Istanbul University (File no: 2021/911). The committee had agreed to the retrospective analysis of routinely collected clinical data without prior informed consent of patients.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – F.F., S.K., N.P.; Design – F.F., S.K., D.T.; Supervision – D.T.; Materials – F.F., N.P.; Data collection &/or processing – F.F., N.P.; Analysis and/or interpretation – F.F., N.P.; Literature search – F.F., S.K.; D.T.; Writing – F.F., S.K.; Critical review – S.K., D.T.

References

1. Poveda A, García Del Muro X, López-Guerrero JA, Cubedo R, Martínez V, Romero I, et al; GEIS (Grupo Español de Investigación en Sarcomas/Spanish Group for Sarcoma Research). GEIS guidelines for gastrointestinal sarcomas (GIST). Cancer Treat Rev 2017;55:107–19. [CrossRef]
2. Miettinen M, Lasota J. Gastrointestinal stromal tumors--definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch 2001;438:1–12. [CrossRef]
3. Nilsson B, Bümming P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era--a population-based study in western Sweden. Cancer 2005;103:821–9. [CrossRef]
4. DeVita VT, Lawrence TS, Rosenberg SA. DeVita, Hellman, and Rosenberg's cancer: principles & practice of oncology. Philadelphia: Lippincott Williams & Wilkins; 2008.
5. Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science 2003;299:708–10. [CrossRef]
6. Miettinen M, Wang ZF, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. Am J Surg Pathol 2009;33:1401–8. [CrossRef]
7. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol 2005;100:162–8.
8. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000;231:51–8. [CrossRef]
9. Gasparotto D, Rossi S, Bearzi I, Doglioni C, Marzotto A, Hornick JL, et al. Multiple primary sporadic gastrointestinal stromal tumors in the adult: an underestimated entity. Clin Cancer Res 2008;14:5715–21. [CrossRef]
10. Blanke CD, Rankin C, Demetri GD, Ryan CW, von Mehren M, Benjamin RS, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol 2008;26:626–32.
11. Blay JY, Kang YK, Nishida T, von Mehren M. Gastrointestinal stromal tumours. Nat Rev Dis Primers 2021;7:22. [CrossRef]
12. Verweij J, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay JY, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004;364:1127–34. [CrossRef]
13. Van Glabbeke M, Verweij J, Casali PG, Le Cesne A, Hohenberger P, Ray-Coquard I, et al. Initial and late resistance to imatinib in advanced gastrointestinal stromal tumors are predicted by different prognostic factors: a European Organisation for Research and Treatment of Cancer-Italian Sarcoma Group-Australasian Gastrointestinal Trials Group study. J Clin Oncol 2005;23:5795–804. [CrossRef]
14. Heinrich MC, Corless CL, Blanke CD, Demetri GD, Joensuu H, Roberts PJ, et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol 2006;24:4764–74. [CrossRef]
15. Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368:1329–38. [CrossRef]
16. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

17. National Institutes of Health. Cancer therapy evaluation program. Common terminology criteria for adverse events version 5.0 (CTCAE). Bethesda: National Cancer Institute; 2017.
18. Den Hollander D, Van der Graaf WTA, Desar IME, Le Cesne A. Predictive factors for toxicity and survival of second-line sunitinib in advanced gastrointestinal stromal tumours (GIST). Acta Oncol 2019;58:1648–54. [CrossRef]
19. Hsu CC, Wu CE, Chen JS, Tseng JH, Chiang KC, Liu YY, et al. Imatinib escalation or sunitinib treatment after first-line imatinib in metastatic gastrointestinal stromal tumor patients. Anticancer Res 2014;34:5029–36.
20. Heinrich MC, Maki RG, Corless CL, Antonescu CR, Harlow A, Griffith D, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol 2008;26:5352–9. [CrossRef]
21. Demetri GD, Garrett CR, Schöffski P, Shah MH, Verweij J, Leyvraz S, et al. Complete longitudinal analyses of the randomized, placebo-controlled, phase III trial of sunitinib in patients with gastrointestinal stromal tumor following imatinib failure. Clin Cancer Res 2012;18:3170–9. [CrossRef]
22. Debiec-Rychter M, Cools J, Dumez H, Sciot R, Stul M, Mentens N, et al. Mechanisms of resistance to imatinib mesylate in gastrointestinal stromal tumors and activity of the PKC412 inhibitor against imatinib-resistant mutants. Gastroenterology 2005;128:270–9. [CrossRef]
23. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24.
24. van der Veldt AA, Boven E, Helgason HH, van Wouwe M, Berkhof J, de Gast G, et al. Predictive factors for severe toxicity of sunitinib in unselected patients with advanced renal cell cancer. Br J Cancer 2008;99:259–65. [CrossRef]