

C-KIT Negative Gastrointestinal Stromal Tumors: Challenges of Management and Prognosis

Mohamed Atef Elkordy^{1*}, Fady Rashad Selim¹, Amani A. Abou Bakr², Eman D. ElDesouky³, Foad AbdElShaheed Foad¹

¹Department of Surgical Oncology, NCI, Cairo University, Egypt

²Department of Pathology, NCI, Cairo University, Egypt

³Department of Statistics, NCI, Cairo University, Egypt

***Corresponding author:**

Mohamed Atef ELKordy, MD

Postal code: 11728, 4h/3 Rubi street

Takseem El Laselky, Maadi, Cairo

Egypt

Phone: 002-01554090340

E-mail: malkordy2001@gmail.com

ABSTRACT

Background: Gastrointestinal stromal tumours (GISTs) are uncommon sarcomas. Surgery and target therapy are the primary modalities in treating GIST. KIT expression is the cornerstone in diagnosis of GIST, yet its expression is absent in a small percent of GISTs. The precise behaviour and treatment effects, particularly target therapy, and the prognosis of these cases are unclear; hence this study was designed to investigate them.

Methods: In the current retrospective cohort research, all patients with GIST who presented and were treated at National Cancer Institute (NCI), Cairo University, between January 2011 to December 2020 were included. The cases were categorized into two groups (positive and negative) based on c-KIT status positivity. Both groups' patient characteristics, clinical and histopathological characteristics of tumours, and treatment modalities outcomes were compared.

Results: The stomach was the site of origin of 56 cases (48.3%) with c-KIT positive compared to only 5 cases (22.7%) without c-KIT expression (P-value = 0.009). The liver was the primary origin of GISTs in only one case (0.86%) in the c-KIT positive group, while it was the primary site in 6 cases (27.2%) in the c-KIT negative group (P-value = 0.002). The median overall survival in the c-KIT positive group was 60 months compared to the c-KIT negative group, which was only 30 months (P-value = 0.004). Regarding c-KIT negative cases, the five years OS of the 9 cases who received adjuvant target therapy was higher than the other 13 cases that did not (55.5 vs. 15.3%) (P-value = 0.05).

Conclusion: GISTs lacking c-KIT expression have different behaviour than those with the c-KIT expression. In terms of OS treatment results and prognosis, c-KIT negative GISTs demonstrated poor outcomes compared to c-KIT positive cases.

Key words: GIST, C-kit negative, Imatinib, Tyrosine kinase inhibitor

Abbreviations:

GIST: Gastro intestinal stromal tumor;

TKI: Tyrosine kinase inhibitor;

OS: Overall survival;

DFS: Disease free survival;

EGIST: Extra gastrointestinal stromal tumor;

PDGFRA: platelet derived growth factor receptor alpha.

INTRODUCTION

Mesenchymal tumors rarely arise from GIT, with GIST accounting for 18% of all sarcomas (1). Despite this, GISTs arise from any site of GIT, but gastric GISTs represent at least 50% of all GISTs. The prognosis for GISTs has historically been considered to be dismal as the median survival for non-metastatic cases was

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only 60 months, while only 19 months in cases with metastasis, as reported by DeMatteo, et al. (2). Over the past 20 years, significant advancements in the treatment of GISTs have been made with the introduction of Target therapy resulting in increased survival rates. In 1998, there was a breakthrough in the detection and management of GISTs as Hirota, et al. described some important characteristics that would aid in the way we identify and treat patients with GIT mesenchymal tumors. Initially, fifty-eight mesenchymal tumors of the GIT were tested by immunohisto-chemistry to have KIT (CD 117) expression. In contrast to leiomyomas and schwannomas, which did not express KIT, 78% of GISTs were shown to be positive for KIT and CD34 (the known marker for GIST at that time) (3).

In addition, KIT is strongly expressed in approximately 95% of all GIST. In GIST, KIT expression is rarely absent. In these cases, confirming the diagnosis is done by other IHCs. To our knowledge, few studies have been conducted on GIST, which lacks c-KIT expression and is less helpful in assessing these tumors' behavior and prognosis. Therefore, this study was designed to compare cases of GIST with c-KIT expression versus those without, aiming to identify differences in clinical, prognosis, and treatment results.

PATIENT AND METHODS

Medical records and data

From January 2011 to December 2020, all GIST cases presented and treated at Cairo University's National Cancer Institute (NCI) were included in this retrospective cohort research. The patients' information was obtained from the medical records of the Biostatistics and Cancer Epidemiology Department of NCI. The cases were divided according to c-KIT status positivity into two groups (positive and negative). Both groups' patient characteristics, clinical and histopathological characteristics of tumours, treatment modalities, and outcomes were compared.

The definitive diagnosis of GIST obtained by histopathological examination of either surgically resected specimen or biopsy from suspected lesion. Starting with microscopic examination of hematoxylin and eosin (H & E) stained slides to evaluate morphological and microscopic characteristics concomitant with GIST, and after correlation with the clinical, radiological findings and the site of lesion, immune-phenotyping was done starting with CD117 (c-KIT) and CD34. In cases with c-KIT negative, Dog1 was done. Also exclusion of other

spindle cell tumours like smooth muscle tumours (by negativity to Desmin and Caldesmon) was done.

Statistical methods

Utilizing version 24 of the Statistical Package for Social Sciences (SPSS), data management and statistical analysis were carried out. Means and standard deviations, or medians and ranges were used to summarise numerical data. Percentages were used to summarise categorical data. The t-test was used to compare the two groups in terms of normally distributed numerical variables. The Mann-Whitney test was used to compare numeric variables that were not normally distributed. When appropriate, the chi-square and Fisher's exact test were used to analyse the differences for categorical variables. The Kaplan and Meier procedure was used to estimate the OS and progression-free rates, and the Log-rank test compared the different prognostic factors. The OS rates were computed from the diagnosis date to the date of death from any cause. Patients who were still living or who were lost to follow-up were censored on the last known alive date. Then significant variables were entered into the Cox Proportional Hazards Model. All p-values are two-sided. P-values ≤ 0.05 were considered significant.

RESULTS

138 patients with GISTs were diagnosed and treated at the NCI, Cairo University, between January 2011 and December 2020. The main presenting symptoms were abdominal distention (58 cases [42%]), Abdominal pain (35 cases [25.3%]).

One hundred and sixteen cases (84.1%) were positive for c- KIT expression, while only 22 cases (15.9%) were negative. Regarding age and gender, there were no significant differences between the two groups, as illustrated in Table 1. In contrast to cases with c-KIT positive, which mostly originated from the stomach (48%), c-KIT negative cases mostly originated from extragastrointestinal sites, mainly as pelvic or abdominal masses (31.8%) without direct continuity with the gastrointestinal tract or primarily originated from the liver (27.2%) without any apparent masses in GIT despite the careful investigation by endoscopy and imaging as depicted in *table 1*.

Other immuno-histochemistry's tests were used for confirmation of diagnosis, as illustrated in *table 2*. Dog1 was less expressed in the c-KIT negative (only 5 cases [22.7%]) compared to 59 (50.9%) cases in the c-KIT-positive group (P-value = 0.015).

Table 1 - Patients' and tumors' characteristics

		c- KIT		P value
		Positive n=116 (%)	Negative n=22 (%)	
Age (Years)	Mean± SD	56.6±13.1	54.9±10.4	0.551
Gender	Male	62(53.4)	11(50.0)	0.766
	Female	54(46.6)	11(50.0)	
Site of primary tumor				
Stomach	Yes	56(48.3)	5(22.7)	0.009
	No	60(51.7)	17(77.3)	
Small_intestine	Yes	32(27.6)	0(0)	0.005
	No	84(72.4)	22(100.0)	
Omentum	Yes	9(7.8)	0(0)	0.177
	No	107(92.2)	22(100.0)	
Colon_Rectum	Yes	6(5.2)	4(18.2)	0.031
	No	110(94.8)	18(81.8)	
Pelvic or abdominal mass	Yes	3(2.6)	7(31.8)	<0.001
	No	113(97.4)	15(68.2)	
Liver	Yes	1 (0.86)	6(27.2)	0.002
	No	115(99.1)	16(72.2)	
Tumor size (cm)	Median (Range)	10.0(2-24)	11.5(2-25)	0.974

Table 2 - Immunohistochemistry markers

IHC Markers		c- KIT		P value
		Positive n=116 (%)	Negative n=22 (%)	
Dog	Positive	59(50.9)	5(22.7)	0.015
	Negative	57(49.1)	17(77.3)	
CD34	Positive	30(25.9)	6(27.3)	0.890
	Negative	86(74.1)	16(72.7)	
Actin	Positive	13(11.2)	5(22.7)	0.141
	Negative	103(88.8)	17(77.3)	
SMA	Positive	4(3.4)	2(9.1)	0.234
	Negative	112(96.6)	20(90.9)	
Pdgfr	Positive	0(0)	3(13.6)	<0.001
	Negative	116(100.0)	19(86.4)	
CD68	Positive	0(0)	1(4.5)	0.159 a
	Negative	116(100.0)	21(95.5)	

a: analysis done by fisher exact test

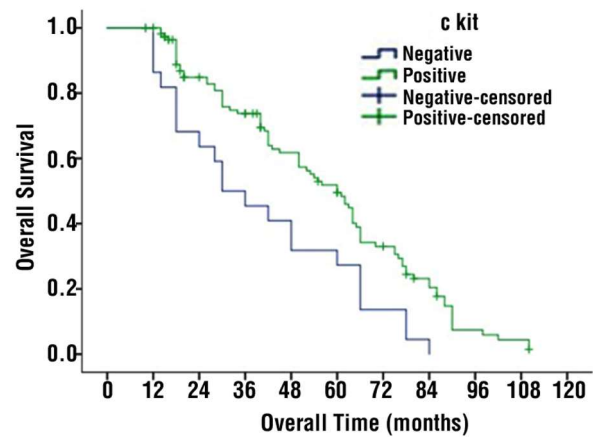
Surgical resection was done for 96 (82.8%) cases in the c-KIT positive group, while only 15 (68.2%) in the c-KIT negative group (table 3).

Survival analysis

According to c-KIT expression, the median OS for

Table 3 - Treatment modalities used in management

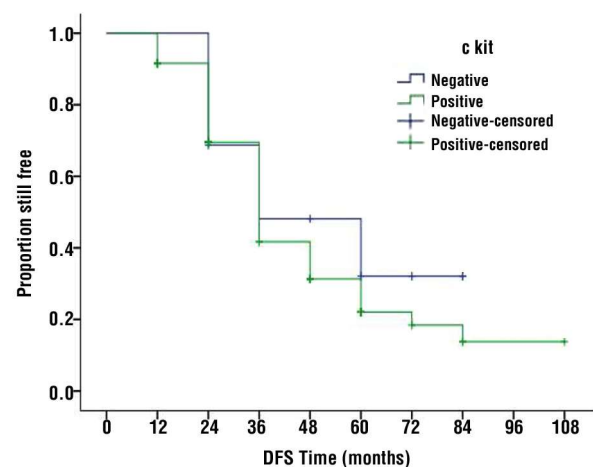
		c- KIT		P value
		Positive N=116 (%)	Negative N= 22(%)	
Surgery	Yes	96(82.8)	15(68.2)	0.114
	No	20(17.2)	7(31.8)	
Target Therapy	yes	116(100.0)	9(40.9)	<0.001
	No	0(0)	13(59.1)	

**Figure 1 - The Cumulative (Cum) survival for cases with c-KIT positive and c-KIT negative GIST (P-value =0.004)**

c-KIT positive was 60 months, whereas it was only 30 months for c-KIT negative cases (P-value =0.004) (fig. 1). With respect to c-KIT negative cases, the five years of OS of the 9 cases who received adjuvant target therapy was higher than the 13 cases who did not receive it (55.5 vs. 15.3%) (P-value 0.05). There was no significant difference in DFS between the two groups (fig. 2).

DISCUSSION

Gastrointestinal sarcomas are rare diseases, and the discovery of the c-KIT gene mutation markedly improved their diagnosis and classification, as it is not expressed in the diffuse matter in sarcomas other than GISTs. Approximately 95% of GISTs express c-KIT; however, to our knowledge, few studies have investigated the behavior, treatment effects, and prognosis of

**Figure 2 - Disease free survival (DFS) for cases with c-KIT positive and c-KIT negative GIST**

GISTs devoid of KIT expression. The analysis identified only 22 cases of c-KIT negative GIST out of 138 cases enrolled in our study. Regarding the age of patients in the conducting study, no significant difference was found between c-KIT positive and c-KIT negative GIST, with a mean age of 56.6 and 54.9 years, respectively. These results are comparable to Kontogianni-Katsarou, et al study on KIT negative GISTs as the mean of age was 62 ± 14.5 years (4). No pediatric cases were present in NCI registries which represents a limitation in this study as Pappo, et al. reported that 85% of paediatric GIST were negative for c-KIT and PDGFRA expression (5). In the current study, no gender predilection was found in the c-KIT negative group, while the incidence of c-KIT positive GIST was relatively higher in males (53.4 %: 46.6 %). These findings are consistent with those in the previous studies, which discussed the incidence of GIST in both c-KIT positive & negative (4,6).

In the current study, c-KIT negative GISTs originated primarily from extragastrointestinal sites (pelvic, abdominal mass of unspecified origin (31.8%) and in the liver (27.2%), whereas c-KIT positive GISTs originated mainly from the stomach (48.3%). The same results were reported by Yamamoto, et al. on 10 cases of c-KIT negative GIST. Five patients had tumors in the omentum, two in the mesentery, one in the retroperitoneum, one in the pelvic cavity, and one in the abdominal cavity (7).

According to Yamamoto H, et al., Extragastrointestinal stromal tumors (EGIST) are GIST that develop outside of the gastrointestinal wall, such as in the omentum, retroperitoneum, pelvic cavity, or mesentery (8). Even though the exact mechanism behind the development of these tumors is unknown, some GISTs may extend outward, eventually they completely lose their primary link to the GIT tract and attach to nearby soft tissue. Additionally, they may represent metastatic deposits from GIST, but the primary tumor is not discovered (8). GIST is thought to develop from interstitial cells of Cajal (ICCs), many organs other than GIT harboring interstitial cells named interstitial Cajal-like cells (ICLCs) like upper and lower urinary tract, pancreas, and other sites. In addition, ICLCs have been found in liver fibrosis, as reported in Fu et al. study (9); this may explain the primary hepatic GIST. In this study, identified 6 cases of primary c-KIT-negative GIST originating from the liver that did not exhibit imaging or endoscopic evidence of metastasis from any site of GIT.

Immunohistochemistry is the cornerstone of the GIST diagnosis. In the current study, the cases of c-KIT negative GIST were positive for CD 34: 27.3 %, Actin:

22.7 %, Dog1: 22.7 %, PDGFR: 13.6%. According to West RB, et al., DOG1 was positive in 98% of c-KIT negative cases (10), whereas Kang et al. demonstrated that the expression of DOG1 was positive in (92%) of c-KIT negative GIST (11), respectively.

One of the obstacles in treating c-KIT negative GISTs is their response to target therapy, as it is necessary as a neoadjuvant to manage some of these cases to down-size the tumor and make them amenable for resection as well as an adjuvant in tumors with advanced stage. Imatinib mesylate works as an inhibitor of tyrosine kinases, such as KIT and PDGFR (12-19). The effect of Imatinib on c-KIT negative GIST is not well known. In our study, all cases of c-KIT positive received target therapy (Imatinib) varied between neoadjuvant & adjuvant and definitive treatment, while only 9 cases with c-KIT negative GIST received Imatinib as an adjuvant treatment. IHC revealed that 3 of 9 cases treated with Imatinib were PDGFR-positive.

In the current study, the effect of Imatinib as an adjuvant treatment in KIT negative can be distinguished from the higher OS of the cases who received it as an adjuvant compared to the others who did not receive it. These findings are consistent with Medeiros et al. study (20), and since some KIT-negative GISTs have imatinib-sensitive PDGFRA mutations, Imatinib therapy shouldn't be denied from KIT-negative GIST patients. In the current study, patients with c-KIT positive GIST showed higher OS with a median of 60 months compared with the c-KIT negative group, which had a median of 30 months. This finding may indicate a difference in tumor behavior or due to omitting or resistance of c-KIT negative cases to target therapy, emphasizing the need for additional research to determine the effects of target therapy on c-KIT negative GISTs. The conducted study emphasized the characteristics of c-KIT negative GIST, but it had limitations due to its retrospective methodology and the limited number of c-KIT negative GIST cases. However, the study's findings were valuable because they demonstrated that c-KIT negative GISTs behave differently from c-KIT positive GISTs from the site of origin and having lower overall survival rates. Also that some cases of c-KIT negative GISTs may respond well to target therapy.

Furthermore, the authors recommend conducting studies on c-KIT negative GISTs as a different category from c-KIT positive, which may need closer follow-up and more aggressive surgical resection as this is the only effective treatment that still aims to improve survival.

CONCLUSION

GISTs lacking c-KIT expression have different behavior than those with the c-KIT expression. A more significant percentage of cases originated from extra-intestinal sites, with a higher percentage originating primarily in the liver. In terms of OS treatment results and prognosis, c-KIT negative GISTs demonstrated poor outcomes compared to c-KIT positive cases.

Conflict of interest

All authors declare no conflict of interest.

Ethical approval

This study is a retrospective analysis of the medical records of 138 GIST patients. All measures were taken to protect the security and confidentiality of the individual patient's information. The approval of the NCI ethical committee was secured through the expedited pathway. IRB approval No: 2106-41004-004.

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