Retrospective Analysis of Outcomes and Toxicity of Adjuvant Imatininb in Patients with Gastrointestinal Stromal Tumor in Clinical Oncology Department at Ain Shams University

Original Article

Khaled Naguib Abdel Hakeem,Riham Essam Abdel-salam,Tarek Hussein kamel ,Waleed Abd El-Moniem Bayomi, Khaled kamal El-din El-Ghoniemy and Sherif Hassanin Ahmed

Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University

ABSTRACT

Background: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of GIT.75% of them are driven by mutations in the genes encoding for tyrosine kinase, KIT, (PDGFRA). Efficacy of the tyrosine kinase Inhibitors (imatinib) is approved for localized and advanced disease. For localized GISTs,3 years imtanib is the standard in the adjuvant settings for high risk patients after surgery.

Aim of the Work: This review aims to describe current knowledge of adjuvant therapy of primary GISTs in view of available results and to refine the most commonly reported side effects of imatinib

Patients and Methods: This study is a retrospective cohort study included 40 patients attending sarcoma clinic at the Clinical Oncology Department, Ain Shams University during the period from 1 January 2016 till 31 December 2022.

Results: A total of 40 patients were included. 47.5% completed 3 year duration of treatment by Imatinib compared to 52.5% who didn't complete treatment duration.Higher DFS was found in the first group compared to the second group with median DFS 67.8 vs 47.9 months respectively *P value* <0.003 highly significant . As regard side effects of imatininb, toxicity was reported in 20% of the patients ,and the commonly found side effect was skin rash (12.5%) , followed by hematological toxicities (10 %), gastritis (5%) then diarrhea (2.5%) and elevated liver enzymes (2.5%) . 22.5% of patients developed recurrence of the disease and higher rate of reccurrence was found among elderly>60 years, tumor size>10 cm , and higher Ki67 with *P value* 0.001.

Conclusion: Treatment with adjuvant Imatinib is proved to increase DFS with well tolerated side effects.

Key Words: GIST, imatinib, KITmutation.

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Corresponding Author: Riham Essam Abdel-salam , Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University. **Tel.:** 01282008710, **E-mail**: reham.selmy@gmail.com

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INTRODUCTION

GIST(gastrointestinal stromal tumor) is the most common sarcoma in gastrointestinal tract (GIT). Globally, the incidence of GIST is 1.5/100,000, mean age 50 to 70 years with equal gender distribution[1]. In Egypt,according to retrospective studies done in different regions allover Egypt, the highest incidence of GIST patients was reported in a study done in Alexandria in which number of patients was 93 from January 2009 to January 2015[2]. The origin of the tumor is the interstitial cells of Cajal, the most common site is the gastric gist 65% of cases and 30 % from jejunum & ileum, 4-5%in duodenum, 1-2% from appendix and colon,1% from esophagus[3,4].

Ninety percent 90% of GIST expresses tyrosine protein kinase c-KIT/CD117 a cell surface transmembrane receptor tyrosine kinase, while 3-5 % harbors platelet derived growth factor receptor Alpha(PDGFRA) which induces the same signal transduction pathway as c-KIT[5,6] those mutations didn't add to the risk classification of GIST, but they are corner stone to anticipate the response to drugs like tyrosine kinase inhibitor (TKI);imatinib.

Surgical resection is the mainstay of treatment of GIST, however 50% of patients who are treated by only surgery develop recurrence within 5 years[7]. And recurrence rate is affected by multiple prognostic factors: tumor site, tumor size, mitotic index, ki70, c-KIT, PDGFRA

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and rupture during surgery (tumor rupture is defined as: (tumor spillage,blood-stained ascites, GIT perforation at the tumor site, microscopic infiltration of an adjacent organ,intralesional dissection or piecemeal resection or incisional biopsy & bleeding)[7].

According to the Armed Forced Institute of Pathology (AFIP), High risk features are size >10 cm with any mitotic index, or> 5cm with mitotic index >5/50 HPF(High Power Field) or tumor rupture[8].

Imatinib is a TKI (tyrosine kinase inhibitor) targeting multiple tyrosine kinase receptors, The Food and Drug Administration (FDA) approved oral imatinib as the standard line in adjuvant settings in treatment of the surgically resected KIT-positive tumors to help prevent recurrence for about 3 years with standard dose 400 mg for 3 years in adjuvant cases based on the Swedish study, SSG XVIII, in which 1 vs. 3 years of adjuvant imatinib 400 mg daily in high risk cKIT positive GISTs were compared, and results showed significant improvement in recurrence free survival (RFS) (5 year RFS 66% vs 48%n patients on 3 years of adjuvant imatinib)[9-11].

EORTC62005 and S0033 trails assessed the efficiency of imatinib at 400 mg/day and 800 mg/day dose. Both studies reported the equivalent response rate. taking into consideration the side effects and toxicity of the drug[12].

In the previously mentioned studies the most common reported toxicities were nausea, diarrhea, fatigue, hematological toxicity, peri-orbital edema, dermatitis and according to ACOSOGZ9001 trial; Patients on 1-year adjuvant imatinib experienced more grade 1 or 2 adverse events mostly involved gastrointestinal effects (diarrhea, nausea, and flatulence), headache, rash, peri-orbital or peripheral edema, fatigue, or myalgias.

Many patients experienced adverse events in the SSGXVIII/AIO trial, however imatinib was generally well-tolerated and most of the events were mild in severity. despite a higher incidence of grade 3 or 4 side effects[13].

AIM OF THE WORK

This study is designed to retrospectively analyze disease Free survival, safety and toxicity of adjuvant imatininb in patients with GIST in clinical oncology department at Ain Shams University.

PATIENTS AND METHODS

Study design:

After obtaining the approval of Ain Shams University research ethics committee, we performed a retrospective cohort study at sarcoma clinic at clinical oncology department at Ain Shams University Hospitals between January 2016 to December 2022.

Inclusion criteria:

Patients age >18 year with GIST proved by histopathological examination ECOG 1 or 2, patients who under went surgical resection with positive CD117 by IHC, and treated by adjuvant imatininb.

Exclusion criteria:

Irresectable GIST, advanced/metastatic GIST at time of presentation, patients received neoadjuvant imatininb, and low risk features of GIST.

This study included 40 patients by consecutive sampling (all eligible patients in the previously determined period fulfilling the eligibility criteria were included).

Sampling method:

Consecutive sampling (all eligible patients in the previously determined period fulfilling the eligibility criteria will be included).

Sample Size:

For estimation of sample size, a 1-year DFS of 83% was used; namelyHo:p=83% and Ha:p=98% where p was the proportion of patients without recurrence. Ho was the null hypothesis and Ha the alternative hypothesis. According to one sample analysis and the power of 0.8, and alpha error 5%, the estimated required sample size was 33 patients. By calculating a 20% drop out rate, the final sample size was 40 patients (the program used for sample size calculation is STATA 10).

Outcome Evaluation:

Primary outcome: Disease Free survival (defined as DFS: duration from date of surgery till radiological evidence of recurrence) of patients with GIST on, evaluated by MRI, CT or PET CT.

Secondary outcome: Treatment related toxicity of adjuvant imatininb in patients with surgically resected GIST guided by Common Toxicity Criteria of Adverse Events (CTCAE) version 4.03.

-Variables

Patients demographic variables; Age: age was divided into two categories (< 60 and >60 years old). Gender: both males and females,medical comribidites; DM, HTN, others,

Tumor variable; Risk stratification; intermediate or high, site of the tumor: esophageal, gastric, intestinal, colonic, ano-rectal, Size of the tumor divided into 2-5 cm, 5-10 cm >10, Ki67 was divided into ≤5% or >5%, mitotic index: ≤5/HPF or>5%/HPF.

Toxicity variable; Was divided into hematological including Anemia, neutropenia or thrombocytopenia & non hematological toxicity including; skin rash, gastritis, diarrhea and elevated liver enzymes.

Treatment variable; Was divided into patients completed the standard 3 years of treatment & those who didn't complete 3 years of treatment duration & its effect on DFS.

RFS variable; And its correlation with clinicopathologic Al data of the tumor.

Statistical Analysis

The collected data was revised, coded, tabulated and introduced to the Statistical package for Social Science (SPSS 15.0 for windows; SPSS Inc, Chicago, IL, 2001).

Data was presented and suitable analysis was done according to the type of data obtained for each parameter. Descriptive statistics: Mean, Standard deviation (± SD), Minimum and maximum values (range) for numerical data, Frequency and percentage of non- numerical data. *P value* statistical significance: defined as <0.05.

The used tests were

-Chi square testing for categorical data.

-Independent t-test for continuous data.

-The Cox proportional hazards regression model is used to identify significant factors for DFS. A *P value* of less than 0.05 is considered statistically significant.

-All data are collected, revised, coded, and entered to the Statistical Package for Social Science (IBM SPSS Statistics) Version 23.

ETHICAL APPROVAL

The study protocol was revised and approved by the research ethics committee Clinical Oncology department, Ain Shams University Hospital.Patients Data confidentiality was maintained.

Date in 23/5/2023, Number; FMASU MS 307/2023

RESULTS

In this study, 40 patients were included fulfilling the eligibility criteria and they were diagnosed with GIST, their demographic data were discussed in (Table 1).

The standard duration of intake of adjuvant imatininb is 36 months At baseline, all patients received 400 mg of imatininb. Also patients received 36 months were 19 (47.5%)showed median DFS 67.8 months while patients received<36 months were 21 cases 52.5% and median DFS was 47.9 months with *P value* 0.003 as shown in (Figure 1).

Table1: Distribution of characteristics of patients with GIST and tumor variables.

Gender	No.	%	
Male	17	42.5%	
Female	23	57.5%	
	Mean	SD	Range
Age	50.6	12.8	25-79
	No.	%	
<60 yr	29	72.5	
≥60 yr	11	27.5	
Medical comorbities	No.	%	
DM	+ve 9	22.5	
	-ve 31	77.5	
HTN	+ve 16	40	
	-ve 24	60	
Other comorbities	+ve 2	5	
	-ve 38	95	
Risk	No.	%	95%CI
Intermediate	24	60%	
High	16	40%	24.56
Site	No.	%	
Esophagus	1	2.5	
Intestinal	15	37.5	
Gastric	19	47.5	
Colonic	3	7.5	
Ano-rectal	2	5	
Size	Mean SD	Range	
	9.2 cm 4.54	3.5-22cm	
	No.	%	
2-5cm	1	2.5	
≥5 - ≤10 cm	29	72.5	
>10 cm	10	25	
Ki67	No.	%	
≤ 5	25	62.5	
>5	15	37.5	12.6-41.1
Mitotic index	No.	%	
≤5	31	77.5	10.8-38.4
>5	9	22.5	

DM: diabetes mellitus
HTN; hypertension
SD; standard deviation

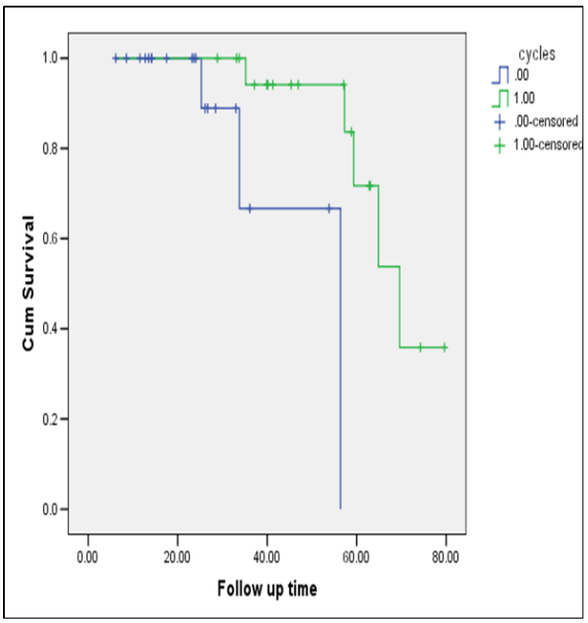

Fig. 1: Kaplan Meier curve for treatment duration and DFS. P value 0.003 highly significant.

Among the study population,9 (22.5%) patients developed recurrence during the follow-up period,with higher recurrence rate noted among elderly>60 yr with *P value* 0.1. Also, gastric and intestinal tumors were associated with high recurrence rate *P value* 0.6. Higher recurrence rate among cases with high risk features compared to intermediate risk 37.5% vs 12.5% *P value*; 0.06 and the difference is borderline significant. Also higher Ki67 >5 seen in 9 (60%) of patient was associated with higher recurrence rate compared to Ki56 <5 in 3(12%) patients with *P value* 0.001 highly significant. as discussed in (Table 2).

As regard toxicity profile and side effects reported during the follow-up period, among the whole study population,8 (20%) patients developed adverse events, 2 of them had to decrease dose of imatininb from 400 mg to 300 mg once daily. One of the 2 patients had to decrease dose due to grade 3 neutropenia according to CTCAE version 4.03, while the other patient decreased the dose due to severe skin rash and pruritis. In this study toxicity was divided into 2 main categories: hematological and non- hematological.

Table 2: Comparison studied variables and recurrence of tumor (*N*=40).

	Negative		Positive		X2	*P*
	No.	%	No.	%		
Gender						
Male N=17	13	76.5	4	23.5	0.01	0.8
Female N=23	18	78.3	5	21.7		
Age group						
< 60 N=29	24	82.8	5	17.2	1.7	0.1
>=60 N=11	7	63.6	4	36.4		
Risk						
Intermediate N=24	21	87.5	3	12.5	3.4	0.06
High N=16	10	62.5	6	37.5		
Site of lesion						
Esophagus N=1	1	100.0	0		2.8	0.6
Intestinal N=15	12	80.0	3	20.0		
Gastric N=19	13	68.4	6	31.6		
Colonic N=3	3	100.0	0			
Ano-rectal N=2	2	100.0	0			
Tumor size						
5-10 N=30	24	80	6	20.0	0.4	0.5
>10 N=10	7	70	3	30.0		
Mitotic index						
<=5 N=31	25	80.6	6	19.4	0.7	0.3
>5 N=9	6	66.7	3	33.3		
Ki 67						
<=5 N=25	22	88.0	3	12.0	10.7	0.001**
>5 N=15	6	40.0	9	60.0		

Four (10%) patients developed hematological toxicity,1 patient had isolated grade 3 neutropenia,1 patient had isolated grade 3 anemia, 1 patient had grade 2 pancytopenia and 1 patient developed bicytopenia (thrombocytopenia G4 & neutropenia G2) according to CTCAE version 4.03 as described in (Table 3). Four patients developed non hematological toxicity, and the most commonly reported toxicity are skin rash (12.5%), gastritis (5%). diarrhea and elevated liver enzymes (2.5% for each respectively) as discussed in (Table 4).

Table 3: Hematological toxicity distribution among study group.

	Frequency	Percent
Hematological toxicity		
No	36	90.0
Yes	4	10.0
Hemat.Grade		
.00	36	90.0
2.00	2	5.0
3.00	2	5.0

Table 4: 5 patients with skin rash, note one patient has combined skin rash and hematological complications.

	Frequency	Percent
Skin rash		
No	35	87.5
Yes	5	12.5
Gastritis		
No	38	95.0
Yes	2	5.0
Diarrhea		
No	39	97.5%
Yes	1	2.5 %
Elevated		
No	39	97.5%
Yes	1	2.5%

DISCUSSION

This study is a retrospective study that investigated the epidemiological and clinicopathological factors of GIST treated by surgical resection followed by adjuvant imatinib to evaluate significance of these factors and their impact on survival.

In the current study, the median age of diagnosis of GIST was 50.6. Similarly found in a study done by[14] in which the median age 50.6+/- 13.7 years; also similar to study done in Alexandria in 2014 the median age of diagnosis was 48.15

OS couldn't be estimated as no deaths occured in the study period. 77.5 % of study population were recurrence free at 36 months, While (22.5%) of study group developed recurrence.

Our data showed, higher rate of reccurrence was associated with high risk patients compared to intermediate risk, (37.5 vs12.5%) similarly found in study done by[15] in which high-risk patients showed RFS rate less than 40%. And according to our results also tumor size ≥10 cm was associated with higher rate of recurrence (*P value;*0.5), similarly observed in a study done in Iran by[16] which tumors more than 5 cm were associated with the recurrence of the disease, *P* = 0.003. Also In ACOSOG Z9001 trial in which large tumor size was associated with shorter RFS on multivariable analysis (*P* <.001).

Also, higher mitotic index >5/50 HPF is associated with higher rate of recurrence (33.3% vs 19.4%) in patients with mitotic index≤5/50 HPF and Lower DFS among patients with higher mitotic index with *P value* 0.1, (33 vs 41.9% in mitotic index >5/50HPF vs ≤5/50 HPF respectively), Similar results were found by[16], in which, the DFS rate was 98.3 % vs 87% vs 66.7% in patients with mitotic count <5 /50 HPF, ≥5 & <10 / 50 HPFs and ≥10 / 50 HPFs respectively. Also, in ACOSOG Z9001 trial in which, mitotic rate>10 /50 HPF was strongly associated with RFS (*P* <.001).

In this study, higher rate of recurrence among cases with ki67 >5%, 60% vs 12% among cases with lower ki67 with *P value* 0.001, also lower 3 year DFS among patients with higher ki 67, 33.3 vs 48 %in patients with ki 67>5% vs <5% respectively, *P value* 0.8

Higher DFS was observed in patients who completed ≥36 months compared to patients who received less than 36 months, median DFS 67.8 vs 47.9 respectively. *P value* =0.003.Similar data were observed in Scandinavian/ German trial SSGX-VIII/AIO trial: which DFS in the 36-month group vs 12-month group was 53.0% vs 41.8% respectively, *P* = .003 by[17]. Also in ACOSOG Z9001 trial in which RFS remained superior in the imatinib arm *P*<.001 in 2014 by[18]. And in EORTC 62, trial; by[19] in which RFS significantly better in the adjuvant imatinib arm than in the observation arm, *P* = 0.002.RFS rates were 70% versus 63% at 5 years and 62.5% versus 61% at 10 years. Smilarly was found in America 2015 by[20], in which RFS and survival was longer in 3 years arm vs 1 year,and the 5-year RFS rates were 71.1% and 52.3%, respectively *P* <.001.

As regard toxicity. Among 40 patients, 20% patients developed adverse events, the most commonly reported toxicity in this study was skin rash representing 62.5%, similar data were observed in study done in South Korea by[21] in which skin rash was the most common grade 3-4 nonhematologic toxicity 17.6%.

As regard other types of toxicity, the most commonly reported were (myelosupression) 10%, gastritis 5%, elevated liver enzymes 2.5%, and diarrhea 2.5%, similar data were found by[22] in which the most commonly reported side effects were mild and included anemia, diarrhea & gastritis.

CONCLUSION

-The mainstay of treatment of GIST is surgical resection followed by adjuvant imatinib daily dose 400 mg for 3 years. The evolution of imatinib had improved disease free survival and became standard choice for adjuvant, locally advanced and metastatic settings, with generally well tolerated side effects during duration of treatment.

Histopathological features as: site, size, risk stratification, mitotic index, ki67, PDGFRA mutation have distinct clinical behavior, response to treatment, and risk of recurrence, which highlights the importance of detection of these factors as predictive indicators for prognosis.

Late recurrence is not rare in GIST, which requires regular follow up for possibility of early detection and management.

For more accurate assessment of the population, it is advised to conduct multicenter studies with more than one center covering wider portion of population and discussing the management plans with other professionals at various facilities.

LIST OF ABBREVIATIONS

Abbr. Full term

1. GIST; gastrointestinal stromal tumor
2. NIH; National Institute of Health
3. KIT: Tyrosine protein Kinase
4. PDGFRA: platelet derived growth factor receptor
5. TKI: Tyrosine kinase inhibitor
6. AFIP: Armed Force Institute of Pathology
7. HPF: High Power Field
8. UICC: Union of International cancer control
9. EUS: Endoscopic Ultrasound
10. SDH: Succinate Dehydrogenase
11. RTK : Receptor Tyrosine kinase
12. DFS: Disease Free survival
13. OS : overall survival
14. RFS: recurrence Free survival
15. BRAF; v-raf murine sarcoma viral oncogene homolog B1
16. NF: neurofibromatosis
17. NTRK-3: neurotrophic receptor tyrosine kinase 3
18. ORR : overall response rate
19. PFS: progression free survival
20. TRK: tropomyosin-related-kinase
21. OD: Once daily

AUTHOR CONTRIBUTION

All the authors contributed to conceptualization and the study design.

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None.

CONFILCT OF INTERESTS

There is no conflicts of interest.

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تحليل بأثر رجعي نتائج وسميه عقار ايماتينب المساعد فى المرضى الذين يعانون من ورم اللحمة المعديه المعويه بقسم الأورام جامعة عين شمس

خالد نجيب عبد الحكيم، ريهام عصام عبد السلام، طارق حسين كامل، وليد عبد المنعم بيومي، خالد كمال الدين الغنيمي و **شريف حسنين احمد**

قسم علاج الاورام بكليه الطب، جامعه عين شمس، مصر

الخلفية: يعد ورم اللحمه المعديه المعويه ورم نادر إذ يمثل حوالي ١ إلى ٢ بالمائة من سرطانات الجهاز الهضمي الأولية. على الرغم من ندرته، فإنه يمثل أكثر اورام الجهاز الهضمي النتاتجه عن الأنسجة الرخوة شيوعاً مع معدل حدوث سنوي يختلف حسب المنطقة: ٣,٢-٦,٨ حالة لكل مليون شخص في الولايات المتحدة.

تعتبر المعده هي أكثر اجزاء الجهاز الهضمي عرضه للإصابة بهذا الورم بنسبة حوالي ٦٥٪ يليهاالأمعاء الدقيقة ٣٠٪، ثم الاثنين عشر ٤-٥٪ , يليه الزائده الدوديه والقولون ١٪ وأخيراً المرئ ١٪.

يهدف هذا العمل: الي تحليل السمات الوبائية والسريرية المرضية لـ GIST وارتباطها بالنتائج السريرية في شكل البقاء خالٍ من المرض، وتحليل استراتيجية العلاج وآثارها الجانبية في الإعدادات المساعدة بعد الاستئصال الجراحي لـ GIST في الفترة من يناير ٢٠١٦ إلى ديسمبر ٢٠٢٢.

تعد هذه الدراسة هي دراسة بأثر رجعي شملت ٤٠ مريضًا تم تشخيص إصابتهم بـ GIST في عيادة الأنسجة الرخوة بقسم الأورام الإكلينيكية بمستشفى جامعة عين شمس، في الفترة من بداية يناير ٢٠١٦ إلى ديسمبر ٢٠٢٢.

الاستنتاجات والتوصيات: يعتبر الاستئصال الجراحي هو الدعامة الأساسية لعلاج GIST يليه جرعة يومية من عقار إيماتينيب المساعد ٤٠٠ ملغ لمدة ٣ سنوات. أدى تطور إيماتينيب إلى تحسين البقاء على قيد الحياة بدون مرض وأصبح خيارًا قياسيًا لعلاج الاورام المعديه المعويه الناتجه عن الأنسجة الرخوة، مع آثار جانبية جيدة التحمل بشكل عام خلال مدة العلاج.

السمات النسيجية المرضية مثل: الموقع، الحجم، التقسيم الطبقي للمخاطر، مؤشرالانقسام، ki67، طفرة PDGFRA لها سلوك سريري متميز، والاستجابة للعلاج، وخطر التكرار، مما يسلط الضوء على أهمية اكتشاف هذه العوامل كمؤشرات تنبؤية للتشخيص.

ويعتبر الارتجاع المتأخر للورم ليس نادر الحدوث، الأمر الذي يتطلب متابعة منتظمة لإمكانية الكشف المبكر والإدارة.

للحصول على تقييم أكثر دقة للمرضي، يُنصح بإجراء دراسات متعددة المراكز معأكثر من مركز يغطي شريحة أكبر من السكان ومناقشة خطط الإدارة مع المتخصصين الآخرين في مختلف المرافق.