ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF MEDICINE

DEPARTMENT OF INTERNAL MEDICINE

Demographics, Clinical Presentation and Outcome of GIST Patients Treated with Imatinib at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia an eleven -year retrospective study

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December 2021

Demographics, Clinical Presentation and Outcome of GIST Patients Treated with Imatinib at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

an eleven -year retrospective study

A thesis Submitted to the Department of Internal Medicine, college of health sciences, Addis Ababa University for the fulfillment of specialty certificate for Internal Medicine.

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Acknowledgment

I would like to express my deepest gratitude to my advisor Dr Amha G/Medhn for the invaluable advises and correction and important inputs he has contributed, from my research proposal to the whole process of this thesis and also goes to Dr Abdulaziz for selecting this important topic.

I would also like also to acknowledge AAU, CHS for giving me this opportunity by providing the necessary funding to run the research.

Last but not least I also extend my appreciation to the department of internal medicine, and like to thank my friends for their support.

Abbreviation

AAU…….Addis Ababa University

ALC……..Absolute lymphocyte count

ANC----------Absolute Neutrophil count

CLD----------Chronic Liver Disease

CR…….....Complete Response

CT……Computed tomography

DM……..Diabetes Mellitus

GIPAP……..Glivec International Patient Assistance Program

GIST……..Gastrointestinal Stromal Tumor

HPF……High power field

IM……Imatinib

KIT 8…….Mutation of KIT EXO-8

MRI…….Magnetic resonance image

MRN……Medical Record Number

RECIST… Response Evaluation Criteria in Solid tumors

RFS……..Relapse-free survival

PR……Partial Response

PDGFRA……platelet derived growth factor receptor alpha

PD……Progressive disease

PFS----------Progression free survival

OS……Overall survival

TASH……Tikur Anbessa Specialized Hospital

TKI……Tyrosine kinase inhibitor

Table of Contents **Pages**

List of tables

Abstract

Background: Gastrointestinal stromal tumor (GIST) is a mesenchyme tumor located primarily in the stomach and small intestine, but can occur in any portion of the alimentary tract including occasionally in the omentum, mesentery, and peritoneum. Up to 80 % of GISTs result from gain-of-function mutations in the KIT gene, and approximately 85–95 % of GISTs stain positive for the KIT protein (CD117). There i slight increases prevalence in males. The median age is around 60–65 years in western population. The use of imatinib to selectively inhibit KIT and PDGFRA receptor tyrosine kinases is highly effective in the treatment of metastatic GIST and as adjuvant treatment.

Objective :The main objective of this to study to characterize ,Demographics, Clinical Presentation and Outcome of GIST Patients Treated with Imatinib at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

Method: A retrospective cross sectional design, patients with GIST enrolled in the Glivec International Patient Assistance Program (GIPAP) from January 1 2004 to August 30, 2021. All adult patients diagnosed with advanced GIST and adjunctive imatinib treatments were included and treatment response assessed using response evaluation criteria in solid tumors (RECIST).

Results: There are more than hundred GIST patients on imatinib at hematology clinic at TASH. Fifty eight patients with pathologically confirmed GIST, with abdominal CT scan taking imatinib were enrolled. The median age is 52 (ranges 20-83). 27.6% of were less than 45 age. Thirty two (55%) of GIST patients were male and twenty six (45%) were females with slight male predominance. Thirty seven (64%) had tumor originated from stomach and, twenty two patients had metastatic stage 4 disease. Metastasis to liver was the commonest site occurred in nine (15.5%). Surgical resection was the most frequent treatment; done for fifty (86.2%) patients. median duration of treatment with imatinib were 2.9 years. Out of sixteen patients with metastatic diseases, six (37.5) achieved PR, three (18.75) had SD four (25%) had PD. From a total of forty two patients taking adjunctive imatinib treatment thirty three (78.5%) achieved CR, and eight (19) patients was in PR.

Conclusion: This study showed Imatinib had a high efficacy both in patients with unresectable GIST/metastatic GIST and in those given as adjuvant treatments at the TASH.However it was more effective as adjuvant treatment.

KEY WORDS: GIST, Imatinib,

Introduction

1.1 Background

Gastrointestinal stromal tumor (GIST) is a mesenchymal tumor located primarily in the stomach and small intestine, but can occur in any portion of the alimentary tract including occasionally in the omentum, mesentery, and peritoneum. The estimated unadjusted incidence is about 1/100 000/year. There is slight increase prevalence in males. The median age is around 60–65 years, in western. [1, 7].

GIST is driven by oncogenic mutations in KIT or platelet-derived growth factor receptor alpha (PDGFRA). Up to 80 % of GISTs result from gain-of-function mutations in the KIT gene, and approximately 85–95 % of GISTs stain positive for the KIT protein (CD117). Mutations in PDGFRA are present in 5–8 % of GISTs and are mutually exclusive with KIT mutations. Approximately 35 % of KIT-negative GISTs have a mutation in PDGFRA.

IM (Imatinib) is a potent and selective inhibitor of tyrosine kinases, including the ABL kinase, KIT, PDGFRa, PDGFRb, and the collagen receptor discoidin domain receptor. Imatinib-mediated blockade of receptor tyrosine kinases interrupts proliferation and survival signaling pathways within the cell. The use of imatinib to selectively inhibit KIT and PDGFRA receptor tyrosine kinases is highly effective in the treatment of metastatic GIST and as adjuvant treatment.

The BFR14 trial, performed within the French Sarcoma Group, addressed the question of optimal imatinib treatment duration by randomizing patients after 1, 3, and 5 years to treatment interruption or maintenance.[5]

If R0 surgery is not feasible, or it could be achieved through less mutilating/function-sparing surgery in the case of volumetric reduction (this includes total gastrectomy and all other major procedures), pre-treatment with imatinib is standard.

Imatinib interruption results in rapid progression in the vast majority of patients with advanced disease, whatever the pattern of response achieved.

The study Results also strongly suggest that patients in complete response (CR) under imatinib still have residual disseminated, persistent active tumor cells and shows that it is not safe to interrupt imatinib on the basis of a CR by standard morphological criteria, even after long treatment. In the metastatic setting, also shown in another study treatment with imatinib should be continued indefinitely, since treatment interruption is generally followed by relatively rapid tumour progression, even when lesions have been previously surgically excised. [14]

The type of KIT/PDGFRA gene alteration largely influences the outcome of advanced GIST patients treated with imatinib. Several risk classifications have been proposed. A widely used risk classification was proposed by the Armed Forces Institute of Pathology, which incorporates the primary mitotic count, tumor size and tumor site, i.e. the three main prognostic factors in localized GISTs [11-12].

Many Phase II and III trials have confirmed the efficacy and safety of imatinib for patients with metastatic GIST. As a result, imatinib has been approved as the first-line treatment option for patients with unresectable or metastatic GIST that expresses KIT. Adjuvant treatment with imatinib for 3 years was associated with a relapse-free survival (RFS) and OS advantage in comparison with 1 year of therapy in high-risk patients in a randomized trial [13-16]

1.2 Statement of the problem

Gastrointestinal stromal tumors (GIST) are one of mesenchymal tumors of the alimentary canal. Most commonly originating from the gastric stroma, they are recognized by their mass effects on the abdominal cavity. GIST main origin is from the interstitial cells of cajal, which are ultimately referred to as the pacemaker cells of the gastrointestinal tract. It is due to a gain of function mutation of the c-kit receptor tyrosine kinase that ultimately gives rise to GISTs. They were described for the first time in 1983 by Mazur and Clark, and in 1988 were broadly acknowledged by the discovery of its c-kit (CD117) mutation from Hirota.

Pathologically, the diagnosis of GIST relies on morphology and immunohistochemistry, the latter being positive for CD117 (KIT) and/or DOG1 [8, 9].

As surgical resection with negative margins remains to be the standard curative treatment, unfortunately, as many as 40% of patients develop recurrent disease after resection of a primary localized GIST. Size and mitotic index are the two strongest predictors of recurrence.

Furthermore, a literature review revealed a statistically significant Difference in the relapse occurrence in a GIST greater than 5 cm and more than 5 mitosis per 50 HPF.

1.2.1 Significance of the study

GISTs are the most common mesenchymal tumor of gastrointestinal tract and gain considerable research and treatment interest, especially in the last 2 decades. As first line TKI, imatinib offers treatment for advanced and metastatic GISTs, adjuvant therapy in high risk and neoadjuvant agent to down size large tumors prior to resection .many clinical trials have been undertaken and are still ongoing to define the best molecular targeted therapy for GISTs.

In Ethiopia the Glivec international patient Assistance program](GIPAP) providing imatinib at no cost to eligible patients for the past seventeen years but the outcome and impact is not known so far. So this study will give the first base line data regarding the outcome and safety profile, patient compliance demographic characteristics a well.

1.3 Literature Review

Despite being the most common non epithelial benign neoplasm involving the GI tract, mesenchymal tumors are thought to constitute only 1 percent of primary GI cancers.

In the Swedish study, 288 of the 1460 cases examined were felt to represent GISTs, for an annual incidence of 14.5 per million populations. The Icelandic study reported an incidence of 11 per million populations. [1]

Families with germ line autosomal dominant mutations of KIT are an extremely rare finding, presenting with multiple GISTs at an early age, possibly along with other associated features such as pigmented skin macules, urticaria pigmentosa and diffuse hyperplasia of the interstitial cells of Cajal in the gut wall. Individuals with neurofibromatosis type I (NF1) also have a high incidence of GISTs. In the setting of NF1, GISTs are frequently in the small intestine (more than 70 percent) and multiple.

Up to 80 % of GISTs result from gain-of-function mutations in the KIT gene, and approximately 85–95 % of GISTs stain positive for the KIT protein (CD117.A significant breakthrough was achieved with the identification of the near-universal expression of this CD117 antigen by GISTs. The cellular morphology of GISTs ranges from predominantly spindle-shaped to

epithelioid in character. Histologically, the appearance of these tumors usually falls into one of three relatively uniform categories: Spindle cell type — 70 percent, Epithelioid type — 20 percent, Mixed type — 10 percent. Asymptomatic and discovered incidentally during an endoscopic or barium study or on a CT done for another purpose in some patients. [2]

More often, they are associated with nonspecific symptoms (ie, early satiety, bloating) unless they ulcerate, bleed, or grow large enough to cause pain or obstruction.

Prior to the development of imatinib, there was no effective treatment for metastatic GIST. Because of the small number of GIST patients in trials that included multiple types of sarcoma and the diagnostic confusion between GIST and leiomyosarcoma, it is impossible to determine the exact response rate of Metastatic GIST to chemotherapy, but it appears to be less than 10% [1].

Prior to the use of imatinib, surgical resection was often employed due to the lack of other effective therapy. Many Phase II and III trials have confirmed the efficacy and safety of imatinib for patients with metastatic GIST. As a result, imatinib has been approved as the first-line treatment option for patients with unresectable or metastatic KIT expressing GIST. Approximately 50% of patients with metastatic GIST have a measurable response after administration of imatinib, while about 75% will have at least stable disease [2–3].

In one study conducted to determine the Outcome of Metastatic GIST in the Era before Tyrosine Kinase Inhibitors identified by a review of a prospectively maintained database of GIST patients treated at Memorial Sloan-Kettering Cancer Center who were diagnosed with metastatic disease Surgical resection was the most frequent treatment of metastatic GIST multiple resections over the course of disease were common as 33 patients (41% of surgical patients) underwent repeat resections .Chemotherapy was used in 56 patients (47%).Doxorubicin was the most commonly employed systemic agent In this study, the survival of patients with metastatic GIST in the era before imatinib was 41% at 2years and 25% at 5 years with a median survival of 19 months. In contrast, the use of imatinib in metastatic GIST is associated with an approximately 72% 2-year survival and the median survival is 58 months. Consequently, imatinib appears to improve survival at 2 years by at least 30%. [4]

Imatinib mesylate (IM) has dramatically improved the outcome of patients with advanced GIST, from a 5-year overall survival (OS) rate of 10% before the imatinib era to around 50% since its introduction.5 The BFR14 trial, performed within the French Sarcoma Group, addressed the question of optimal imatinib treatment duration by randomizing patients after 1, 3, and 5 years to treatment interruption or maintenance [5]. Imatinib interruption results in rapid progression in the vast majority of patients with advanced disease, strongly suggest that patients in complete response (CR) under imatinib still have residual disseminated, persistent active tumor cells and show that it is not safe to interrupt imatinib on the basis of a CR by standard morphological criteria, even after long treatment 5 . After a median follow-up of 73 months 84 events (deaths) were observed (38%), overall median OS was 99 months, Overall median PFS was 33 months. This analysis shows that the nature and topography of KIT exon 11 mutations, along with specific clinic biological factors, are prognostic and predictive of PFS and OS for advanced GIST patients treated with standard-dose IM. Despite a favorable sensitivity to imatinib, GIST patients harboring a codon 557e558 alteration develop secondary resistance more rapidly. [5]

According to Phase III Trial of Imatinib Mesylate for Treatment of Advanced Gastrointestinal Stromal Tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group, Correlation of Kinase Genotype and Clinical Outcome in the North American, 2008, The presence of KIT exon 11–mutant genotype (n 283) correlated with improved treatment outcome when compared with KIT exon 9–mutant (n 32) and wild-type (WT; n 67) genotypes for objective response.[6]

At 24 weeks, according to the Southwest Oncology Group criteria (SWOG), 49.3 % of patients had a partial response [21] and 31.5 % had stable disease (SD) in the 400 mg imatinib group, while 58.1 % had a PR and 24.3 % had SD in the 600 mg imatinib group .[6]

It is therefore important to identify the patients with metastatic GIST who are more likely to have sustained disease control on long-term imatinib therapy to ensure compliance and avoid treatment interruption.

Although the 2-year survival of patients with metastatic GIST treated with imatinib approximates 72%, half of the patients develop disease progression by2 years. Patients with tumours harbouring the KIT exon 9 mutations have significantly better progression-free survival (PFS) on

a higher dose level, i.e. 800 mg daily, which is therefore held as standard treatment in this subgroup [18]

According to French Sarcoma Group study Long-term responders had the following characteristics: female gender, good performance status, long delay between diagnosis and imatinib treatment, low tumor volume at inclusion, normal hemoglobin level at inclusion, and normal lymphocyte count at inclusion. Association between tumor size at treatment initiation and PFS and OS supports the importance of early diagnosis and early treatment with imatinib. [5].

Minor gastrointestinal effects are commonly associated with imatinib treatment. Nausea is one of the most common dose-related adverse events observed with imatinib. A common hematological side effect in GIST patients is anemia. Long-term imatinib treatment can effectively control disease progression in many patients with metastatic GIST, but this can only be achieved if patients stay on imatinib therapy and maintain appropriate dosing. [2]

2. Objectives

2.1 General Objectives

To the study Demographics, Clinical Presentation and Outcome of GIST Patients Treated with Imatinib at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, a 17 year's retrospective study.

2.2 Specific objective

- To asses Specific response of imatinib in metastatic and adjuvant therapy.
- To study the safety profile of imatinib in patients with unresactable or metastatic GIST and adjuvant therapy.

3. Methodology

3.1 Study Design

A retrospective cross sectional design

3.2 Study site

The study conducted in the hematology referral clinics of Tikur Anbessa specialized hospital (TASH), a teaching hospital in Addis Ababa, Ethiopia.

3.3 Study period

The study included patients with GIST enrolled in the Glivec International Patient Assistance Program (GIPAP) from January 1 2004 to August 30, 2021.

3.3 Populations

3.3.1 Source population

All patients diagnosed to have histologically proven GIST taking imatinib as adjuvant or for metastatic disease in the study period, from January 1 2004 to August 30, 2021.

3.3.2 Study Population

All patients diagnosed to have histologic proven, GIST taking imatinib as adjuvant or for metastatic disease in the study period, from January 1 2004 to august 30, 2021.

3.4 Sample size

All patients diagnosed with advanced GIST on imatinib on follow up at Hematology clinic from January 1 2004 to June 30, 2021 were included.

3.5 Inclusion Exclusion criteria

3.5.1 Inclusion criteria

Histologically confirmed GIST which is unresactable and/or metastatic or the need for Adjuvant therapy.

3.5.2 Exclusion criteria: No exclusion criteria

3.6 Variables

3.6.1 Independent variables

Age, sex, functional status, complete blood count, weight, serum albumin, comorbid illness

3.6.2 Dependent variables

- Complete remission
- Partial remission
- Stable disease
- Progressive disease

3.7 Data collection and analysis method

Data of all patients linked to hematology referral clinics with tissue examination and diagnosis of GIST, for metastatic/adjuvant imatinib treatment from January 1 2004 to august 30, 2021 gathered from patents chart, computer I care system using validated structured questionnaire analyzed using SPSS 25 statistical package. Mainly descriptive analysis is done.

3.8 Operational definition

Complete remission: Disappearance of all target lesions

Partial remission: ≥30 percent decrease in the sum of the longest diameter of the target lesions compared with baseline

Progressive disease:≥20 percent increase in the sum of the longest diameter of the target lesions compared to the smallest sum of the longest diameter recorded since treatment started OR The appearance of one of more new lesions.

Stable disease: Neither Progressive disease nor Partial remission

4. Ethical consideration

Ethical clearance obtained from research ethics committee of the College of Health Sciences, school of medicine in written form.

5. Dissemination of Results

After the completion of the research, the result will be presented to the department of Internal medicine. Research findings will be sent to both national and international medical journals for possible publishing and it will be disseminated through internet to different medical sites.

6. Results

6.1 Demographic characteristics

Out of hundred GIST patients, Fifty eight patients with pathologically confirmed GIST with complete clinical information and CT was analyzed. The median age is 52 and 41% of them were above fifty five years of age .Thirty two (55%) of GIST patients were male and twenty six (45%) were females with slight male preponderance (1.2:1). Majority of the patient are from Addis Ababa (62%), followed by Amhara (17%) region. (Table1).

Table 1.Demographic Data

Variable	**Demographics**	**Number of patients (Percentage)**
Sex	Male	32 (55%
	Female	26(%45)
Age	<=34	4(6.9%)
	35-44	12(20.7%)
	45-54	18(31%)
	>=55	24(41.38%)
Address	Addis Ababa	36(62%)
	Amhara	10(17%)
	SNNPPR	5(8.6%)
	Oromia	5(8.6%)
	Tigray	2(3.45%)
Residency	Urban	51(88%)
	Rular	0
	Unkown	7(12%)
Total	Total	58(100%)

6.2 Patient characteristics

According to ECOG performance status scoring, forty five (86%) of patients had score of 0, seven (20%) had a score of 1, and six (10%) had a score of 2. Eighteen patients had comorbid condition commonly hypertension Nine(15%), followed by Diabetes and Cardiovascular disease

(5.1% each).Renal disease, Chronic liver diseases, HIV each of them accounts only 1 % (table 2).

Those whose baseline investigation was determined seventeen (29.3%) had low hemoglobin, six (10%) low absolute lymphocytes counts, two (3.5%) had raised serum creatinine, and forty (24%) had low serum albumin. (Table3.)

Table 2.Comorbid condition and performance status

Hypertension	9(15.5%)
Diabetes	3(5.17%)
Cardiac disease	3(5.17%)
Renal disease	1(1.7%)
Chronic liver disease	1(1.7%)
HIV	1(1.7%)
Performance status (ECOG)	
0	45 (77.59 %)
1	7 (12.07 %)
2	6 (10.34%)

Table 3.Baseline investigation

Variable		Number of patients (%)			
CBC		Normal	Low	High	Total
	ANC	51(88%)	1(1.7%)	6(10.3%)	58(100%)
	ALC	49(85%)	6(10%)	3(5%)	58(100%)
	Hemoglobin	39(67.24%)	17(29.31%)	2(4%)	58(100%)
	Platelet	46(79%)	1(1.7)	11(19%)	58(100%)
RFT	Creatinine	55(96.5%)	0	2(3.5%)	57(100%)

LFT	ALT	53(95%)	0	3(5%)	56(100%)
	AST	51(91%	0	5(7%)	56(100%)
	Albumin	44(79%)	14(24%)	0	58(100%)

6.3 Tumor characteristics

Thirty seven (64%) had tumor that originated from stomach, seventeen (29.3%) from small bowel, two (3.4%) from omentum, respectively .Morphologically predominantly spindle-shaped in thirty five (60%) to epithelioid in character in five (8.6%), mixed in three (5.5%).

Thirty four (59%) had stage 1 disease and identified as high risk characteristics and twenty two (38%) had stage 4 disease classified as metastatic disease. Metastasis to liver occurred in nine (15.5%) of patients, to the lung in three (5.1%), to the peritoneum two (3.4%) to, one had bone metastasis. The median tumor size was 10.7 and Surgical resection was the most frequent treatment, done on fifty (86.2%) patient, and one patient had resection two times for recurrent disease There was no prior treatment with systemic chemotherapy or radiation.(table 4).

Table 4. . Patient and tumor characteristics

Median age (range)	52 (20-83)
Number of males (%)	32(55%)
Median of GIST diagnosis in years	3.32
Site of tumor origin	
Stomach	37 (63.79%)
Small bowel	17 (29.31%)
Large bowel	1 (1.72%)
Omentum	2 (3.45%)
Peritoneum	1(1.72%)
Morphology	

Spindled	35(60.34%)
Epithelioid	5(8.62%)
Mixed	3(5.17 %)
Unknown	15(25.86 %)

First site of metastasis

Peritoneum only	2(3.45%)
Liver only	9(15.52%)
Peritoneum and liver	2(3.45 %)
Other	4 (6.90%)

Table 4.1 Tumor characteristic

Size of tumor at baseline

<5cm	1(1.75%)
5-10 cm	35 (61.40%)
>10cm	21(36.84%)

Stage of the diseases

Stage one	34(58.62%)
Stage two	0
Stage three	2(3.45%)
Stage four	22(37.93%)

Treatment modalities

Total tumor resection	50(86.21%)
None	8 (13.79 %)

6.4 Response Assessment

The median duration of treatment with imatinib was 2.9 year (range 0.3-10 year),out of five patients , who had follow up CT scan at three month, one patient achieved complete remission (CR), three had Partial response (PR),only one showed progressive disease(PD) with development of new lesion .

At 6month follow up CT, out of a total of eighteen patients, ten patients achieved CR,seven had PR ,one had stable disease (SD).there was no PD.

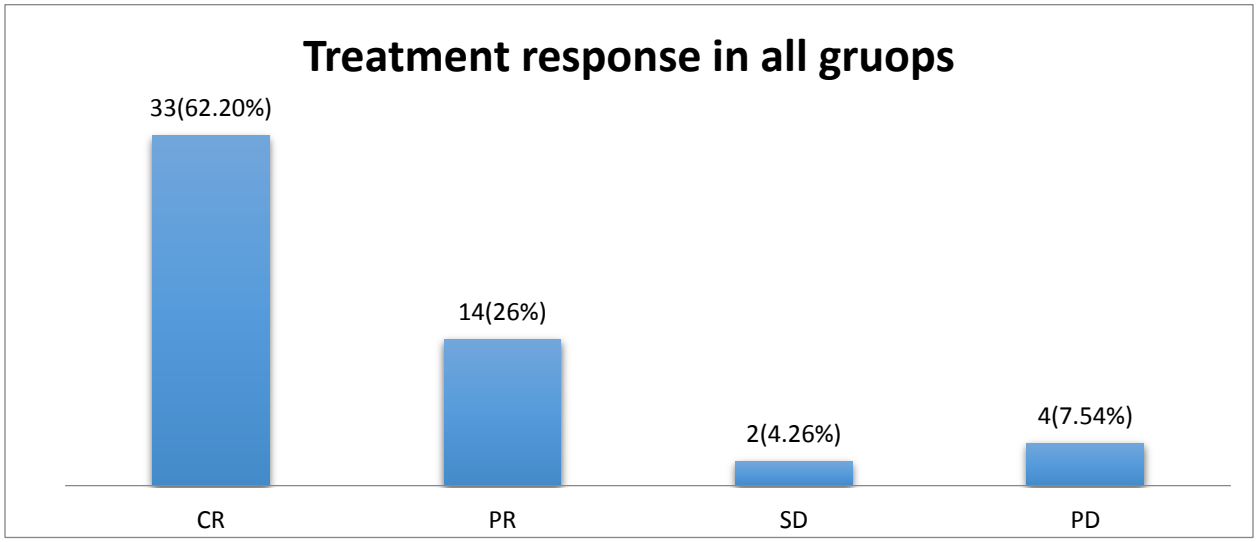
At twelve month follow up CT, from a total of twenty one patients eighteen patients achieved CR, two had PR, only 1 had PD.Among nine patients who had follow up CT at 2 year CR is achieved in four , PR in two, two had PD with new lesion , and one had SD.(table 5).

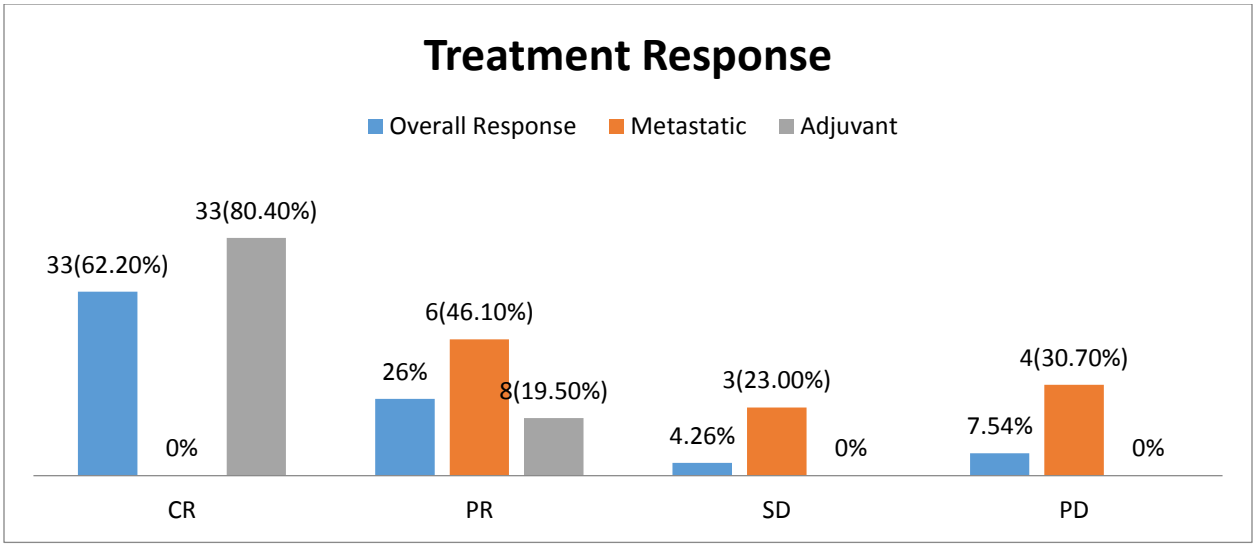
Out of the fifty eight patient seven patients died. Six of them had metastatic disease, old, with poor performance status and had more than one comorbid condition. Only one had stage 1 disease but old had hypertension and diabetes. For those patients the median duration of imatinib treatment was six month (ranging from 2-12 month).

Putting together the overall response at any duration, out of 53 patients who had follow up CT, thirty three(62.2%) patients achieved CR, fourteen (26%) had PR ,two patients had SD and only four(7.54%) patients had PD.

Table 5.Response assessment

RESPONSE	Number of patients (%			
	At 3 month	At 6 month	At 12 month	At 24 month
CR	01(20%)	10(55.5%)	18(85.7%)	04(28.57%)
PR	03(60%)	07 (38.8%)	3 (11.54%)	02(22.2%)
SD	0 (0%)	01 (5.5%)	0(%)	02 (22.2 %)
PD	01(20%)	0(0%)	01 (4.7%)	01 (11.1%)





6.5 Imatinib toxicity

Dose of Imatinib initiated was 400mg later increased to 800mg for advancing disease in 3 patients. In this analysis imatinib treatment was well tolerated .only two patients had discontinued Imatinib for, one leukopenia, for poor compliance for two weeks. Twenty seven of GIST patients treated with Imatinib experienced mild adverse effect transiently .Fatigue skin rash, edema were the commonest compliant.

Table 6.Durationof treatment and documented complications of Imatinib treatment

Duration of Imatinib treatment	
<1	12(20.69%)
1-4	34(58.62%)
4-8	11(18.97%)
>=8	1(1.72%)
Adverse events	
Fatigue	9
Skin rash	8
Edema	7

Diarrhea	7
Nausea	3
Myalgia or musculoskeletal pain	3

7. Discussion

This study provides the first retrospective description of GIST patients treated with Imatinib in Ethiopia. Imatinib Mesylate is a potent and selective inhibitor of tyrosine kinases, including the ABL kinase, KIT, PDGFRa, PDGFRb, and the collagen receptor discoidin domain receptor, was the first agent with significant activity to be used in the treatment of metastatic GIST. The treatment modalities and outcome of patients before imatinib era is unknown in Ethiopia.

A total of 58 histologically confirmed, with CD 117 positivity patients with complete clinical and CT scan were analyzed .The median age at diagnosis in of our patients was 52 years, which makes our patients younger than the mean age at diagnosis of 65 years in western countries, which is around 60–65 years and about 27.6% of our patients in this study were less than 45 age. There is a slight male predominance and majority of the patients are from Addis Ababa.

According to French Sarcoma Group study Long-term responders had the following characteristics: female gender, good performance status, and imatinib treatment, low tumor volume at inclusion, normal hemoglobin level at inclusion, and normal lymphocyte count at inclusion.(2). Of the 58 GIST patients at baseline, 44(79%) had normal serum albumin, 49(85%) had normal lymphocyte count, 39(67%) had normal hemoglobin and 45(78%) had good performance status.

Stomach was the commonest origin of GIST accounting for 64% in our patient, and spindle shape is the predominant histologic variant. The median size of the tumor was 10.7cm. Histologic analysis of eighteen tumor done in TASH between 2007 to 2007 ,82% was spindle cell tumors, in contrast there was only a single tumor which arise from stomach, ,the most common site was small bowel 53% and large bowel 35% , in this study 29% from small bowel and only one tumor from large bowel.(18)

From the fifty eight patients referred to hematology clinic, sixteen patients had metastatic disease and the remaining was high risk patients referred for adjuvant imatinib treatment. Metastasis to liver was the commonest site occurred in nine (15.5%) patients, to the lung in three (5.1%), to the peritoneum two (3.4%), one had bone metastasis. Based on the Japan study on, the most metastatic GISTs were located in the liver (n = 11; 55%). The other metastatic sites were the peritoneum (n = 7), bone (n = 4), lung (n = 2), soft tissue (n = 2) which is similar patterns of spread with our study. (19)

The majority of patients were treated with surgical resection of the primary tumor. From a total of forty two patients taking adjunctive imatinib treatment thirty three (78.5%) achieved CR, and eight (19) patients was in PR. Adjuvant treatment with imatinib for 3 years was associated with a relapse-free survival (RFS) and OS advantage in comparison with 1 year of therapy in high-risk patients in a randomized trial.(13)

Out of sixteen patients with metastatic diseases, six (37.5) achieved PR, three (18.75) had SD four (25%) had PD, showed similarity with the Japan study, two out of 20 patients achieved PR (10%) and 18 patients (90%) were classified with SD. Only 4 patients showed PD during imatinib treatment. At 24 weeks, according to the Southwest Oncology Group criteria (SWOG), 49.3 % of patients had a partial response [21] and 31.5 % had stable disease (SD) in the 400 mg imatinib group. The use of imatinib in metastatic GIST is associated with an approximately 72% 2-year survival and the median survival is 58 months (19,6, 3).

Of Seven patients, (six with metastatic GIST, one patient from adjuvant treatment group) died. The exact cause and circumstance of death was not documented .Three out of six had two comorbid conditions (hypertension, DM,RVI).The median duration of imatinib treatment for the patients was six month and had poor performance status .From the Japanese study only One patient died with pneumonia who under imatinib treatment.(19).

The maximum duration of imatinib treatment in this study is eleven years .The long-term results from the BFR14 study demonstrate that rapid disease progression occurs if imatinib is interrupted or stopped in non-progressive GIST patients who achieve an objective response or SD with imatinib therapy. These results support the conclusion that imatinib should not be

interrupted or stopped in non-progressive patients with advanced GIST who are able to tolerate the drug. (5).

Imatinib treatment was well tolerated drug for all patients in this study. Only one discontinued for two week for neutropenia. Fatigue occurred in nine(33%) patients, Skin rash eight(28.5%),edema in seven(25%) , diarrhea in seven(25%),nausea in three(10.7%) patients ,myalgia in three(10.7%) which shows similarity with the Japanese study , frequent adverse events were fatigue (65%), edema (35%), diarrhea (35%), nausea (25%) and skin rash (10%).No patients had discontinued imatinib treatment due to toxicity or adverse events.). Grade 3 or 4 adverse events occurred in neutropenia (n = 2; 10%), anemia (n = 3; 15%) and elevated creatinine (n = 1; 5%). (4).

8. Strength and limitation of the study

8.1. Strength

This study is the first study showing the status of GIST patients treated with imatinib in Ethiopia in general and provide baseline information for designing prospective follow up of patients.

8.2 Limitations

Early decrease in tumor density, disease progression in patients with GIST may also fail to be captured by standard RECIST.

9. Conclusion

This study showed Imatinib had a high efficacy both in patients with unresectable GIST/metastatic GIST and in those given as adjuvant treatments at the TASH.However it was more effective as adjuvant treatment. Since this is an ongoing study, more matured data will be obtained soon.

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Annex 1

Data Collection Form.

Serial No: _____ (use only 3 digit)

Chart Number (MRN):_____

A. Demographic data

Sex: _____

Age: _____

Address (Region): _____

Area of residence: 1, Urban___2, Rural___3, Unknown___

Date of GIST diagnosis (pathology report): _____

Stage of the disease; _____

Date of Surgical treatment: _____

Presence of comorbid illness(can mark multiple answer)

1, HTN_____ 2, DM_____3, Cardiac illness_____4, Renal disease _____5, CLD_____6, HIV____

Performance status

1=0

2=1

3=2

Baseline investigations (before initiation of IM)

CBC = Total WBC _____Neutrophil %, _____ANC_____ lymphocyte %_____

Hemoglobin _____, platelets_____

RFT, Scr_____, BUN_____

Liver biochemical test, ALT_____, AST_____serum Albumin ____

B.Tumor characterstics

Site of tumor origin

1, stomach

2, small bowel

3, large bowel

4, omentum

5. Unknown

Primary tumor size

1, 5cm

2, 5-10cm

3,10cm

D, unknown

Morphology

1, Spindled 2, Epithelioid

3, Mixed 4, Unknown

Margin status of primary tumor

4.1, Microscopic

1, Negative 2, Positive 3, Unknown

4.2, Gross

1. Negative 2, Unknown

First site of metastasis

1, Peritoneum only

2, Liver only

3, Peritoneum and liver

4, other, specify

5, Unknown

C, Treatment modalities

1, Total tumor resection

2, Liver resection

3, percutaneous ablation of liver lesion

4, Embolization

5, Radiofrequency ablation

6, Alcohol injection

Any chemotherapy

Yes_____,No_____

If yes which

1, Systemic chemotherapy_____

2, Intraperitoneal chemotherapy _____

Any radiation

Yes ____No_____

If yes which

1, External beam _____

2, Brachytherapy _____

Multiple resections, for relapse No_____Yes_____If yes how many

1=2 resections

2=3 resections

D. Medical Treatment

1. Date of imatinib initiation, _____Dose of Imatinib suggested_____

2, Duration _____

3, History of discontinuation of imatinib? Yes_____No_____

4, if the answer to number 3 is a yes how long? _____

5, Reason for discontinuation___

1. Adverse effect

1. Leukopenia, 2, Anemia, 3, thrombocytopenia

2, Imatinib not available

3, Personal (poor compliance

4, Death

5, Other,specify _____

E, Response

1, computed tomography Result

Size of the tumor at baseline, prior to imatinib initiation_____

1, <5cm

2, 5-10cm

3,>10cm(mention the size_____)

Size of the tumor after imatinib initiation _____

1, at 3 month _____ 2, at 6 month _____3, at 12 month

Is there new lesion? YES_____NO _____if yes how many? _____

D, Lesion disappeared? Yes___,No____

F. Current status

1, Alive in remission

2, Alive in partial remission

3, No response, referred back to surgery

4, Not respond to imatinib, shifted to sunitinib

5, Dead

G,Toxicity

1, Any adverse effect during treatment? Yes_____ No_____

2, If the answer to the above question is a yes which of the following occurred (can mark multiple answer)

1, Edema

2, Nausea

3, Diarrhea

4, Myalgia or musculoskeletal pain

5, Fatigue

6, Dermatitis (skin rash)

7, Headache

8, abdominal pain

9, Cytopenia ___9.1, Neutropenia, _____9.2, Anemia, _____ 9.3, Thrombocytopenia, _____9.4, Elevated creatinine ,_____