





Gastrointestinal stromal tumours at Inkosi Albert Luthuli Central Hospital from 2005 to 2015



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Background: Gastrointestinal stromal tumour (GIST) is the commonest mesenchymal malignancy of the gastrointestinal tract. Patient demographics and outcomes following imatinib therapy in South Africa are unknown.

Aim: To establish the patient demographics of GIST and the clinical outcomes following imatinib therapy.

Setting: Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa.

Methods: A quantitative, retrospective, descriptive chart review study was conducted. The study population included patients with a histologic diagnosis of GIST who presented between January 2005 and December 2015 to the facility. Only patients who received imatinib were included in the clinical outcome analysis.

Results: Sixty-nine patients were seen during the study period. The mean (SD) age at diagnosis was 57.3 (13.5) years. The male gender (53.6%) was predominant, the black ethnic group (53.6%) was the commonest and the stomach (69.6%) was the most common disease site. Localised disease (53.6%) was the commonest disease category, while high risk (29.7%) and intermediate risk (29.7%) were the majority risk categories. Thirty-six (52.2%) patients received imatinib with a median (IQR) follow-up time of 20.5 (38) months. Eighty-one per cent of patients with localised disease remained in remission after adjuvant imatinib, and 18.2% developed metastatic recurrence. Among patients with locally advanced disease, 81.8% attained partial response on neoadjuvant imatinib, while 9.1% had stable disease. Most (75%) patients with metastatic disease attained partial response as the best response to imatinib. The most common adverse effects were anaemia and fluid overload.

Conclusion: At IALCH, GIST is more common in the male gender, black ethnic group and in the stomach. The majority of localised and locally advanced GIST patients have favourable outcomes on imatinib. However, most metastatic GIST patients eventually develop resistance to imatinib necessitating further treatment options.

Keywords: imatinib therapy; gastrointestinal stromal tumours; imatinib; sunitinib; Inkosi Albert Luthuli Central Hospital.

Introduction

Gastrointestinal stromal tumour (GIST) is a malignancy that arises from the mesenchyme of the gastrointestinal tract (GIT). Despite being the commonest mesenchymal malignancy in the GIT, it constitutes less than 1% of all GIT malignancies.^{1,2,3,4} Globally, the epidemiology of GIST is not well known. According to a population-based study from the United States, the age at diagnosis ranges from 20 to 98 years, with a mean age of 62.9 years. Eighty per cent of patients are diagnosed above the age of 50, with those presenting below the age of 20 being rare. This study has also shown a slight male predominance in the prevalence of GIST with 54% of the cases occurring in male patients. Seventy-four per cent of patients were white people, 14% black people and 15% belonged to other ethnic groups.⁵ The interstitial cells of Cajal, found in the myenteric plexus of the GIT, are the cells of origin of this malignancy.^{6,7} Gastrointestinal stromal tumour occurs throughout the GIT with 60% to 70% occurring in the stomach and 30% in the small intestine.^{1,2} Of these tumours, 5% have been found to arise from the colon, 4% from the rectum and 1% from the oesophagus.⁵ There is a lack of information on the demographic and anatomic distribution of GIST in South Africa.

Several genetic mutations are responsible for the pathogenesis of GIST. *c-KIT* and platelet-derived growth factor receptor alpha (*PDGFRA*) mutations are the commonest, occurring in 80% and

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5% – 10% of GISTs, respectively.^{8,9,10} These mutations are mutually exclusive¹⁰; 10% – 15% of GISTs lack both *c-KIT* and *PDGFRA* mutations and are known as wild-type GIST.¹¹ These constitute mutations on succinate dehydrogenase (*SDH*), *BRAF* and neurofibromatosis type 1 (*NF-1*) genes.^{12,13,14,15,16,17,18} A South African series found *c-KIT* and *PDGFRA* mutations in 78.3% of GISTs, while wild-type GIST was found in 21.7% of the population.¹⁹ Immunohistochemical staining for CD117 (*KIT* immunostaining), *DOG1* and *CD34*, and genetic molecular testing for *c-KIT* and/or *PDGFRA* mutations are used to diagnose GIST.^{4,8,20} Both *CD34* and *DOG1* are highly expressed in GIST, and *DOG1* immunostaining may be useful for cases that cannot be categorised as GIST based on *CD117* immunostaining.^{8,20}

Despite being the treatment modality of choice, surgery alone is not curative for all GIST patients. Half of the patients with operable disease undergoing surgery alone develop local or metastatic recurrence.²¹ The 5-year survival rate of these patients is approximately 50%,²² while the median time to recurrence after resection alone of high-risk GIST is 2 years.^{8,23} These facts underscore the importance of additional therapy in the management of this disease. Imatinib, a small molecule tyrosine kinase inhibitor (TKI) with activity against *c-KIT* and *PDGFRA* tyrosine kinases, is the first-line treatment agent for GIST patients with locally advanced and metastatic disease. Imatinib use has improved the overall survival of these patients.⁶

Several prognostic factors have been shown to affect the outcome of patients treated with surgery. These include tumour size, mitotic index, anatomic disease location and tumour rupture (before or during surgery).^{1,2,9,24,25,26} Tumour size and mitotic index are used to stratify GISTs, according to their postoperative risk of recurrence and metastasis, into very low, low, intermediate and high risk.⁹ High-risk GIST patients who receive adjuvant imatinib for 3 years have 5-year overall and recurrence free survival rates of 92% and 65.6%, respectively,²⁷ while those with metastatic GIST on palliative imatinib have a 9-year survival rate of 35% – 49%.²⁸ Locally advanced GISTs are often unresectable or borderline resectable with significant surgical morbidity. Cytoreduction with neoadjuvant imatinib reduces this surgical morbidity.²⁹ It is generally accepted that patients who require neoadjuvant imatinib should receive imatinib postoperatively for a cumulative period of 3 years. After prolonged exposure to imatinib, patients with metastatic GIST eventually develop resistance to it. Sunitinib and regorafenib are small molecule TKIs approved to treat patients with advanced GIST in the second- and third-line settings, respectively.^{8,30,31} Sorafenib, nilotinib, dasatinib and pazopanib are TKIs that have shown activity in phase II trials.^{32,33,34,35} There is a lack of information on the clinical outcomes and prognostic factors of GIST patients treated with imatinib in South Africa.

Aim

To establish the patient demographics of GIST and the clinical outcomes following imatinib therapy.

Methodology

This was a quantitative, retrospective, descriptive chart review study that was conducted at Inkosi Albert Luthuli Central Hospital (IALCH). The study population included patients with a histologic diagnosis of GIST who presented between January 2005 and December 2015 to the facility. Only patients who received imatinib were included in the clinical outcome analysis. This analysis was performed separately for patients with localised, locally advanced and metastatic disease. Localised disease was defined as operable disease with no distant spread. Locally advanced disease was defined as inoperable or borderline operable disease with no distant spread, and metastatic disease was defined as disease with distant spread at the time of diagnosis. There was no direct patient contact in this study, and therefore, informed consent was not required.

Patient data were collected from an electronic medical records database (speed minor) using ICD-10 codes. Age, gender, ethnicity, anatomic location, immunohistochemical stain, disease category, risk category (for localised disease), clinical outcome, adverse effects and death were analysed. Patients with localised disease were stratified according to their postoperative risk of recurrence and metastasis, using the American National Institutes of Health criteria.⁹

Clinical outcome analysis was based on the evaluation of serial computer tomography (CT) and positron emission tomography (PET) scan imaging. Patients with localised disease were analysed as either being in remission, local recurrence or metastatic recurrence. Objective responses (partial response, stable disease and progressive disease) for locally advanced and metastatic disease were analysed using Response Evaluation Criteria in Solid Tumors (RECIST 1.1)³⁶ and European Organisation for Research and Treatment of Cancer (EORTC)³⁷ criteria. Factors affecting clinical outcomes were analysed for each disease category. Adverse effects experienced by more than 5% of patients on imatinib were analysed. Stratification of adverse effects was done for the two most common adverse effects: anaemia according to the Common Terminology Criteria of Adverse Effects (CTCAE)³⁸ and fluid overload according to the site of fluid overload. Patients were censored at the time of loss to follow-up, when they got transferred to a different hospital, placed on best supportive care only and at the end of the study period.

Statistical analysis and ethics

IBM SPSS Statistics version 25 was used to perform statistical analysis. Descriptive statistics (frequencies and percentages) were calculated to summarise categorical data. Measures of central tendency (mean and median) and measures of dispersion (standard deviation and interquartile range) were calculated for numerical variables. A histogram and bar graphs were used to display distribution of numerical data. One-sample Kolmogorov–Smirnov test was used to test the distribution of age. Spearman's rho correlation coefficient

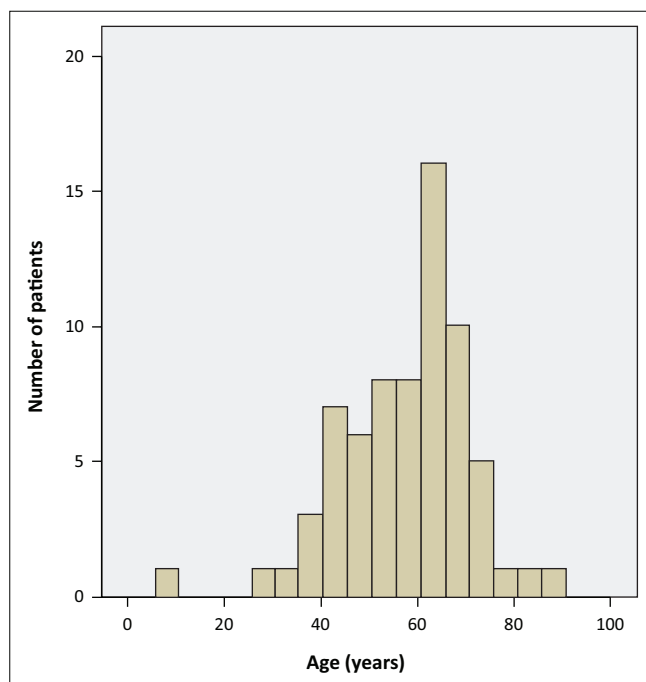
was calculated to measure the strength of linear correlation between age and number of adverse effects. Kruskal–Wallis test was used to test the null hypothesis that number of adverse effects is the same on average for patients in different disease categories and risk categories. Mann–Whitney U test was used to test the null hypothesis that the number of adverse effects is the same for male and female patients. Fisher’s exact test was used to test for association between categorical variables. A *p*-value less than 0.05 was considered statistically significant.

Ethical considerations

Ethical approval was granted by the KwaZulu-Natal Department of Health (reference number: HRKM234/16 KZ_2016RP25_355) and the Biomedical Research Ethics Committee of the University of KwaZulu-Natal.

Results

Between January 2005 and December 2015, 69 patients with GIST were evaluated at IALCH. The mean (SD) age at diagnosis (Figure 1) was 57.3 (13.5) years. Seventy-five per cent of the patients were above the age of 50, and only one patient was younger than 20 years at the time of diagnosis. In the study population (Table 1), there was a slight male predominance (53.6%), and majority of the patients were of black ethnicity (53.6%). The stomach (69.6%) was the commonest disease site followed by the small intestine (13%). The urinary bladder (1.4%) and oesophagus (1.4%) were the least common anatomic sites of disease. Out of the three disease categories (Table 1), localised disease (53.6%) was the commonest, while high risk (29.7%) and intermediate risk (29.7%) were the commonest observed postoperative risk categories. CD117 (Figure 2) was the



Mean = 57.26; standard deviation = 13.519; total number of patients = 69.

FIGURE 1: Age distribution.

commonest observed immunohistochemical marker in this patient population, with 21.7% of the cases having unknown immunohistochemical expression.

Thirty-six (52.2%) patients were treated with imatinib during the study period (Figure 3). The follow-up time ranged from 1 month to 108 months with a median (IQR) of 20.5 (38) months. Eleven patients were lost to follow-up during the study period. The median (IQR) duration of imatinib treatment was 12 (10) months, 18.5 (36.1) months and 43.5 (35) months for localised, locally advanced and metastatic disease, respectively. Eleven patients with localised disease received imatinib in the adjuvant setting. Six of these had

TABLE 1: Patient demographics and disease characteristics.

Variable	Number (%)
Gender	
Male	37 (53.6)
Female	32 (46.4)
Ethnicity	
Black people	37 (53.6)
Asian people	17 (24.6)
White people	9 (13.0)
Mixed race people	5 (7.2)
Unknown	1 (1.4)
Anatomic location	
Stomach	48 (69.6)
Small intestine	9 (13.0)
Mesentery	4 (5.8)
Rectum	2 (2.9)
Peritoneum	2 (2.9)
Oesophagus	1 (1.4)
Urinary bladder	1 (1.4)
Unknown	2 (2.9)
Disease category	
Localised	37 (53.6)
Locally advanced	13 (18.8)
Metastatic	18 (26.1)
Unknown	1 (1.4)
Risk category (localised disease)	
Very low risk	2 (5.4)
Low risk	6 (16.2)
Intermediate risk	11 (29.7)
High risk	11 (29.7)
Unknown	7 (18.9)

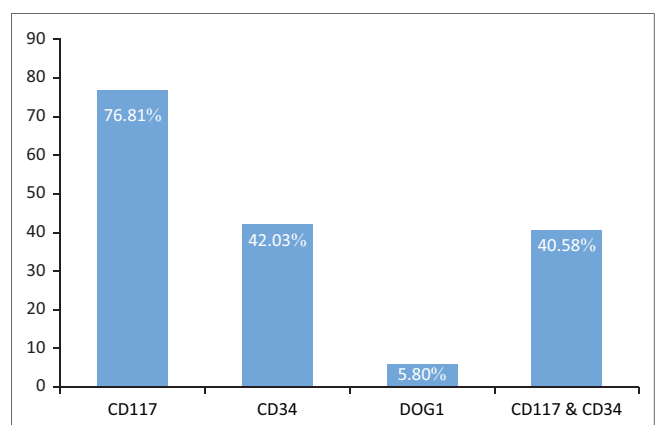


FIGURE 2: The immunohistochemical expression of gastrointestinal stromal tumour.

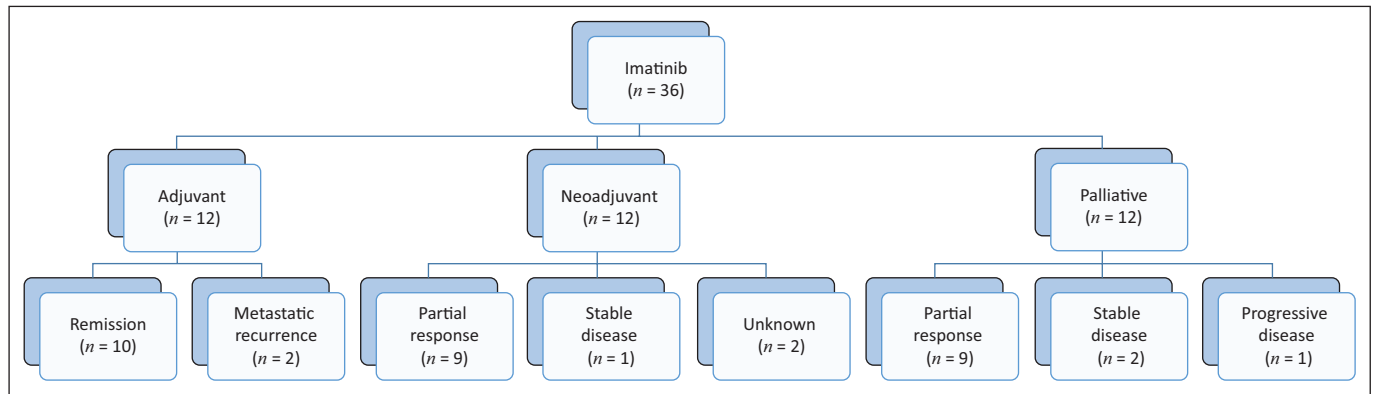


FIGURE 3: Imatinib indications and objective responses.

high-risk disease, while five had intermediate-risk disease. Five patients with high-risk disease did not receive imatinib. One of them died of postoperative complications, while the remaining four were not referred for adjuvant therapy. Nine (81.8%) of the 11 patients treated with adjuvant imatinib remained in remission, and two (18.2%) developed metastatic recurrence. Seven (77.8%) of the patients who remained in remission had the stomach as the primary disease site, five (55.6%) had intermediate risk disease and six (66.7%) had complete gross resection. Three patients in remission had incomplete surgical resection (two with microscopic and one with macroscopic residual disease). Both patients with metastatic recurrence had high-risk disease. One of them declined adjuvant imatinib after receiving it for 12 months. There were no locoregional recurrences observed among these patients.

All 13 patients with locally advanced disease were treated with imatinib. One of these (9.1%) had primary resection and remained in remission after adjuvant imatinib. The remaining 12 patients received neoadjuvant imatinib for a median (IQR) of 8.5 (11.25) months (range 2–36 months). Partial response (PR) was observed in nine (81.8%) patients. Six of these underwent surgical resection, two declined surgery and one was medically inoperable. Most patients (four) who attained partial response had disease located in the stomach. Stable disease (SD) was observed in one (9.1%) patient who subsequently underwent debulking surgery. None of the patients with locally advanced GIST had complete response (CR) or progressive disease (PD) after neoadjuvant imatinib. The outcome of two patients with locally advanced disease was not known.

A total of 12 (66.7%) patients with metastatic disease received imatinib treatment, while six did not. Two of these six patients were in a poor clinical condition to receive imatinib. It is unknown why the remaining four patients did not receive imatinib. Out of the patients that received imatinib, nine (75%) attained PR, two (16.7%) attained SD and one (8.3%) developed PD. Eight (88.9%) of the patients that attained PR, and two patients that attained SD had the primary disease in the stomach. The patient that developed PD had the peritoneum as the primary site of disease. Nine (75%) patients

with metastatic disease eventually progressed on imatinib with a median (IQR) time to progression of 40.5 (47.25) months (range 3.5–84 months). Seven of these patients were placed on an increased dose imatinib (800 mg daily), while the remaining two were placed on best supportive care because of their poor clinical condition. Four patients developed disease progression on increased dose imatinib and three patients could not tolerate it. Across all disease categories, there was a total of three deaths recorded during the study period. Two of these deaths occurred as a result of surgical complications and one as a result of disease progression.

Out of the 36 patients treated with imatinib, 31 (86.1%) experienced adverse effects. The two commonest adverse effects (Figure 4) were anaemia (83%) and fluid overload (31%). Grades III, II and I anaemia were found in 43.3%, 23.3% and 33.3% of the patients, respectively. Grades IV and V anaemia were not observed in this patient population. Fluid overload was in the form of pedal oedema (72.7%), facial oedema (18.2%), ascites (18.2%), hand oedema (9.1%) and pleural effusion (9.1%). Male patients (64.5%) had more adverse effects than their female counterparts. Patients with metastatic disease experienced the most adverse effects with a median of 4 (range 0–10) adverse effects. These were followed by those with locally advanced and localised disease with a median of 2 (range 0–4) and 1 (range 0–6) adverse effects, respectively. Risk category and age, however, did not influence the occurrence of adverse effects in this patient population. A total of five (13.9%) patients had their imatinib treatment interrupted because of adverse effects. One of these was as a result of Grade III anaemia, two as a result of fluid overload (ascites and pleural effusion) and two as a result of Grade III diarrhoea.

Discussion

This study describes the demographics of GIST patients and their treatment outcomes after imatinib therapy at IALCH. Similar to previous research,^{5,39} GIST has been found to occur mainly in older patients with three quarters of the study population having been diagnosed above the age of 50. This study has also established that GIST is rarely diagnosed below the age of 20 with only 1.4% of the study population

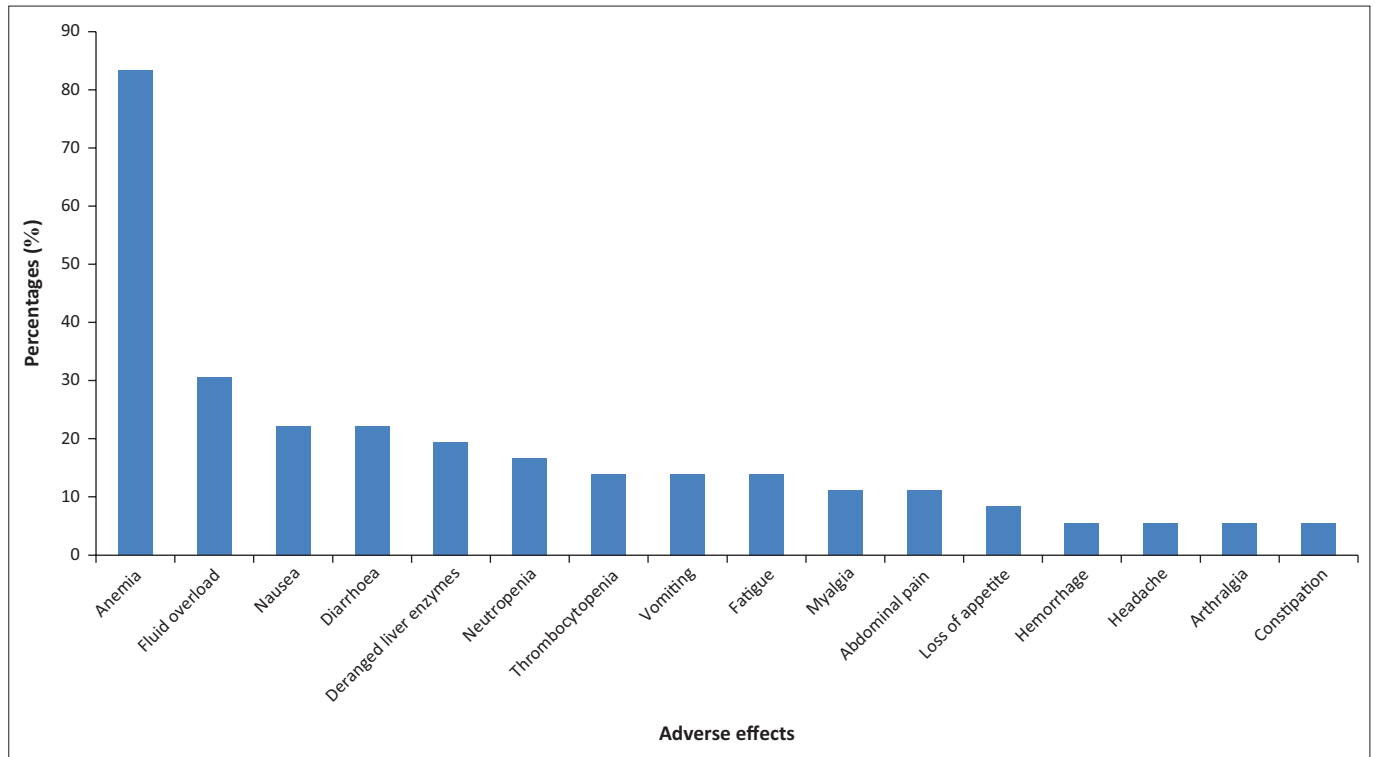


FIGURE 4: Adverse effects occurring in more than 5% of patients on imatinib.

diagnosed below this age. The first ever population-based study using the Surveillance Epidemiology and End Result (SEER) data showed a slight male predominance with 54% of the cases occurring in male and 46% in female patients.⁵ Contrary to this finding, there was a significant male predominance in a Pretoria series with a male-to-female ratio of 1.5:1.³⁹ In our local setting, this study has found a slight male predominance, commensurate with the SEER study. The ethnic distribution of GIST in this study is proportional to the local population demographics, a finding similar to previous research.^{5,39}

In this study cohort, the stomach was the commonest anatomic site affected by GIST followed by the small intestine, similar to previous research. However, the small intestine was affected at a much lower percentage in our local setting and the Pretoria series, compared to previous research that found the small intestine affected in 30% of patients.^{1,39} The oesophagus, rectum, mesentery, peritoneum and urinary bladder were the other anatomic sites involved by GIST in the local setting. Anatomic sites described in literature that were not affected by GIST in the local setting include the colon, anus, appendix, omentum and gall bladder.⁵ Among patients with localised disease, high and intermediate risks were the majority postoperative risk categories. Patients with high-risk disease are the group with the highest risk of recurrence and metastasis after surgery and would therefore benefit from adjuvant imatinib therapy.^{24,27} This finding underscores the role of imatinib in the local setting.

CD117 (KIT) was the commonest expressed immunohistochemical marker in our study. However, CD117 was expressed at a lower percentage compared to previous

research where it was expressed in more than 90% of the population.^{1,2} This can be explained by the fact that a significant proportion of GIST cases in our setting had unknown immunohistochemical expression. CD34 and DOG1 were also expressed in a minority of GIST cases, contrary to previous research.^{20,40} At IALCH, DOG1 staining is only done as a confirmatory test, when CD117 and CD34 staining are equivocal. This explains the low expression observed in our study. DOG1 staining was done for four GIST cases, all of which stained positive. The occurrence of *c-KIT*, *PDGFRA*, *SDH*, *BRAF* and *NF1* mutations could not be established because genetic molecular mutation testing is not routinely done at IALCH.

At IALCH, adjuvant imatinib is prescribed for 3 years to localised GIST patients with postoperative high-risk and select intermediate-risk disease. Adjuvant imatinib for a duration of 3 years reduces the risk of local and metastatic recurrence in high-risk GIST patients.²⁷ Incidentally, patients with localised disease that required adjuvant imatinib presented during the latter part of the study. This explains the short duration of adjuvant imatinib therapy because patients were censored at the end of the study period. Throughout the study period, most patients with localised disease remained in remission after adjuvant imatinib. The majority of patients in remission had disease located in the stomach. It is, however, not clear whether the stomach anatomic site contributed to this positive outcome because other anatomic disease sites were not sufficiently represented for comparison. Three patients with localised GIST attained remission after imatinib therapy despite having residual disease postoperatively. In this era of imatinib, the optimal management of such patients with

positive margins is still unclear.⁴¹ All patients that developed metastatic recurrence had high-risk disease, in keeping with previous studies that established tumour size and mitotic index as strong risk factors for treatment failure.^{1,2} One of the patients that developed metastatic recurrence did not complete adjuvant treatment. This patient may have benefited from completing adjuvant imatinib. It is important, therefore, to educate patients on the benefits of imatinib therapy.

Imatinib treatment has enabled a number of GIST patients with locally advanced and metastatic disease to undergo surgical resection, thereby improving their clinical outcomes. Patients with locally advanced GIST who respond to neoadjuvant imatinib benefit from surgery. Surgery may also be considered in patients with limited PD on neoadjuvant imatinib. In contrast, surgery has little to offer to patients with generalised PD after receiving neoadjuvant imatinib.^{8,42} In the local setting, most patients with locally advanced GIST required neoadjuvant imatinib, with the majority of them attaining PR. This is in keeping with previous research in which 60% of the patients attained PR after neoadjuvant imatinib. In the same study, SD (28%) and PD (12%) were also observed.⁴³ Most of the patients that attained PR had disease located in the stomach. However, similar to the localised disease cohort, the prognostic significance of this anatomic location could not be established.

Metastatic GIST is often an incurable disease. The majority of patients with metastatic GIST in our cohort initially attained favourable responses on imatinib. This is commensurate with initial studies where imatinib has produced favourable objective responses in more than 50% of patients with advanced GIST.^{6,44,45,46} To achieve response induction, imatinib is safe and efficacious at an initial standard dose of 400 mg daily.^{44,46} Dose escalation to 800 mg daily is indicated for patients progressing on 400 mg.⁴⁵ Almost all patients with metastatic GIST in our study progressed on the standard dose imatinib leading to dose escalation. However, these patients either progressed on or could not tolerate high-dose imatinib.

Most patients treated for metastatic disease eventually develop resistance to imatinib leading to disease progression and death. Sunitinib has been shown to improve outcomes in patients that have progressed on imatinib. In this second-line setting, the median time to tumour progression was significantly improved with sunitinib (27.3 weeks) compared to placebo (6.4 weeks).³⁰ At IALCH, sunitinib is not available for the treatment of patients with GIST and leaves patients with advanced GIST without systemic therapeutic options once they develop resistance to imatinib. This situation underscores the need to avail sunitinib as the second-line treatment of GIST patients in the public health sector.

The majority of patients treated with imatinib in this study experienced adverse effects. However, grades of adverse effects were not documented for all patients that experienced them. Imatinib is well tolerated with most adverse effects

being mild to moderate, seldom requiring treatment interruption or dose adjustment. Serious adverse effects like bone marrow suppression, impaired liver function tests and neutropenic fever have been found to be rare with this molecule.⁴⁷ In the local setting, imatinib is also well tolerated with only five patients having their treatment interrupted because of adverse effects. However, anaemia, which is as a result of bone marrow suppression, was the commonest adverse effect observed in patients treated with imatinib in this study. Furthermore, the majority of these patients had Grade III anaemia. It is not clear why anaemia was common in this patient population. Male gender and metastatic disease category were shown to increase the occurrence of adverse effects in our local population. However, age and risk category did not influence the occurrence of adverse effects in our local patient population.

This study has some weaknesses. Firstly, its retrospective nature subjects it to potential bias. Secondly, incomplete record-keeping with regard to death, pathology reports and failure to treat several patients with imatinib hampered the study. While it is possible that more patients died during the study period, only three deaths were recorded because most deaths that occur outside IALCH are not captured in the hospital records. Seven patients with localised disease had unknown risk categories because of lack of pathology information vital in decision-making (tumour size and mitotic index). In addition, there was no documentation as to why eight patients (four with high-risk and four with metastatic GIST) were not treated with imatinib. We recommend that a mechanism be put in place that will enable peripheral hospitals or caregivers to inform IALCH of patients' demise. Open communication between the oncologist and pathologist is encouraged to ensure that vital information is provided for treatment decision-making. Clinicians are also encouraged to ensure adequate documentation of decisions made in the clinic. Thirdly, the patient population in this study was small. A larger, multi-institution study is recommended in order to better describe the different variables of this rare disease.

Conclusion

This study describes the patient demographics and clinical outcomes after treatment with imatinib in GIST patients at IALCH. The majority of GIST patients were diagnosed above the age of 50, and male patients were slightly more numerous than their female counterparts. Most patients belonged to the black ethnic group, a fact attributable to the local population distribution. The stomach was the commonest anatomic site affected by GIST. High- and intermediate-risk GISTs were the commonest risk categories among patients with resected disease, with a significant number of patients having presented with locally advanced and metastatic disease. Therefore, imatinib therapy has an important role in the local setting. As expected, patients with advanced GIST (locally advanced and metastatic disease) initially attained favourable responses during imatinib therapy thereby improving their clinical outcomes. Imatinib was well

tolerated with anaemia being the commonest adverse effect observed. Clinicians should, therefore, anticipate and manage anaemia timeously to improve patient tolerance to imatinib. The majority of patients with metastatic GIST eventually develop resistance to imatinib. It is therefore important to avail sunitinib, as the second-line treatment agent, in the public health sector.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

S.N.M. was the primary author responsible for the research concept, research design, study protocol, literature review, data collection, data analysis, initial draft of the manuscript, manuscript editing and final draft of the manuscript. F.A. was responsible for the research concept, data collection and proofreading of the initial draft and final draft of the manuscript. Both N.E.N. and K.G.M. assisted with proofreading the initial draft and final draft of the manuscript.

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