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Imatinib (Glivec) and gastrointestinal stromal tumours in Nigerians

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Abstract

Background: To assess the response and the impact on the overall survival (OS) on c-KIT-positive (CD117+) gastrointestinal stromal tumours (GISTs) patients treated with imatinib mesylate.

Methods: Between July 2003 and December 2012, consenting patients with advanced c-kit-positive GISTs were enrolled to receive imatinib mesylate therapy at a dose of 400mg – 800mg daily, supplied gratis by Novartis Pharma (Basel, Switzerland) under its GIPAP initiative. Disease severity was based on tumour site, size and mitotic index at diagnosis. Clinical features together with drug toxicity, haematological and biochemical parameters were monitored. Overall survival (OS) reviewed at 12 months intervals over 5 years was computed using Kaplan-Meier

Results: There were 27 patients in all (17 males and 10 females with a median age of 52 years (range 26 - 83). Twenty three patients, 15 males and 8 females that have been followed up for at least 6 months were evaluated, aged 26 - 83 years (median = 56). There were 17 (73.9%) gastric tumours and 6 extragastric including 3 cases of peritoneum and 1 each of small gut, colon and rectum. At diagnosis, 21 (91.3%) cases were high risk, and 1 each fell into the intermediate and low risks, respectively. Ten patients (43.4%) including 5 with metastases presented with unresectable lesions. Five patients (21.7%) had complete tumour resection, 5 (3 with metastases) had partial resections and 3 others with non-bulky, non-metastatic diseases underwent no surgery. Imatinib was used as the primary therapy for all patients, except the 5 patients that underwent complete tumour resection. Nine (39.1%) patients were lost to disease progression with a median survival of 16.7 ± 10.7 (±SE) (95% CI = 0-37.6) months. The overall survival at 2 years for all patients was 71.9%, which dropped to 65.9% at 4 years.

Conclusions: Although a small number of GISTs, imatinib induced an extended remission in patients with advanced disease, most of whom would have been dead within a few months of diagnosis.

Keywords: *Gastrointestinal stromal tumor, Imatinib, survival, surgery, Nigeria,*

Résumé

Contexte: Afin d'évaluer la réponse et l'impact sur tous les survivants des patients de tumeurs gastro-intestinales c-KIT-positif (CD117 +) puis traités par l'imatinib mésylate.

Méthodes: Entre Juillet 2003 et Décembre 2012, des patients consentants patients sérieusement atteints de c-kit positif ont été admis afin d'être traités par l'imatinib mésylate à la dose de 400 mg - 800 mg par jour, fourni gratuitement par Novartis Pharma (Bâle, Suisse) grâce à son initiative GIPAP. La gravité de la maladie était basée sur le la localisation de la tumeur, sa taille et l'index mitotique au moment du diagnostic. Les caractéristiques médicales ainsi que la toxicité des médicaments, les paramètres hématologiques et biochimiques ont été suivis. Les statistiques de la survie globale (OS) examinée a été faites à l'aide Kaplan Meier à 12 mois d'intervalle sur une période de 5 ans

Résultats: Il y avait au total 27 patients (17 hommes et 10 femmes âgés de 52 ans (tranche d'âge : 26-83). Vingt trois (23) patients dont 15 hommes et 8 femmes qui ont été suivis pendant au moins 6 mois, ont été évalués, âgés de 26 - 83 (âge moyen = 56). Il y avait 17 patients (73,9%) souffrant de tumeurs gastriques dont 6 extra- gastrique y compris 3 cas de péritoine et chacun de petit intestin grêle, du côlon et du rectum. Au moment du diagnostic, 21 cas (91,3%) étaient élevé, et chacun soit dans les risques moyen et faibles, respectivement. Dix patients (43,4%) dont 5 présentant les cas de métastases avec des lésions non résumables. Cinq

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C-kit is a polyclonal antibody for identification of type III tyrosine kinase KIT that is expressed by most cases of GIST using immunohistochemical technque. CD117 is a KIT receptor antibody and it is used interchangeably with c-kit.

patients (21,7%) ont eu une résection complète de la tumeur, (3 avec le métastases) ont eu des résections partielles et 3 autres avec des maladies non volumineux, non métastatiques n'ont subi aucune intervention chirurgicale. L'imatinib a été utilisé comme traitement de premier soin à tous les patients, sauf les 5 patients qui ont subi une résection complète de la tumeur. Neuf patients (39,1%) ont rendu l'âme au cours du processus de l'évolution de la maladie avec en moyenne 16,7 ± 10,7 (± SE) (IC à 95% = 0 à 37,6) survie au cours des mois. La survie globale de tous les patients à 2 ans était de 71,9%, puis chuté à 65,9% à 4ans.

Conclusions: Bien qu'un petit nombre de GIST, d'imatinib induise une rémission prolongée chez les patients atteints de graves maladies, la plupart mourait quelques mois après le diagnostic.

Introduction

Gastrointestinal stromal tumours (GISTs) are of interest because they are the most common sarcoma of the gastrointestinal tract, and they only became distinctly characterised recently [1]. Furthermore, the knowledge of the molecular pathogenetic basis and the role of KIT activation have greatly influenced treatment of the disease. The tumours possibly originate from the interstitial cells of Cajal (ICC), the pacemaker cells of the gastrointestinal tract responsible for generating electrical impulses for peristalsis [2-5]. GISTs are in general very rare, the estimated annual incidence being between 6.8 and 14.5 per million people [1,5-7], and are mainly prevalent in adults (median age of 58 years) with slight male preponderance [4,7-9].

The stomach have been reported to be the site of occurrence for 50 – 60% of cases while the small bowel accounts for 25%; rare extra gastro intestinal locations includes the omentum, mesentery, and retroperitoneum [10-12]. Gastric GISTs tend to have better prognosis and a lower risk of recurrence when compared to nongastric tumors of the same size and mitotic index [13]. The spectrum of tumour biological behaviour ranges from benign disease to aggressive sarcomas; many patients are, however at significant risk of tumor recurrence and progression to metastatic disease even after complete excision [5,8,11]. Metastatic spread is most commonly to the liver, followed by the peritoneum, and rarely to extraabdominal sites such as the lungs, pleura and bones. Peripheral lymph node involvement is also unusual [8,11]. A life-threatening complication of gastrointestinal disease is tumour rupture into the peritoneal cavity and/or erosion into the lumen of the intestinal tract resulting in severe haemorrhage [11].

Immunohistochemical staining with specific antibodies helps with disease confirmation at the molecular level. Over 95% of GISTs express CD117 antigen (marker for c-KIT, an oncogenic tyrosine kinase protein)[11,12,14]. Other markers include CD34, which is positive in about 70% of cases but unfortunately is not specificas it is also expressed by haemopoietic stem cells, smooth muscle and Schwann cell tumours; DOG-1 and platelet derived growth factor receptor alpha (PDGFR-á)[14,15]. Response of the tumours to conventional cytotoxic therapy was found to be generally poor usually less than 5% [16]. Therefore surgery aimed at complete tumour resection was the first line therapy for resectable primary disease [17], but recurrence is common, being over 50% within 5 years [8].

Imatinib mesylate is an oral 2-phenylaminopyrimidine derivative that acts as a selective inhibitor against several receptor kinases including c-kit, ABL, BCR-ABL, and PDGFR. Targeted treatment of GISTs with imatinib is based on the knowledge that phosphorylation of tyrosine residues in the intracellular domains of KIT activates the signal transduction pathway of KIT proto-oncogene with stimulation of cellular proliferation and inhibition of apoptosis resulting in neoplastic cell growth [14,15,18,19]. The identification of germline activating KIT mutation gene in individuals with familial GIST, an autosomally inherited disorder, further confirmed the pathogenesis [20]. Patients with wildtype *c-kit* (unmutated KIT) have gain-of-function mutations in the structurally related tyrosine kinase PDGFR-á with similar oncogenic propensity [21]. Sixty to 90% however have activating mutations in the KIT protooncogene, as opposed to 5 - 8% in PDGFR-á oncogene[18,19]. A single site of mutation in the *KIT* gene is seen at presentation in the majority of cases and complex genetic mutations are rare. The most frequent mutation type is the gain-of-function mutations in exon 11 found in70% of cases; cases of exon 9 are less frequent, and those of exons 13 and 17 are rare [19]. Treatment with imatinib is often associated with impressive objective response and durable disease control in patients with exon 11 mutations as opposed to patients with exon 9 mutations or nondetectable/ absence of any KIT mutations or PDGFR-á[22,23].

The use of imatinib in the treatment of GISTs has improved survival in all grades be they metastatic or non-metastatic primary tumours [24], and the drug has also been effective both as neoadjuvant [25,26] and/or as adjuvant therapy[27]. Risk-classification systems based on tumour size, mitotic index, and tumour location, amongst others have been

developed to guide in selection of patients with resectable tumours that will benefit maximally from adjuvant imatinib therapy [28,29]. Although most patients benefit from the medication, total cure is hardly achieved as many patients go on to develop resistance to the drug [28,29].

This is a presentation of our experience with the response and the overall survival rates of Nigerian patients with GISTs treated with imatinib.

Materials and methods

All consenting patients with histologically (Figs 1 and 2) and immunohistochemically confirmed GISTs treated with imatinib on a daily dose of 400mg, which was increased as appropriate to 600-800mg daily in cases with resistant disease recruited between July 2003 and July 2012, and prospectively followed-up were the subject of this study. The medication was obtained through the *Novartis' Glivec International Patient Assistance Programme* (GIPAP) and dispensed gratis to beneficiaries. Tissue samples were biopsied by the referring surgeons using the best available means. Measurements of tumour size from the onset of therapy was by periodic manual palpation but more objectively by comparisons of serial ultrasonography with or without additional CT scanning

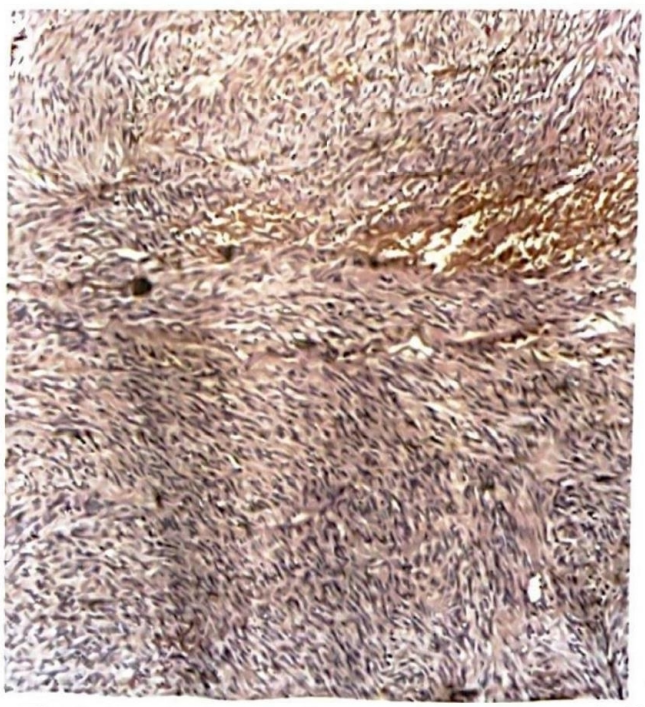

Fig 1: Histological section of GIST showing spindle shaped cells arranged in fascicles. Haematoxyllin and Eosin x4

The clinical features, tumour characteristics, haematological and biochemical parameters, drug toxicity and treatment outcome were monitored and documented. The Eastern Cooperative Oncology Group (ECOG) Performance Status was used for patients' assessments at presentation. It is graded as follows: 0 (fully active); 1(symptomatic but ambulatory); 2 (in bed < 50% of time); 3 (in bed > 50% of time); 4 (100% bed-ridden) and 5 (Dead).

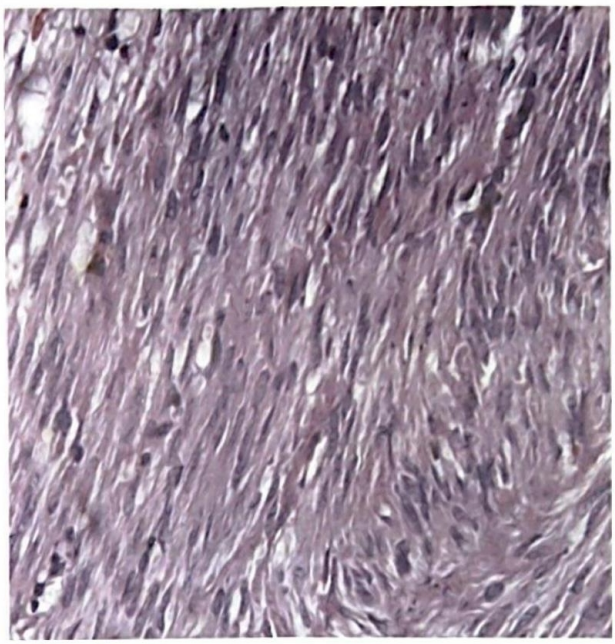

Fig. 2: Histological section of GIST showing spindle shaped cells arranged in fascicles. Haematoxyllin and Eosin x 40.

For the purposes of statistical analysis, patients with unresectable tumours and cases of high-risk diseases (based on the NIH consensus classification at diagnosis [28]) were grouped together as advanced tumours; the 2 others groups (a low risk [LR] and an intermediate risk [IR] tumour) as less advanced. Because of the huge disparity in number, comparative survival between the groups was not attempted. Survival measured from the date of imatinib intervention to the date of demise or loss to follow-up of patient was used for probability estimates of the overall survival (OS) using Kaplan-Meier technique. Living patients were censored on the date they last visited the hospital. SPSS for Windows version 16 (SPSS Inc, September 13, 2007, USA) was used for computing all statistical calculations, including Kaplan Meier survival studies.

Monitoring and follow-up

The presenting features and side effects of the drug were noted at every clinic attendance. Two-weekly complete blood count and monthly serum biochemical parameters were determined in the first 3 months and 3 monthly thereafter. Other observations of the patients themselves were recorded. Response to therapy was monitored by

both clinical and ultrasound assessment of tumour size (Figs 3 and 4). Tumour relapse was determined by monthly abdominal ultrasound in the first 2 years, repeat gastroscopic examinations and annual CT scanning. The length of treatment and status at the cut-off date were recorded.

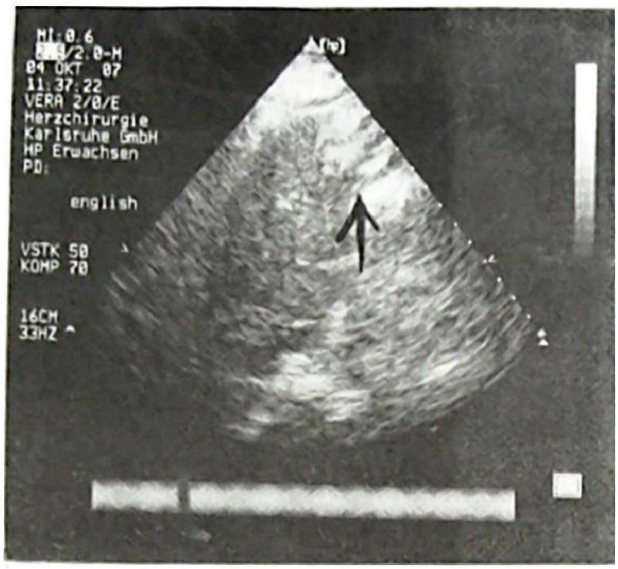

Fig 3: Stomach ultrasonography with arrow showing Thickened stomach cell wall in a patient with gastric GIST before Glivec

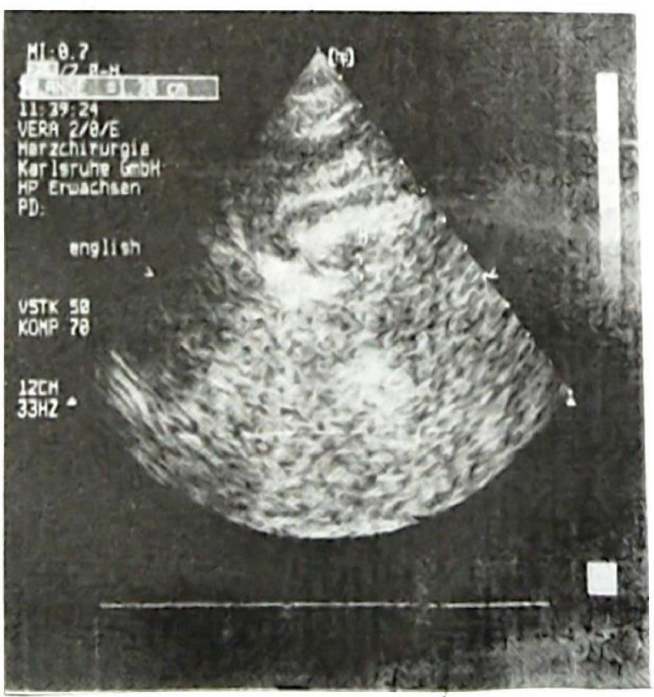

Fig 4: Stomach cell wall in a patient with gastric GIST on glivec

Results

Clinical characteristics

During the study period, 27 (10 females and 17 males with a median age of 52 years [range 26-83]) patients were diagnosed to have GISTs. Only 23 (65.2%), 15 males and 8 females (male to female ratio of 1.9:1) patients who had been followed-up for between 6 months and 126 months were included in the study. The median age was 56 (range, 26-83) years. The majority (70%) of the patients had ECOG performance status of 2. Seventeen (73.9%) and six (26%) patients presented with gastric and extragastric tumours, respectively (Table 2).

Table 1: Proposed modification of consensus classification for selecting patients with GIST for adjuvant therapy [28]

Risk category	Tumor size (cm)	Mitotic index (per 50 HPFs)	Primary tumour size
Very low risk	<2.0	≤5	Any
Low risk	2.1-5.0	≤5	Any
Intermediate risk	2.1-5.0	> 5	Gastric
	< 5.0	6.10	Any
	5.1-10.0	≤5	Gastric
High risk	Any	Any	Tumour rupture
	> 10cm	Any	Any
	Any	> 10 cm	Any
	> 5.0	> 5	Any
	2.1-5.0	> 5	Nongastric
	5.1 -10.0	≤5	Nongastric

The tumours were unresectable in 10 (43.4%), partially resectable in 5 (21.7%), completely excised in another 5(21.7%) while 3 (13.0%) had no surgery. Imatinib was used as the primary therapy in patients that underwent no surgical intervention, but as adjuvant therapy in patients that had partial or complete tumour resection. All patients presented with weight loss, abdominal swelling and pain. Other symptoms included loss of appetite, malaise, dyspepsia, generalised body weakness, and gastrointestinal bleeding.

Follow-up and survival

Time from definitive diagnosis to commencement of imatinib varied from 0.13-19.4 (median, 3.5) months. A few numbers of the patients reported adverse events (Table 3), which were generally mild but for a case of imatinib-related pancytopenia for which the drug was reduced to 300mg daily until full recovery. The events were reported at varying times into therapy, neutropenia, usually transient was reported in 5 (21.7%) patients after , 0.5-29 (median 23) months of starting Glivec; two patients gave history of

nausea/vomiting at 2 and 3 months, respectively and 2 other patients reported weight gain and mild oedema at about 2-3 months of starting therapy. Generalised lightening of the skin were reported by another 2 patients, but they were not certain of how soon into therapy. There was a case of Herpes zoster in one patient, who subsequently had complete recovery [30].

Table 2: characteristics of patients with gastrointestinal stromal tumours on Imatinib (N=20) patients

Variables	Median (range)
Age (year)	56 (26-83)
Time to imatinib therapy (weeks)	11 (1-84)
Variables	**No (%)**
Sex	
Males	15 (65.2)
Females	8 (34.8)
M/F ratio	1.9:1
ECOG performance status	*No (%)*
1	2(8.7)
2	16 (69.6)
3	5 (21.7)
Time in weeks from diagnosis to imatinib therapy	
Range	1.0-84 (median, 11.0) weeks
Tumour sites	No (%)
Gastric	17(73.9)
Extragastric	06(26.1):
Peritoneum	03
Small gut	01
Colon	01
Rectum	01
Disease Stage (size/mitotic index basis)	*No (%)*
Advanced Disease	21 (91.3)
Intermediate	1 (4.3)
Low risk	1(4.3)
Disease Amenability to Operation	*No (%)*
No surgery	3 (13.0)
Unresectable (locally advanced)	5 (21.7)
Unresectable (metastatic)	*5 (21.7)*
Partial resection	3 (13.0)
Partial resection (+ metastases)	2 (8.7)
Total resection (+ metastases)	5 (21.7)
Imatinib Treatment type	*No (%)*
Primary therapy	18 (78.3)
Adjuvant therapy	5 (21.75)

The median survival was 55.5 ± 6.7 (SE) (95% CI = 42.2-68.4) months
The OS was 82.6%, 71.9%, 65.9% and 44.0% at 12, 24, 48 and 60 months, respectively (Fig 1)

Nine patients (39%) died of disease progression despite increase in imatinib dosage to 800mg daily with a median survival of 55.5 ± 6.7 (SE) (95% CI = 42.2-68.4) months. Seven of the patients had gastric disease and two had diseases involving peritoneum. All of the patients presented with advanced tumours, including seven unresectable tumours (four with metastases) and two with high risk disease confirmed at diagnosis [28]. No incidence of recurrence in patients who had complete resection with adjuvant imatinib.

The OS was 82.6%, 71.9%, 65.9% and 44.0% at 12, 24, 48 and 60 months, respectively (Fig 5).

Table 3: Major adverse events noted in the patients

Symptoms	No (%)
Weight loss	23 (100%)
Abdominal swelling	23 (100%)
Abdominal pain	23 (100%)
Malaise	23 (100%)
Poor appetite	17 (74%)
GIT bleeding	01 (4.3%)

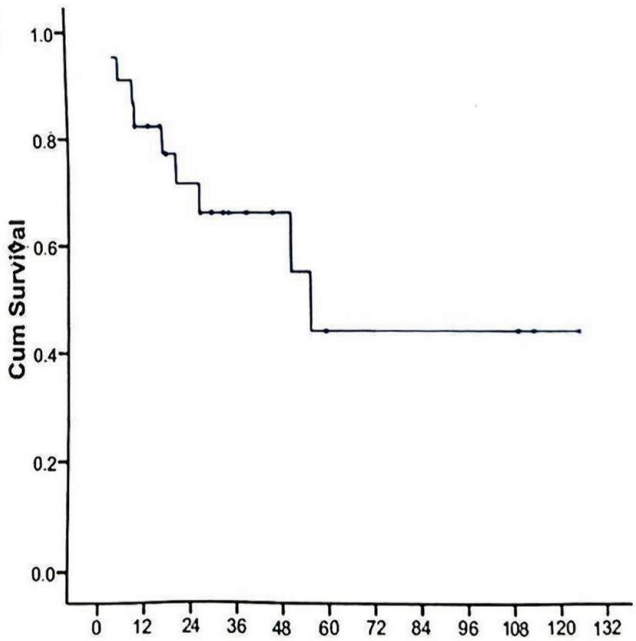

Fig 5: Overall survival curve of all patients
Duration of treatment in months since Imatinib intervention

Discussion

GISTs occur predominantly in the fifth and the sixth decades of life [7,9,31], and are unusual in individuals under age 40 years [9]. It is worthy of note that about one-third of the patients in the current series were young adults under the age of 40 (median, 34.5; range, 26-39) years. Although the 56-year median age (range, 28-83) in this study was slightly lower than 60 (range of 40-80) years usually reported among the Caucasians [4,7], and this finding was

similar to previous reports by others [31,32]. While some studies have demonstrated male predominance as observed in this study, others have not found any gender differences [31,33-35]. The current study further confirmed the fact that the majority of GISTs are primarily localised in the GIT, 87% of cases with special predilection for the stomach [10-12].

The introduction of imatinib has increased survival of patients with advanced disease from 12 months between 1995 and 2000 (before the era of imatinib) to 33 months between 2001 and 2004 in the era of imatinib ($p < 0.001$); while the overall survival of patients at 47 months also increased from 21% to 41%, respectively ($p < 0.001$)[36]. This may explain the high overall survival rate of 82.6% at 12 months recorded in this series. Our experience was comparable to 88% reported by Croom and Perry [37] for the same duration in their series. Richter *et al*,[38] and Rutkowski *et al*.,[39] reported even higher rates. The 2-year survival rate of 72% in this series was comparable to the 70% obtained for patients with metastatic disease reported by Verweji, *et al* [40]. An overall survival of 66.4% was obtained in the current series of predominantly advanced disease at 48 months (Fig 1), which was even higher than the 41% reported by Artinyam *et al* [36], for their series of metastatic GISTs treated with imatinib and the 21% for such patients before the era of imatinib, thus confirming the reported efficacy of imatinib for disease control [24-27].

The nine (39%) patients that died must have developed resistant to imatinib because of failure of disease response to the maximum 800mg dose of the drug. The uncensored median survival was 16.7 (range, 4-55) months. The poor survival outcome in this small series could be attributed to predominance of high risk disease, late presentation and drug resistance as previously documented [28, 29]. Late presentation being a major characteristic of our patients could possibly be because the majority of patients seek alternative treatment before presenting at the hospital as well as late diagnosis of recently described disease. Also the poor prognostic features seen in 87% of the patients presenting with high-risk disease (such as tumour size $\geq$ 10cm) and high mitotic index could be a factor.

The observed adverse effects of imatinib in this study such as mild nausea and vomiting, peripheral oedema, lightening of the skin, mild-moderate anaemia, are not uncommon in patients on the drug. However, severe haematologic adverse effects are less common in GISTs patients on standard imatinib dosage compared to those with chronic myeloid leukaemia (CML) on the same dosage. The primary involvement of marrow tissue in CML may explain the higher incidence of pancytopenia in CML compared to GIST. In this series, only one (4.4%) patient had a grade 3 adverse neutropenia requiring temporary withdrawal until full recovery.

The ready availability of imatinib to our patients through GIPAP facilitated early initiation of drug treatment once diagnosis was made and accounted for achieving the median period of 3.5 months from disease confirmation to imatinib initiation. In general, early access to imatinib improved survival and quality of life of GISTs patients [36]. This cohort showed that early introduction of imatinib in resource-constrained populations like Nigeria through GIPAP facilities can replicate similar excellent outcome of treatment to patients with GISTs irrespective of social class. We, however, did not observe complete disease remission in any of our surviving patients with inoperable tumours and those with non-bulky, non-metastatic disease. This may be because total cure is hardly achieved even in patients on adjuvant therapy following total tumour resection, as many patients go on to develop resistance to the drug [41,42]. The need to develop strategy to delay or prevent development of resistant is very apparent. A possible suggestion is to combine chemotherapy with imatinib as the backbone at the initiation of treatment. It is however noteworthy that none of our patients on adjuvant therapy after complete tumour resection has relapsed.

Although small, this series, has demonstrated the efficacy of imatinib as an adjuvant therapy. It has also shown an extended remission induced by the drug as a primary therapy in patients with advanced inoperable GISTs, most of whom in our experience and as confirmed by others would have died within a few months of diagnosis [37].

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