THE PATTERN OF IMATINIB DOSE CHANGE AND ITS IMPLICATIONS IN CHRONIC MYELOID LEUKEMIA IN A COHORT OF PATIENTS ATTENDING THE GLIVEC INTERNATIONAL PATIENT ASSISTANCE PROGRAM (GIPAP) IN NAIROBI, KENYA

DR BONGINKOSI SHADRACK SHOBA

MBBCh (Witwatersrand), FCP (SA)

H113/5559/2017

A DISSERTATION SUBMITTED AS PART OF THE FULFILLMENT OF THE PREREQUISITES FOR THE FELLOWSHIP IN MEDICAL ONCOLOGY, UNIVERSITY OF NAIROBI

DECLARATION

This dissertation is my original work and has not been submitted for a degree at any other institution or previously published

Signed……

Dr Bonginkosi Shadrack Shoba

Fellow in Medical Oncology

Department of Internal Medicine and Therapeutics

University of Nairobi, Kenya

ACKNOWLEGEMENTS

My heartfelt gratitude goes to my supervisors, Professor NA Othieno-Abinya and Dr MD Maina for guidance in the development of the concept, the analysis of data and the preparation of the dissertation.

Tonya Esterhuizen for time spent discussing structure, methods and statistics

Collins Ondiek for helping with data collection

SUPERVISORS

Professor N.A Othieno-Abinya, MBCHB, MMED, FRCP

Professor of Medicine

Consultant Medical Oncologist

Department of Internal Medicine and Therapeutics

University of Nairobi

Signed……

Dr MD Maina, MBChB, MMed, FRCP

Consultant Haemato-Oncologist

Kenyatta National Hospital

Nairobi, Kenya

Signed…….

TABLE OF CONTENTS

ABBREVIATIONS

BCR/ABL: Breakpoint Cluster Region/Abelson gene

BSA: Body surface area

CI: Confidence Interval

C: current

CML: Chronic Myeloid Leukemia

GIPAP: Glivec International Patient Assistance Program

IRIS: International Randomised Study of Interferon and ST1571

KNH: Kenyatta National Hospital

L: lost

SPSS: Statistical Package for the Social Sciences

DEFINITION OF TERMS

Current denotes all patients seen at clinic into the beginning of 2018 until data collection.

Equivocal (E) denotes a change in the dose of imatinib that shows no clear trend, i.e. one visit it is increased and the next visit it is changed down and so on.

Lost denotes patients last seen until end of 2017, not seen at follow-up at any time in 2018.

ABSTRACT

Background: Imatinib has been used clinically to treat chronic myeloid leukaemia since 2002. The standard starting dose for all patients was determined in early studies and set at four hundred milligrams orally once a day.

Our experience at the Nairobi GIPAP has been that this dose of four hundred milligrams is sometimes decreased or increased in some of our patients for different reasons.

This phenomenon has not been studied in Nairobi and elsewhere before.

Objectives: We undertook to quantify the magnitude of this phenomenon. Secondly, we want to study how it affects patient outcomes on follow-up.

Study methods: Seven hundred and nine (709) patient files were studied from our GIPAP clinic in Nairobi. All were adults aged eighteen and above. They were all diagnosed with CML and they were on imatinib for varying lengths of time. Data on their gender, age, phase of disease, changes made to dose and follow-up phase were extracted.

Results: Three hundred and fifty eight **(**51%) of the patients studied experienced the change in their dose. Fifty five percent (55%) of them were male and the remainder were female. Forty six (14.6%) of females under study had their dose increased, fifty three (16,8%) of females under study had their dose decreased and sixty two (19,6%) of all females in our study had an imatinib dose change that was equivocal.

Sixty four males (16.3%) had an increase in the dose of their imatinib, fifty seven (14.5%) had their dose decreased and sixty four male (19.3%) had a change that was equivocal.

These changes between genders were not statistically significant (p=0,638).

Among females the change of the dose of imatinib, whether it was increased or decreased, did not influence the outcome of these patients in a statistically significant way (p=0.549).

However, males who experienced increased dosage of imatinib were lost to follow-up (p=0.003)

The attrition rate was high, reaching 40%, even amongst patients who had experienced no change in the dose of imatinib.

Conclusions: The change in imatinib dose reaches 50% in the GIPAP clinic in Nairobi. Males who had an increase in their imatinib dose did not do well. This observation begs to be explored further. Our clinic however has a high attrition rate.

1. BACKGROUND TO THE STUDY

The Glivec International Patient Assistance Program based in Nairobi has been in operation since 2005. In the year 2009 the program had accumulated over 200 patients (Kiarie and Othieno-Abinya). At that time the compliance rates with imatinib at the clinic were in excess of 80%. There were slightly more males than females enrolled in the program.

Currently the program looks after more than 800 patients. These patients are mainly Kenyan, there are a few patients coming from the neighboring countries mainly Rwanda, the DRC and parts of Ethiopia.

The staff in our program comprises consultant medical oncologists, clinical hematologists and fellows in Medical Oncology.

The program sees mainly patients diagnosed with chronic myeloid leukemia and a few gastro-intestinal stromal tumours. The main drug prescribed to our patients is imatinib mesylate at a dose of 400mg once a day by mouth. Imatinib has a few side effects, few of them severe enough to discontinue therapy. Patients do experience cytopenias especially in the first few months after starting therapy.

Our patients seek care mainly in the chronic phase of CML. Few patients are admitted in the accelerated and blastic phases of CML.

Doses of imatinib do vary from the standard 400mg depending on patient side effect profile, cytopenias and disease presentation.

In June 2017, a pilot study was performed in our program to look at the variability of imatinib dose, the magnitude of the variability and its implications for patient prognosis.

One hundred and forty patients were studied. The important findings of the study were as follows:

(i) Males were four times more likely to need a dose escalation compared to females. They did not progress. On follow-up at 60-80 months these patients had stable disease. The hypothesis was that males were probably under dosed on 400mg because their body surface area was larger.

(ii) Females who need dose escalation were lost to follow-up within 40mweeks of that change.

Our present study sought to test these hypotheses on a larger sample.

2. LITERATURE REVIEW

2.1 DEFINITION AND EPIDEMIOLOGY

Chronic myeloid leukemia (CML) is a clonal myeloproliferative cancer characterised by neutrophil leucocytosis, see Fig 1.

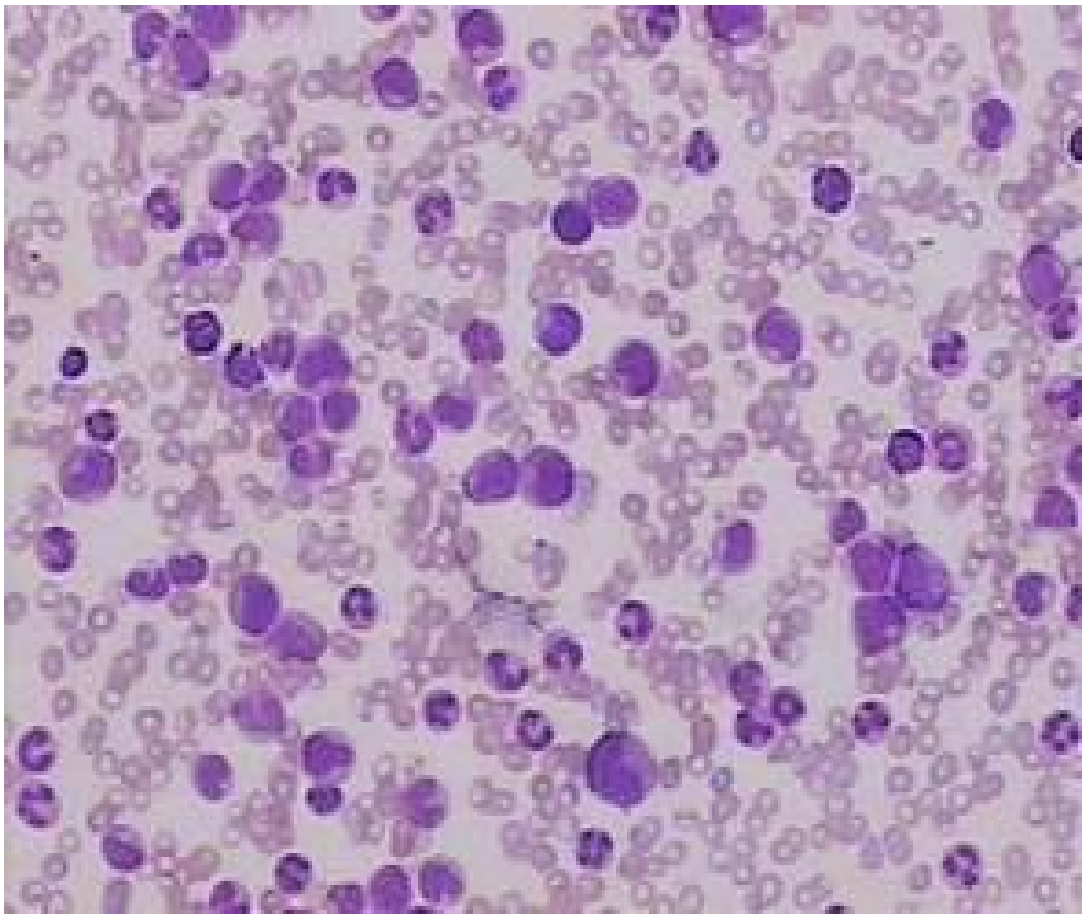


Fig 1: Courtesy of Nikhil Sangle MD copyright © 2002-2018, Pathology outlines.com, Inc

CML is steadily linked with the Philadelphia chromosome which coded for the BCR-ABL1 fusion protein, see fig 2.

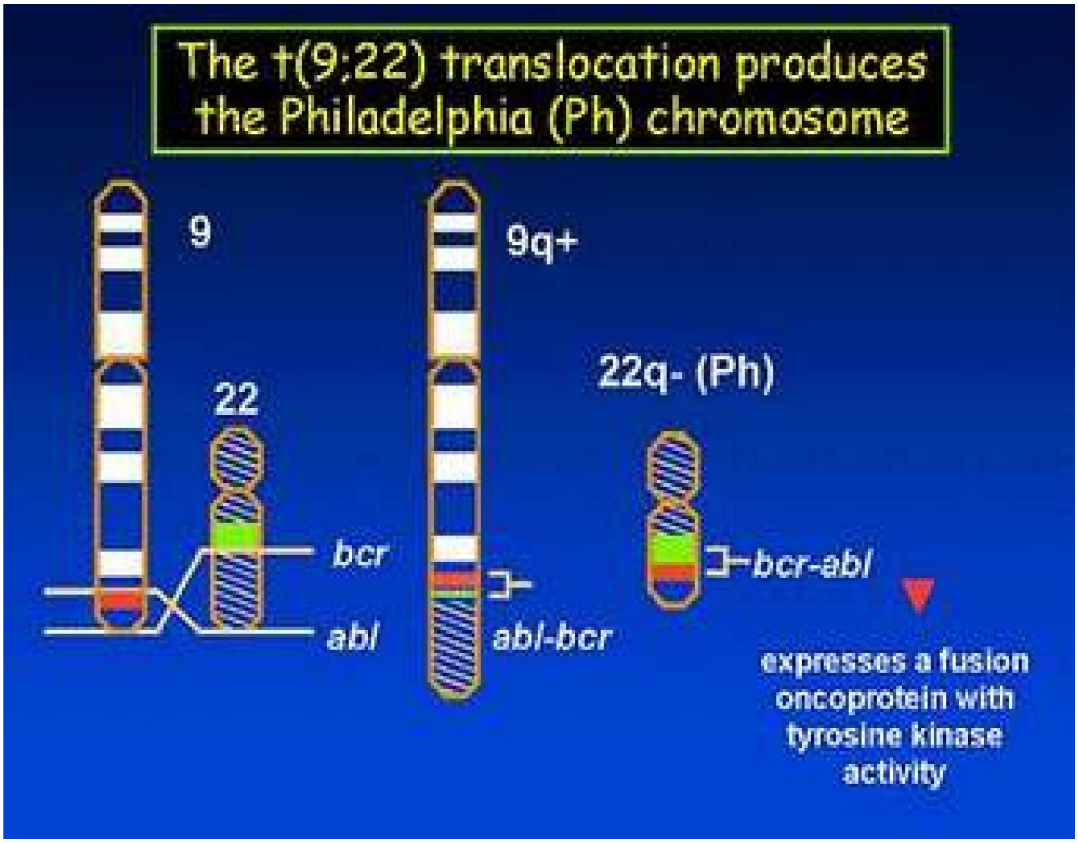


Fig 2: Courtesy of Jessica Waphner: yeastgrrl.blogsp.com/2014

CML accounts for 20% of all leukemias among adult patients (3). The incidence is 1-2 per 100 000 per year, figures in Africa are not known.

2.2 HISTORICAL PERSPECTIVE

CML was described by John Hughes Bennet in 1845 (4,5). In subsequent years the study of CML has changed the practice of Medicine. Today, molecular targeted therapies are used. in the clinics worldwide. It was Peter Nowell in 1960 who first noticed that the short arm of chromosome 22 was short (22q-) in patients with CML (6). In 1973, Janet Rowley determined that 22q- was a product of an unequal and reciprocal exchange of chromosomal material between chromosome 22 and 9 (6). In the 1980s Nora Hesterkamp realised that this sharing of chromosomal material created a new fusion gene called BCR-ABL1 (7). Owen Witte in 1986 worked out that the product of this gene was a tyrosine kinase (8)

Alex Matter in 1993 synthesized a compound that could inhibit this enzyme, Brian Druker tested this compound in clinical trials starting in 1998 (3). This compound was eventually called imatinib mesylate, see **FIG3**. It was approved for therapy of CML in 2001 at 400mg dose, the overall survival of newly diagnosed CML was 89% at 5 years (3, 7, 8).

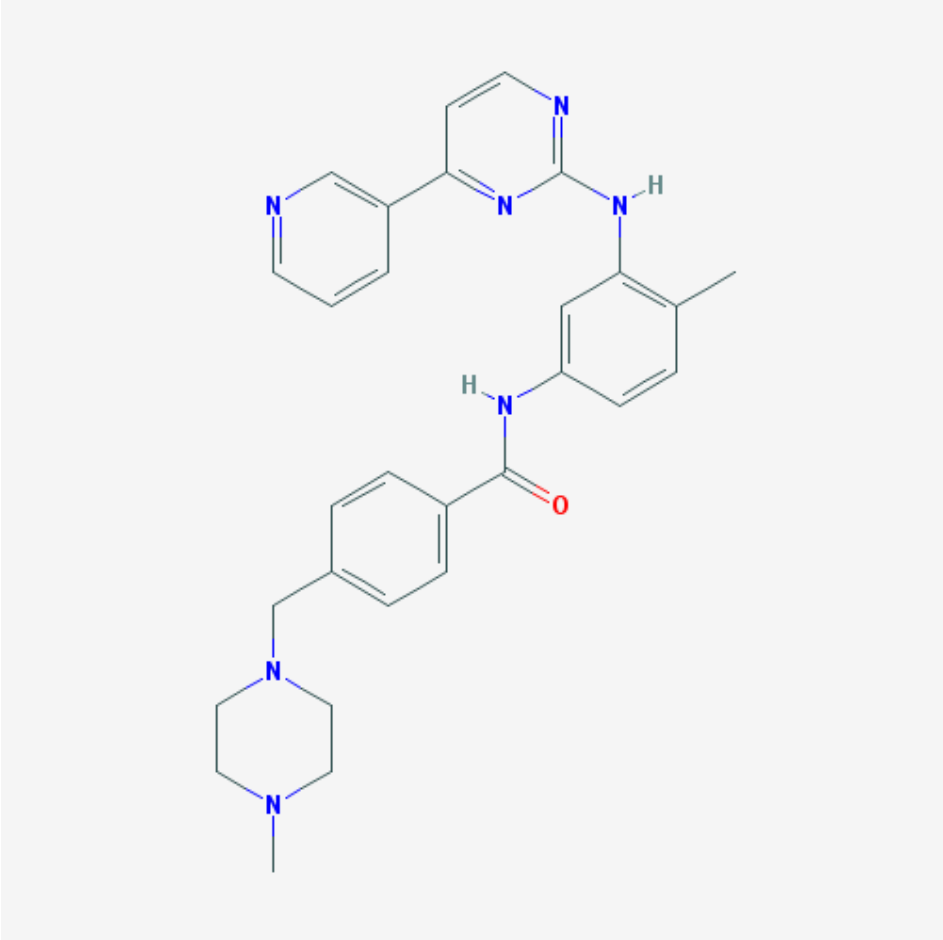


Fig.3: From National Centre for Biotechnology Information. PubChem Compound database.

2.3 PHARMACOLOGY OF IMATINIB

Imatinib specifically inhibits of BCR/ABL oncogenic action in chronic myeloid leukemia. BCR/ABL gene activity is needed and enough to induce leukemogenesis (19). In CML, the BCR/ABL gene product, a tyrosine kinase, is auto-phosphorylated. This dysregulated protein activates signal pathways i.e., RAS, RAF, CRKL, PKC which are involved in gene transcription, altered messenger RNA processing, nuclear export and protein translation (20, 21). These processes result in enhanced proliferative potential and survival and altered motility (22, 23, 24). Imatinib has specific activity for ABL, platelet derived growth factor receptor, c-kit and Abelson-related gene (25).

Dose reductions of imatinib did occur for grade 2 and worse haematological and non-haematological side effects, the long-term effects and outcomes of these reductions have however not yet been investigated (5). The Eutos and Sokal scores are recommended to assess risk before initiation of imatinib, this does not happen readily in our clinic in Nairobi (9,10). Studies have shown that higher doses of imatinib are linked with better cytogenetic and molecular responses (11). Age, gender and body surface could be factors that determine pharmacokinetics (12). Most adverse effects are experienced before the first two years elapse and some can be reversed. Some patients become lethargic, develop rashes (27), others bone pain. Rare instances of QTc prolongation have been reported. Few patients may undergo cytopenias the same year they begin therapy (26).

3. JUSTIFICATION OF THE STUDY

In our daily practice at the Nairobi GIPAP we have noticed that patients do need dose adjustments either an increase or a decrease. This is done as a response to cytopenia, increase of cell counts or other toxicities that patients present with. Results from our pilot study suggest that male patients may need a higher dose of imatinib. These males subsequently presented with stable disease. We hypothesized that this was due to their higher body surface area. Females who needed a higher dose seemed not to do well. These females subsequently disappeared from our follow-up program.

These hypotheses demand further testing

The sheer magnitude of the phenomenon of dose change also has not been quantitated in Kenya or the rest of the world.

4. RESEARCH QUESTION

1. What is the magnitude of dose change in our clinic?
2. How many patients need an increase or a decrease in their dose of imatinib?
3. What are the outcomes following the changes?

5. OBJECTIVES OF THE STUDY

The primary objectives are:

1.0 To work out the absolute quantity of the practice of dose change in our clinic

2.0 To work out whether these changes are increases or decreases.

The secondary objectives are:

1.0 To determine the impact of the dose changes on the outcomes of patients

2.0 To determine whether gender has any effect on the type of change

6. METHODOLOGY

a) **Study design:** The study was a cross-sectional, descriptive, cohort study. Cross sectional studies provide a snapshot of the outcome and characteristics at a specific point in time (13).

b) **Study site:** The GIPAP clinic currently being conducted from the Nairobi Hospital

c) **Study population:** All the patient files obtainable from records since 2005 until the present were studied.

d) **Inclusion and exclusion:** We included all adult patients aged at least 18 years. Patients on other cytotoxics were excluded.

e) **Sample size and sampling method:** All available files from our records were studied.

6.1 DATA MANAGEMENT AND ANALYSIS

A data collection instrument was used, see appendix 1. No blood or other samples were taken from patients. Data was kept under lock and key by principal investigator. Data was entered, cleaned and analysed by SPSS version 21.0. T-tests were used to compare variables where necessary. A p-value < 0,005 was considered statistically significant.

6.2 STUDY LIMITATIONS

The study was carried out in a single institution therefore the findings are not generalisable. Confounding variables including patient age, overall performance status, pharmacokinetics and socio-demographic issues were not controlled.

7. ETHICS

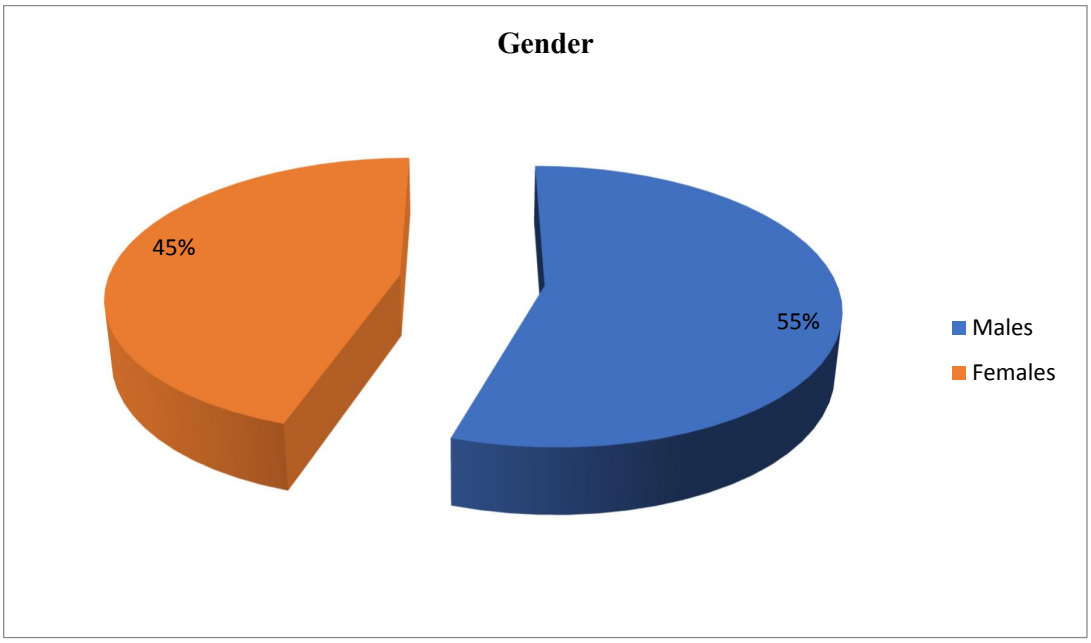
Permission to commence the study was obtained from the Kenyatta National Hospital/University of Nairobi's Ethics and Research Committee after presentation and clearance from the Department of Clinical Medicine and Therapeutics, University of Nairobi. Ethics remains the most vital component of biomedical research to protect patients from harm mainly (14). Confidentiality was strictly maintained; no personal patient details were recorded.

8. RESULTS

Seven hundred and nine (709) patient files were studied. Fourteen files were excluded because the patients were under the age of 18 at enrolment to the clinic. All these files were sourced from the GIPAP clinic, Nairobi. Files as far back as 2005 were included to the most recent in 2018. They were all adult patients, eighteen years old and above. The patients were on imatinib. They were not on any other cytotoxic treatment.

Three hundred and ninety-three of the patients were males (55%) three hundred and sixteen were females (45%). See **figure 4** below. The mean age was 40,2 years. The youngest patient is male at 5 years of age, the oldest is an 83-year-old man.

Figure 1: Gender distribution of patients studied



One hundred and sixty- one (161) female patients in total experienced the change in dose, this is 50,9% of all females under study and 22,7% of all patients in the clinic. One hundred and ninety- seven (197) male patients experienced a change in their dose which is 50.1% of males under study and 27,8% of all patients in the clinic in total. Fifty one percent (50, 49%) of patients in the clinic had a dose changed at some time during their treatment.

8.1 TRENDS OF THE CHANGING DOSES OF IMATINIB (SEE TABLE 1)

8.1.1 TRENDS AMONG FEMALE PATIENTS

Forty-six female (46) patients had their dose of imatinib increased, this constitutes 14,6% of all females under study and 28,6% of female patients who had a change in the dose.

A total of fifty -three (53) female patients had their dose of imatinib decreased which is 16,8% of all females in the study and 32,9% of those female patients who had their dose changed.

In total, sixty-two (62) female patients had equivocal changes to their dose of imatinib which is 19,6% of all patients in the study and 38,5% of female patients who had a change in dose.

8.1.2 TRENDS AMONG MALE PATIENTS

Sixty-four males (64) had their doses of imatinib increased which is 16,3% of all males under study and 32,5% of all male patients who had a dose change.

A total of fifty-seven males had their imatinib dose decreased which is 14,5% of all males under study and 28.9% of all males who had a dose change

In total seventy-six male patients had their equivocal changes to their dose which is 19,3% of all males under study and 38,6% of all males who had a change in their dose of treatment.

TABLE 1: CROSS TABULATION OF THE DOSE CHANGES AMONGST MALES AND FEMALES

Gender * CHANGE Cross tabulation						
			CHANGE			Total
			d	e	u	
Gender	female	Count	53	62	46	161
		% within Gender	32.9%	38.5%	28.6%	100.0%
	male	Count	57	76	64	197
		% within Gender	28.9%	38.6%	32.5%	100.0%
Total		Count	110	138	110	358
		% within Gender	30.7%	38.5%	30.7%	100.0%

P=0.638

There was no difference between the genders in terms of alteration of dosage.

8.2 THE EFFECTS OF THE CHANGES OF THE DOSES OF IMATINIB AT FOLLOW-UP (SEE TABLE 2)

8.2.1 FEMALE INCREASE OF DOSE

Twenty-six (26) of the forty-six (46) female patients, which is 56,5%, who experienced an increase in their treatment dose have subsequently been lost to follow up, five cases reported as dead in their files and the rest unaccounted for. Twenty (43,5%) are still attending clinic but two (10%) of these are documented as accelerated disease.

8.2.2 FEMALE DECREASE OF DOSE

Twenty-five (25) of the 53 female patients, which is 47,2% of the 53 female patients who had a decrease in their imatinib dose have been lost to follow-up, are presumed dead or non-compliant.

Twenty-eight (28), 52,8% of the 53 female patients who had a decrease in their imatinib dose are still being seen at the clinic on follow -up, their disease is controlled.

8.2.3 FEMALE EQUIVOCAL CHANGE OF DOSE

Sixty-two female (62), which is 38,5% patients had no clear direction in the change of their imatinib dose. Thirty-three (53%) of these patients are still in chronic phase and being seen on follow-up. Twenty-nine are lost to follow-up (46.8%).

8.2.4 MALE INCREASE OF DOSE

Thirty-one of the 64 males, (48,4%) who had a dose increase are currently stable and on follow-up at the clinic. Thirty-three (51,6%) are lost to follow-up. Six males (9,4%) whose doses were increased subsequently developed accelerated CML. Of these patients one has demised.

Six of the male patients who had increased dose had accelerated CML at the outset, five of these patients went into stable phase CML and are still on follow-up.

One patient who had his dose increased had blastic phase CML, he has since been lost to follow-up.

8.2.5 MALE DECREASE OF DOSE

Thirty-five of the 57 patients (61,4%) who had their doses of imatinib decreased are still alive and on follow-up. Twenty-two (38,6%) were subsequently lost to follow-up.

8.2.6 MALE EQUIVOCAL CHANGE OF DOSE

Seventy-six male patients (38,6%) had no clear direction in the change of their doses.

Seventy-six percent (76%) of these patients are currently on follow-up, the rest are lost (24%)

8.3 OUTCOMES AMONGST PATIENTS WHO DID NOT HAVE A CHANGE IN IMATINIB DOSE

Three hundred and fifty-one patients did not have a change in dose which is 49,5% of all patients studied.

8.3.1 FEMALES

A total of one hundred and sixty-eight female patients (47,9%) did not have their doses of imatinib changed either way. On follow-up 68 (41%) were lost and 100 patients (59%) are alive and still attending the clinic

8.3.2 MALES

A total of one hundred and eighty-three male patients (52,1%) did not have their doses of imatinib changed either way. On follow-up 63 (34,42%) were lost and 120 patients (65,57%) are alive and still attending clinic

9. DISCUSSION

There is scantiness of literature data about the phenomenon of the change of the dose of imatinib in the CML clinics.

We collected data from 709 files. These patients attend the Nairobi GIPAP clinic. They were all adults. The diagnosis of CML was made on peripheral blood studies, bone marrow examination and molecular studies as defined by WHO. All the patients studied were on imatinib. None were on any other cytotoxic treatment. The clinic started operating in 2005, therefore we collected data on patients spanning 13 years.

Fifty one percent of the patients studied had their dose of imatinib changed at some time during their treatment. The changes were either an increase, a decrease or were equivocal. The changes between males and females were not statistically significant, p=0,638.

Among females there was no statistically significant association between the change of the dose of imatinib and the results at follow-up, p=0,549.

Male patients who experienced an increase in the dose of imatinib were however more likely to be lost to follow-up than those who had a decrease or equivocal changes to their imatinib dose, p=0,003. **See fig 5 and Table 2.** Once again it is noted that the attrition rate is high once the dose changes, fifty-two percent (52%) when the dose was increased and 39% amongst those who had their dose decreased.

Six of the male patients had their imatinib started at a higher dose because they had accelerated disease at the outset, five of these patients subsequently went into stable phase CML, it seems that the higher dose of imatinib is good for these males who had accelerated CML (16).

The attrition rate at our clinic is high. The average rate is 48,75%. This is noted across all patients whether their doses were changed or not. There are no studies to compare these rates within the literature.

In a similar setting, Qatar, non-adherence to medication was noted to be a factor in treatment failure and attrition (16). In 2009 the adherence rate at GIPAP was 80% (9).

The confounding finding is that, at GIPAP, even patients who did not change dose are lost to follow-up at a rate exceeding 40%.

TABLE 2: CROSS-TABULATION OF THE EFFECTS OF THE CHANGES OF THE DOSE OF IMATINIB ON FOLLOW-UP

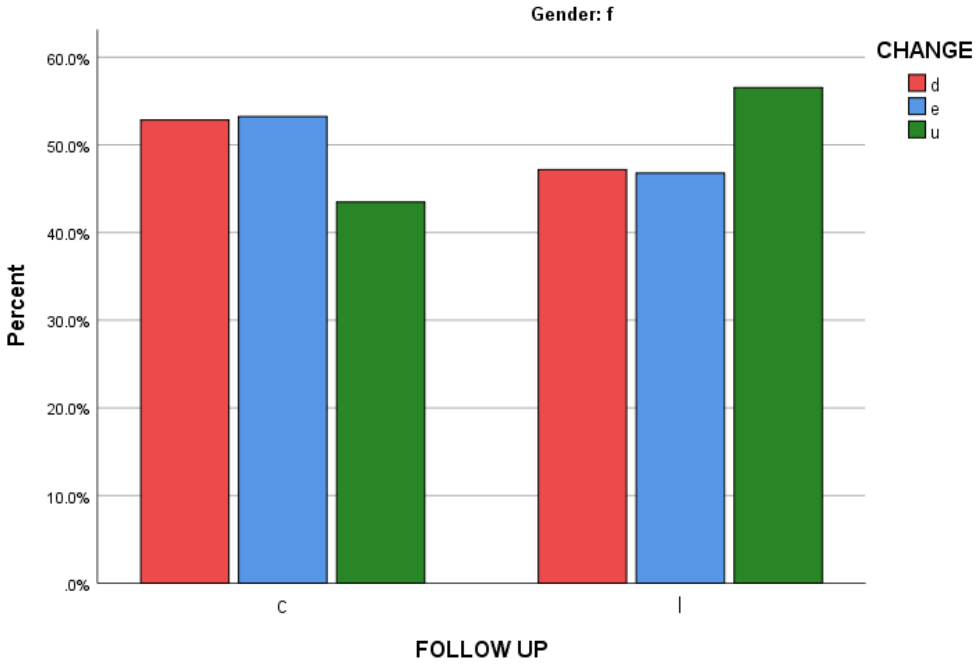
Crosstab						
Gender				FOLLOW UP		Total
				c	l	
female	CHANGE	d	Count	28	25	53
			% within CHANGE	52.8%	47.2%	100.0%
		e	Count	33	29	62
			% within CHANGE	53.2%	46.8%	100.0%
		u	Count	20	26	46
			% within CHANGE	43.5%	56.5%	100.0%
	Total		Count	81	80	161
			% within CHANGE	50.3%	49.7%	100.0%
male	CHANGE	d	Count	35	22	57
			% within CHANGE	61.4%	38.6%	100.0%
		e	Count	58	18	76
			% within CHANGE	76.3%	23.7%	100.0%
		u	Count	31	33	64
			% within CHANGE	48.4%	51.6%	100.0%
	Total		Count	124	73	197
			% within CHANGE	62.9%	37.1%	100.0%

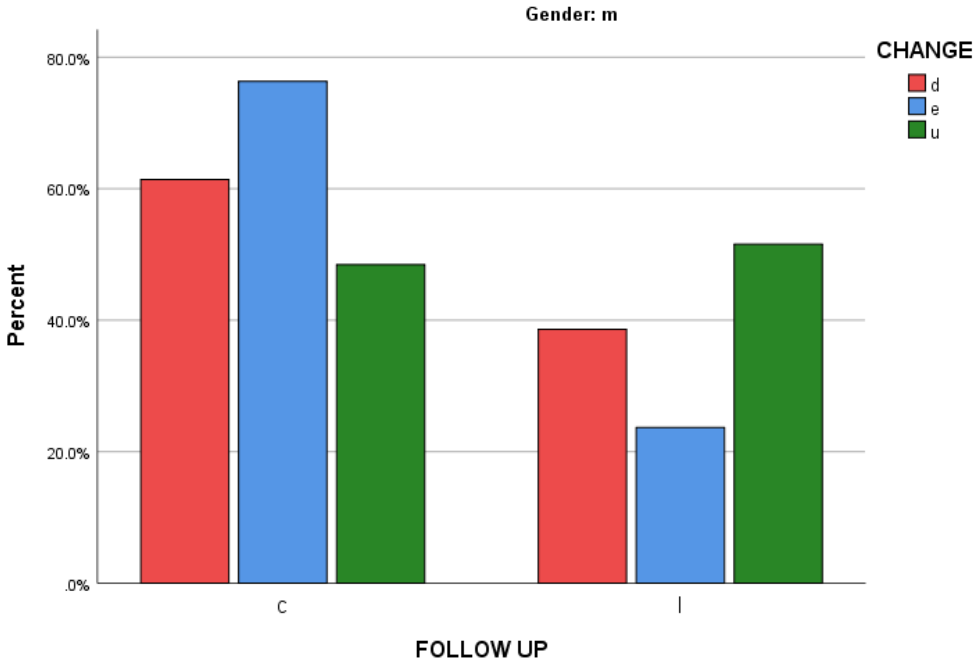
Females: p=0.549

Males: p=0.003

In females there was no association between change and follow up. In males there was a significant association (p=0.003). Those males who changed up were more likely to be lost to follow up than those who changed down or equivocal.

FIGURE 5: FOLLOW-UP ACCORDING TO DOSE CHANGE





Once the dose of imatinib in males is increased our study shows that the outcome is significantly worse. Four questions arise from this observation:

1. Was their disease biology poor from the outset?
2. Do they metabolise imatinib faster than other patients?
3. Were these patients under-dosed at 400mg?
4. Are males less compliant compared to females in our clinic?

The first question was not examined by this study. Belsey SI et al have examined the second question, in their study, they found that women had higher imatinib trough levels compared to men (11), this question was not the subject of our study. In answer to the third question, Kawaguchi et al, found that patients who needed a smaller dose had a consistent lower body surface area (18). Our cohort of patients showed no significant differences in their body surface area, **see Table 3.**

10. CONCLUSION

The rate of the change of dose in our clinic exceeds 50%. Change indicates poor prognosis in general. This change is significant amongst males whose doses were increased. These males were lost to follow-up in a statistically significant way. This cohort of patients calls for a further study.

The clinic loses patients at a high rate exceeding 40%. This observation too demands to be investigated further.

11. RECOMMENDATIONS

The attrition rate needs further investigation. Men who need a higher dose of imatinib need further investigations for disease progression and resistance and possibly further pharmacodynamic and pharmacokinetics investigations. There is an urgent need to investigate the reasons for such high patient losses in our clinic. Whether change of dose indicates bad outcomes must also be investigated given the generally high rate of patient loss in our clinic.

It is important that the subgroup of males who do poorly be investigated as a special subset to determine if this is related to peculiar circumstances for example high risk disease among them, drug metabolism or result of socio-demographic factors.

TABLE 3

T-Test

A t-test was done to compare the mean male and female BSA.

Group Statistics					
	sex	N	Mean	Std. Deviation	Std. Error Mean
BSA	males	33	1.8255	.17646	.03072
	females	23	1.7300	.19022	.03966

Independent Samples Test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
BSA	Equal variances assumed	.134	.716	1.929	54	.059	.09545	.04949	-.00376	.19467

There was a marginally non-significant difference between mean male and female BSA (p=0.059). The mean difference was 0.095 (units?) higher in males than females.

REFERENCES

1. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *New England Journal of Medicine* 2001; 344: 1031-1037.
2. Swerdlow SH, Campo E, et al. *WHO classification of tumors of hemopoetic and lymphoid tissues*. IARC: Lyon 2008.
3. Druker BJ. Translation of the Philadelphia chromosome into therapy for chronic myeloid leukemia. *Blood Journal* 2008; 112: 4808-4817
4. Bennett JH. Case of hypertrophy of the spleen and liver in which death took place from suppuration of the blood. Edinb Med Surg J. 1845; 64:413-423
5. Virchow R. Zur pathologischen physiologiedes blutes weisses blut. Arch Pathol Anat Phys. 1847; 1: 563-572
6. Newell PC, Hungerford DA. A minute chromosome in human chronic granulocytic leukemia. Science 1960; 132:1497
7. Druker BJ, Guilhot F, et al. Five year follow up of patients receiving imatinib for chronic myeloid leukemia. N Eng J Med 2006; 355: 2408-17
8. Witte ON, Dasgupta A, et al. Abelson murine leukemia virus protein is phosphorylated in vitro to form phosphotyrosine. Nature. 1980; 283: 826-831
9. Kiarie GW, Othieno-Abinya NA, et al. The glivec international patient assistance program: The Nairobi experience. *East African Medicine Journal* 2009; 86(12): 106-109
10. Baccarani M etal. European LeukemiaNet recommendations for the management of chronic myeloid leukemia. Blood 2013 122: 872-884
11. Kantarjian H, Talpaz M, et al. High-dose imatinib mesylate therapy in newly diagnosed Philadelphia chromosome–positive chronic phase chronic myeloid leukemia. *Blood Journal* 2004; 103: 2873-2878. doi: https://doi.org/10.1182/blood-2003-11-3800

12. Belsey SL, Ireland R, et al. Women administered standard dose imatinib for chronic myeloid leukemia have a higher dose-adjusted plasma imatinib and norimatinib concentrations that men. *Ther Drug Monit* 2017; 39(5): 499-504. doi: 10.1097/FTD.0000000000000440
13. Israel, GM. Determining sample size. Florida Cooperative Extension Service 1992: 1-5.
14. Schurink WJ. *Qualitative Research Design: Part 1. Lecture notes to Doctoral and Masters Students for the Leadership in Performance and Change Program at the University of Johannesburg.* Johannesburg 2005
15. Rowley JD. A new consistent chromosomal abnormality in chronic myeloid leukemia identified by quinacrine fluorescence and giemsa staining. Nature 1973; 243:290
16. Kantjian H, Talpaz M et al., Survival benefit with imatinib mesylate therapy in patients with accelerated phase chronic myeloid leukemia – comparison with historic experience. Cancer 2005; 103: 2099-2108.
17. Kawaguchi t. et al., Relationship between an effective dose imatinib, body surface area and trough drug levels in patients with chronic myeloid leukemia. Int J. Hemat 2009 Jun; 89 (5): 642-8
18. Al- Dewik NI et al,. Is adherence to imatinib mesylate treatment among patients with chronic myeloid leukemia associated with better clinical outcomes in Qatar. Clin Med insights Oncol. 2016; 10:95-104
19. Sawyers CL. Chronic myeloid Leukemia. N Engl J Med, 340: 1330-1340, 1999
20. Van Etten RA. Studying the pathogenesis of BCR-ABL leukemia in mice. Oncogene 21: 8643-8651, 2002
21. Perotti D, et al. Post-translational mechanisms in BCR-ABL leukemogenesis: role of shuffling RNA-binding proteins. Oncogene 21: 8577-8583, 2002

22. Trotta R, et al. BCR-ABL activates mdm2 mRNA translation via the La antigen. Cancer Cell, 3: 145-160, 2003

23. Osarogiagbon UR, et al. Chronic myeloid leukemia. Curr Opin Hematol, 6: 241-246, 1999

24. Gordon MY. Biological consequences of the BCR-ABL fusion gene in humans and mice. J. Clin. Pathol, 52: 719-722, 1999

25. Druker BJ. Imatinib alone and in combination for chronic myeloid leukemia. Semin. Hematol. 40: 50-58, 2003

26. Mughal TI, et al. Principal long-term adverse effects ofimatinib in patients with chronic myeloid leukemia in chronic phase. Biologics 2010; 4: 315-323

27. Van Glabbeke, et al. Predicting toxicities for patients with advanced gastro-intestinal tumours treated with imatinib: A study of the European Organisation for Research and treatment of cancer, the Italian Sarcoma group and the Australian Gastro-intestinal trials group. Eur J Cancer 2006; 42; 2277-2285

APPENDIX I: IMATINIB DOSE CHANGE STUDY IN CML

Age at diagnosis……

Gender…….

Phase at diagnosis……..

Date of diagnosis ……..…….

Imatinib start date……

Imatinib start dose……

Dose changes

	Date	Dose
Date of first dose change		
Date of second dose change		
Date of third dose change		
Date of fourth dose change		
Date of fifth dose change		
Date of sixth dose change		

Current dose……

Current phase……..

Last date of review……

APPENDIX II: CONSENT FORM

I_____ do confirm that I have read/been explained to the above study, understood the information presented to me and have had the chance to ask questions. I understand that my participation is voluntary and that I can freely withdraw from this study at any time without giving reason.

I agree to participate out of my own free will and no coercion or incentive has been offered.

Signature of participant_____ Date: _____

Signature of investigator_____ Date: _____

APPENDIX III: PARTICIPANT INFORMATION AND CONSENT FORM

(To be administered in English or any other appropriate language e.g. Kiswahili translation)

Title of study: the pattern of imatinib dose change and its implications in chronic myeloid leukemia in a cohort of patients attending the glivec international assistance program (gipap) in Nairobi.

Principle investigator and institutional affiliation

My name is Dr. Bonginkosi Shoba, I am a fellow in Medical Oncology in the Department of Clinical Medicine and Therapeutics in the University of Nairobi.

Supervisors

The supervisors are Professor Abinya and Dr. Maina.

Objectives

Ningependa kukualika uwe mmoja wa wale wanaoshiriki katika utafiti wenye manufaa kuhusu "**the pattern of imatinib dose change and its implications in chronic myeloid leukemia in a cohort of patients attending the glivec international assistance program (gipap) in Nairobi.**

The principal investigator of the study is Dr. Bonginkosi Shoba supervised by Professor Abinya and Dr. Maina.

Study background

We are studying the patterns of the change in the dose of the medication, imatinib or glivec, that patients use at the gipap clinic; how the dose changes; who is affected; what does it mean to you, the patient, after change. We hope this study will help us understand how to give this medication better in the future.

(Huu utafiti unaangazia jinsi ile dawa ya leukemia iitwayo Glivec ambayo wagonjwa wanaokuja katika kliniki zetu za GIPAP hupewa. Tungependa kugundua iwapo kuna utaratibu wa kubadilika kwa kipimo cha hii dawa, jinsi huo ubadilishaji hufanyika na vile inamaanisha kwako kama mgonjwa anayeugua. Tunatumai kwamba huu utafiti utatusaidia kuwa na ujuzi kuhusu vile tunaweza kuimarisha jinsi tutapeana hii dawa hivi karibuni ile kuifanya iwe bora zaidi kwako kama mgonjwa).

What will happen if you decide to take part in this research study?

We will be looking through your file to see when and how the dose was changed since the time when you first came to the clinic. No blood or bone marrow or any tissue will be taken from you. There will be no cost that you will be required to pay. Your appointments at the clinic will not change and you will be seen in the usual way as before.

(katika huu utafiti, tutakuwa tunakagua rekodi zako zenye ziko hospitalini ili kugundua vile utaratibu wa ubadilishaji wa kipimo cha hii dawa hufanyika. Hutahitajika kutoa damu wala

sehemu yoyote ya mwili wako. Kadhalika, hutalipishwa chochote katika utafiti huu. Siku zako za kuja kliniki pia hazitageuka kamwe.

Are there any risks, harms or discomforts associated with this study?

We will treat all the information we retrieve from your file as confidential as possible and will not share with anybody who is not participating in this study. All the information will be identified using code numbers and stored in a password protected computer database. During the entire period of data gathering, files, papers and other records will be kept in a locked file cabinet.

(Rekodi zako za hospitali zitalindwa nasi, na zitakuwa siri mno. Hakuna mtu yeyote ambaye hashuguliki na huu utafiti atakayeweza kuziangalia kamwe. Rekodi zote zitapewa nambari na hizo nambari ndizo tutatumia katika utafiti wala sio majina yako).

Will you get reimbursement of any money spent as part of this study?

There will be no compensation for any money spent as part of this study. You will not be required to contribute any money and in addition, you will not be compensated for taking part in it.

What are your other choices?

Your participation in this study is completely voluntary. You may withdraw from the study at any point you wish. There will be no negative consequences if you refuse to participate or withdraw from the study.

(Kuwa mmoja wa wanaoshiriki katika hili somo ni kwa hiari yako na hutalazimishwa kujisajili. Iwapo umeamua kutoshiriki, bado itakuwa sawa na utaendelea tu kupata matibabu katika kliniki zetu bila shida yoyote).

What if you have questions in the future?

You are free to ask me any questions you have at any point during the study. If you have understood this explanation and are willing to take part in this study I will ask you to sign the form indicating your willingness to participate in the study.

Should you require any further details about this study please call me on 0796088711

Uko huru kuniuliza swali lolote kulingana na hili zoezi. Kama umeelewa maelezo ambayo nimepeana hapa juu na ungependa kuwa mmoja wa wale ambao wanashirikiana nami katika huu utafiti, nakuomba utie sahihi katika fomu ili uonyeshe kwamba u tayari kushiriki. Tena, kama uko na maswali mengine ama ungependa kupata maelezo zaidi, nipigie simu katika 0796088711.

In case of any ethical concerns kindly contact: **The secretary, KNH/UON Ethics Review Committee; telephone 2726300 ext 44102, email, uonknherc@uonbi.ac.ke**.

Thank you