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Treatment Outcome and Adherence to Imatinib among Newly Diagnosed Patients with Chronic Myeloid Leukemia at Tikur Anbessa Specialized Hospital: A Prospective Cohort Study.

By:

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This is to certify that the thesis prepared by Atalay Mulu Fentie entitled **"*Treatment Outcome and Adherence to Imatinib among Newly Diagnosed Patients with Chronic Myeloid Leukemia at Tikur Anbessa Specialized Hospital: A Prospective Cohort Study*"** and submitted in partial fulfilment of the requirements for the degree of Master of Pharmacy in Pharmacy Practice complies with the regulations of the university and meets the accepted standard with respect to originality and quality.

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Abstract

Treatment Outcome and Adherence to Imatinib among Newly Diagnosed Patients with Chronic Myeloid Leukemia at Tikur Anbessa Specialized Hospital: A Prospective Cohort Study.

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Imatinib has been highly efficacious in the treatment of chronic myeloid leukemia (CML). However, lifelong treatment, continuous dosing, and patient adherence are essential for treatment success. The study aimed at assessing treatment outcome and adherence to Imatinib in patients with CML treated at outpatient hematology unit of Tikur Anbessa Specialized Hospital. A prospective cohort study was conducted from October 1, 2016 to November 30, 2017. All newly diagnosed patients were screened for eligibility and 147 were enrolled for the cohort. Patients were followed for 3-months and data abstraction format was used to collect pertinent information. The 8-items Morisky Medication Adherence Scale was used to assess adherence. Participants' median age at time of diagnosis was 36 years (Ranged: 14-74); with 95(64.6%) of them in the age group of ≤40 years. Male comprised 59.2%. Apart from the lost-to-follow-up (n=3), 132(91.7%) of the patients achieved complete hematologic remission with median treatment response period of 6-weeks. Peripheral blast count ≥5%(AOR=0.33, 95%CI: 0.16, 0.79) was found to be predictors for CHR failure, whereas adherence (AOR=8.60, 95%CI: 4.32, 11.10) was positively associated with CHR. After Imatinib initiation hematologic and gastrointestinal adverse drug events were common and grade III-IV hematologic toxicities were major reasons for physician led temporary treatment discontinuation in 19(12.9%) and dose decrement in 5(14.3%) of patients. Low platelet count at Imatinib initiation (AOR=5.3, 95%CI:2.35, 8.7) and being female (AOR=2.82, 95%CI:1.32, 4.94) were significantly associated with treatment discontinuation and dose decrement due to adverse drug events. Adherence rate to Imatinib was found to be 55.6%. Residence, income, presence of adverse drug events and comorbidity were significantly associated with adherence. Most (68.8%) of the patients also reported that adverse drug events were the common reason for their non-adherence. This study reflects the Ethiopian patients with CML were predominantly presented at productive age group

with differed high cell count compared to other countries. Imatinib is effective with manageable safety profile although treatment adherence is still suboptimal which in return is crucial for better treatment outcome. Hence, concerted effort has to be made by all stakeholders to increase adherence rate and further study is also required to explore cytogenetic and molecular response.
Key words: Chronic myeloid leukemia, Imatinib, treatment adherence, complete hematologic response, adverse drug events.

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Contents.....…..Page

Acronyms

ABL	Ablson
ADAGIO	Adherence Assessment with Gliveec: Indicators and Outcomes study
BAAS	Basel Assessment of Adherence Scale
BCR	Break point Cluster Region
CCR	Complete Cytogenetic Response
CHR	Complete Hematologic Response
CHS	College of Health Sciences
CML	Chronic Myeloid Leukemia
CMR	Complete Molecular Response
ELN	European Leukemia Net
EUTOS	European Treatment and Outcome Study
FISH	Fluorescent Insitu Hybridization
HSM	Hepatosplenomegaly
HU	Hydroxyurea
MEMS	Medication Event Monitoring System
MMAS	Morisky Medication Adherence Scale
MMAS-8	Eight item MMAS
MMR	Major Molecular Response
NCCN	National Comprehensive Cancer Network
Ph	Philadelphia Chromosome
RT-QPCR	Real Time-Quantitative Polymerase Chain Reaction
SD	Standard Deviation
TASH	Tikur Anbessa Specialized Hospital
TK	Tyrosine Kinase
TKI	Tyrosine Kinase Inhibitor
WBC	White Blood Cell Counts

List of Figures

List of Tables

1. Introduction

1.1 Background

Chronic myeloid leukemia (CML) is a slowly progressive and clonal myeloproliferative disorder resulting from neoplastic transformation of the primitive hematopoietic stem cell (HSC), which is monoclonal in origin and affecting mainly myeloid cell lines (Deininger *et al*., 1998, Vardiman, 2009, Jorge *et al*., 2014).

Presence of the Philadelphia chromosome (Ph) is the characteristics of CML. The normal chromosomes 9 and 22 carry the break point cluster region (BCR) and Abelson (ABL) genes, respectively, but the translocation between the long arms of chromosome 9 and 22 results in a shortened chromosome 22, commonly known as the Ph chromosome (BCR-ABL fusion genes). It took more than two decades until this reciprocal translocation and the resulting fusion gene to be identified. CML can occur at any age but is predominantly a disease of adults (Salesse and Verfaillie, 2002, Vardiman, 2009, Leitner *et al*., 2011, Jabbour and Kantarjian, 2014).

Philadelphia chromosome is present in >90% of patients and the BCR-ABL fusion gene is seen in up to 95% of CML patients and gets translated into a dominant oncoprotein-p210BCR/ABL, which is necessary and sufficient for malignant transformation of CML. Other less common oncoproteins include p190BCR/ABL and p230BCR/ABL. Once oncoproteins phosphorylated, they produces an active enzyme called tyrosine kinase. Tyrosine kinases contribute to growth factor independence, increased proliferation, genetic instability and suppression of apoptosis in leukemia cells, which all responsible for malignant transformation of CML (Van Etten, 2004, Ren, 2005). The typical clinical course of CML has three stages: Chronic phase (CP), accelerated phase (AP) and blast crisis (BC) phase. The natural history of CML is a CP for three to five years followed by rapid progression to the fatal BC phase. In two-thirds of patients, the BC phase is preceded by an AP (Baccarani *et al*., 2012, Jabbour and Kantarjian, 2014).

Little is known about the global incidence of CML. In the United States, it accounts for 15% of all leukemia cases (Union for International Cancer Control, 2014). The estimated new cases in 2017 were 8950 and 0.2% life time risk of developing CML with median age at diagnosis of 64 years with male to female ratio of 1.7:1 (National Institute of Health, 2017). The estimated

incidences of CML in Africa and Europe in the year 2017 were 0.4 and 1.4 cases per 100,000 populations per year (Tadwalkar, 2017).

In Ethiopia, national data on prevalence and incidence of CML are lacking. However, patient attendance and medical admission rates are rising. According to Gleevec International Patient Assistance program (GIPAP) sponsored CML patient registry at Tikur Anbessa Specialized Hospital (TASH); the only center in the country treating CML, showed that more than 1400 CML patients had been treated by Imatinib January, 2004 to December 2017. The drug is available free of charge; regardless of financial status for the treatment of all patients with CML, dermatofibrosarcoma protuberans and gastrointestinal stromal tumor. The funders' of Imatinib (Gleevec) are Gleevec International Patient Assistance program (GIPAP) now called Max Access Solution in collaboration with Novartis Pharma, which is the innovator and manufacturer of the drug (GIPAP, 2018). There were 920 actively treated CML patients in the unit since January 2018 (Gleevec International Patient Assisstance Programme, 2018). In addition, though there was no formal survival study done on Ethiopian CML patients; based on treating physicians report and witness, there are patients who survived ≥14 years through Imatinib treatment since confirmed diagnosis as compared with maximum 2-years survival by conventional drugs either by Busulphan or HU.

The history of CML treatment has undergone different paradigm shifts. CML treatment by Arsenic was the first and the only well-documented therapy in the 19th century followed by the introduction of radiotherapy in the first half of the 20th century, which was largely limited to splenic irradiation, offering pain control but no survival benefit (Woessner *et al*., 2011, Report of the Medical Research Council's working party for therapeutic trials in leukemia, 1968). Since then, in 1953 Busulfan and 1972 Hydroxyurea were introduced with better improved median survival rate in the later drug from 44 to 58 months. However, neither therapy prevented progression to AP and BC CML. Later in the 1970s, allo-HSCT was introduced to limited eligible patients and then followed by IFNα which largely replaced Busulfan and Hydroxyurea treatment (Silver *et al*., 1999). In 1998, the era of tyrosine kinase inhibitors (TKIs) began thereby replacing the two main treatment options that existed for CML previously. The development of these targeted therapies not only overcame limitations faced by prior conventional treatments but also improved survival of patients with CML (Cortes *et al.*, 2013, Hamad *et al.*, 2013).

Imatinib mesylate (Imatinib) was the first TKI to receive approval by the Food and Drug Administration (FDA) for the treatment of patients with Ph positive CML in 2001 (Cohen *et al.*, 2002) and is a major advance in the pharmacologic treatment of CML with regard to efficacy and safety with improved survival (Hehlmann *et al*., 2005). It acts via competitive inhibition at the ATP-binding site of the BCR-ABL TK, which then results in inhibition of phosphorylation of proteins involved in cell signal transduction (Schindler *et al.*, 2000) and has been found effective in the treatment of CML (NCCN, 2018).

Although Imatinib improved overall survival rate, continuous and adequate Imatinib dosing is required for the management of CML for optimal efficacy and to limit additional health-care costs associated with management of disease progression in CML (Stone, 2004). Hence, patient adherence, the extent to which patients take their medications as prescribed by their health-care provider, with respect to timing, dosage, and frequency (Cramer *et al.*, 2008), is critical for better treatment outcomes. Even if good adherence is known to be crucial, studies have demonstrated that non-adherence to Imatinib is frequent, and thus may significantly affect therapeutic outcomes (Noens *et al.*, 2009, Marin *et al.*, 2010).

Hence, assessing treatment response rate, determining the significance of Imatinib treatment adherence, contributing factors for adherence to a prescribed treatment and assessing safety of Imatinib through a continued research can assist in planning interventions to overcome the barriers and improve patient treatment response. Hence, this study was carried out to:-

(i) Give information on CML treatment response rate and patient adherence and, related factors that may help in the healthcare system for whom it concerns;

(ii) Design an interventional method that can solve problems related to long term Imatinib treatment adherence;

(iii) Forward recommendations on how to manage problems that affect CML treatment response.

(iv) Help as a baseline for further study on long term CML treatment outcome and patient's adherence to Imatinib treatment.

1.2 Statements of the Problem

Imatinib has transformed CML from an inexorably fatal illness to a chronic illness due to its dramatic improvements on survival (O'brien *et al.*, 2003, Sasaki *et al.*, 2015). But patients response status must be closely monitored; clinically, hematologicaly, cytogenetic and molecular response by using Real-time quantitative polymerase chain reaction(RT-QPCR) (NCCN, 2018, Baccarani *et al.*, 2013). The later provides an accurate measure of the total leukemia cell mass and the degree to which Ph chromosome transcripts reduced by Imatinib therapy that correlates with progression-free survival. Because a rising level of BCR-ABL transcripts is an early indication of loss of response and thus the need to reassess therapeutic strategy, regular cytogenetic and molecular monitoring of individual patients is clearly desirable (Kantarjian *et al.*, 2008). According to the NCCN (NCCN, 2018) and ELN (Baccarani *et al*., 2013) treatment guidelines recommendation, monitoring treatment response to TKI therapy should be done at 3, 6, 12 and 18 months. Then after, treatment response monitoring decision can be made according to local CML treatment guidelines. According to these guidelines, optimal response to Imatinib requires a complete hematologic response (CHR) within 3-months; a partial Cytogenic response (PCyR) within 6-months and complete cytogenic response (CCyR) at 12 months and a major molecular response (MMR) at 18 months. Failure of Imatinib treatment is considered when there is no CHR at 3 months, less than PCyR at 6 months, no CCyR at 12 months and no MMR at 18 months. When this happens, Imatinib should be switched to other alternative TKIs such as nilotinib, dasatinib and Bosutinib (Baccarani *et al.*, 2013, NCCN, 2018).

In addition; to achieve therapeutic outcomes, continuous and adequate Imatinib dosing is essential and a patient adherence is critical. But since then ongoing treatment approach faces challenges due to frequent non-adherence of patients. For example; in a study that tracked patient prescription data to assess a 24-month period adherence of CML patients to their treatments, adherence level was only 78% (Tsang *et al.*, 2006). In the other prospective Adherence Assessment with Glivec: Indicators and Outcomes (ADAGIO) study, one-third of all patients were considered as non-adherent to Imatinib over a 90-day period (Noens *et al.*, 2009).

Due to the above facts, globally there is a continuing need to routinely assess the likely reasons for treatment failure and non-adherence among patients with CML in clinical practice. This is

due to shift of treatment approach from IV chemotherapy to oral Imatinib therapy that transfers the responsibility of taking medication somewhat to patients alone in addition to other factors responsible for non-adherence. This is especially important in developing countries like Ethiopia where restricted access to healthcare facilities i.e. the availability of only one hematology center with in the country, transport and related costs, the preponderance of economic instability and low literacy level might have led to the increased incidence of medication non-adherence. Patients' adherence behavior could also be affected intentionally by their beliefs about treatment, religious views, or hopelessness and non-intentionally due to forgetfulness, level of understanding of treatment instructions, carelessness, etc (Jimmy and Jose , 2011, Jabbour *et al*., 2012).

In general, clinical practices reports and research findings showed that non-adherence to Imatinib for the treatment of CML has its own impact on treatment outcomes either due to missing doses or taking extra doses. If the doses are missed it significantly affects desired treatment outcome and also risk of treatment failure or relapse is high (Marin *et al.*, 2010, Noens *et al*., 2009). On the other hand, taking extra dose of Imatinib increases toxicity of the drug which may predispose the patient to develop further treatment related complications. In one study, poor adherence was found to be a principal factor contributing to cytogenetic relapse and failure of therapy in patients with CML who received long-term Imatinib therapy (Ibrahim *et al.*, 2011).

Non adherence of patients to Imatinib treatment is also associated with unnecessary dose escalation of Imatinib or regimen change and increased health care costs incurred by both the institution and the patient himself (Dalziel *et al.*, 2004). For example a retrospective study done in US showed that patients with a medication possession ratio (MPR) (adherence) of ≤75% incur an additional 4072 US dollars in medical costs annually compared with patients with MPR of ≥85% (Darkow *et al.*, 2007).

Additionally in Ethiopia, patient attendance rates and medical admissions in TASH are rising. According to TASH CML cancer registry report; incidence of CML is rising with parallel increments of attending physicians' report of treatment relapse and suboptimal response. This might be due to non-adherence of treatment in addition to natural course of the disease, which will be the focus of this study.

Since CML is a chronic disease, patients should take their medication lifelong. Knowing this and the above evidences; still there is no evidence-based research done in Ethiopia that assesses Imatinib treatment adherence and treatment outcomes among patients with CML. Therefore the purpose of this study is to fill the gap in knowledge of prevalence and contributing factors for non-adherence to Imatinib treatment, treatment outcomes and the association between adherence and treatment response in CML patients in TASH.

1.3 Literature Review

The major advance in pharmacologic treatment of CML following imatinib can be witnessed from a study by Kantarjian *et al.* (2012), which reviewed survival of CP CML patients from 1965-2010 in a single institution. This study showed that the 8-year survival was ≤15% before 1983, 42%-65% from 1983-2000, and 87% since 2001. In addition to better survival benefit, Imatinib also showed better response rate and decreased progression of CML to AP and BP. To this end, a study involving 1,106 patients randomly assigned to receive Imatinib 400 mg/day or INFα plus low-dose subcutaneous cytarabine demonstrated that the Imatininb group had better molecular responses, better tolerated, and higher rate of freedom from progression through the different phases than the combination group (O'Brien *et al.*, 2003).

According to a multicenter study done in Algeria, 83% of patients achieved a complete hematologic response to "generic" Imatinib treatment at the end of 3-months and the projected 5-year overall survival rate was 83% (Entasoltan *et al.*, 2017). Other multicenter study done by de Lavallade *et al* (2008); the 5 -year cumulative incidences of CCgR and MMR were 82.7% and 50.1%, respectively, with respective estimated overall survival and progression free survival of 83.2% and 82.7%. But in this study 25% of patients discontinued their treatment due to unsatisfactory response and toxicity.

Since then ongoing treatment approach faces challenges due to increased or frequent non-adherence of patients. Adherence to oral anticancer treatment, like Imatinib, is a complex issue and a number of factors have been shown to predict non-adherence. One is shift of treatment approach from IV chemotherapy to oral Imatinib therapy (NCCN, 2018) that transfers the responsibility of taking medication somewhat to patients alone in addition to other factors responsible for non-adherence. The presence of depression, disbelief in the benefits of the drug, having to take other drugs for co-morbidities, chronicity of disease, and length of treatment, are all important factors that may contribute to non-adherence in cancer patients (Cornelison *et al*., 2012). In addition, TKIs adverse effects, clinicians' and site staff experience, practice behavior, setting, and patients' level of knowledge were also shown to have an impact on adherence. Furthermore, illiteracy, poor education, and lower cognitive level are factors that can restrict patients' comprehension of the instructions given on treatment schedules and effects. In addition,

adherence behavior is also influenced by the economic and social factors (Vermeire *et al.*, 2001, Cramer *et al*., 2008, Noens *et al.*, 2009). Patient related factors could also be classified into two categories: intentional or unintentional. Patients might discontinue treatment intentionally due to personal beliefs about taking medications. Conversely, unintentional behavior is associated with patients' individual traits (e.g. forgetfulness, carelessness, socioeconomic factors) (Clifford *et al*., 2008).

Thus, non-adherence is likely to become an issue for the proper management of CML. For example, in a 24-month period multicenter retrospective study organized and sponsored by Novartis Pharma, adherence of CML patients to Imatinib was only 78% (Tsang *et al.*, 2006). Another retrospective study having study participants of 430 done by Charles *et al* (2009) also showed that 40% of patients were classified as non-adherent (having MPR of <85%) to their treatment over a 12-month follow-up period. According to ADAGIO prospective study, which is done on 169 Belgian patients with CML only, 14% took Imatinib exactly as prescribed and achieved 100% adherence according to pill counts and patient self-reports (Noens *et al.*, 2009).

In general, it has been estimated that non-adherence with Imatinib therapy increases up to three times the risk for poor treatment outcomes of CP-CML patients (Noens *et al*., 2009). In a study using various microelectronic monitoring systems to measure adherence levels during a three-month period in 87 consecutive CP-CML patients who had received Imatinib as first-line therapy, it was demonstrated that treatment adherence is a critical factor for achieving and maintaining molecular response in this group of patients. The probability of achieving MMR and complete molecular response (CMR) was significantly better in patients having >90% of treatment adherence (28.4% vs. 94.5% and 0% vs. 43.8% respectively) as compared to patients having <90% adherence level (Marin *et al*., 2010). Other study done in Egypt was also showed that among 40 patients whose treatment not interrupted in the 3- year treatment period, 95%, 70% and 32% of patients achieved CHR, MMR and CMR, respectively as compared to among 20 patients whose treatment interrupted with respective response status of 85%, 30% and 0% (Edesa and Abdel-malek, 2015).

2. Objectives

2.1. General Objective

- To assess treatment outcome and adherence to Imatinib among newly diagnosed patients with CML in TASH, Addis Ababa, Ethiopia.

2.2. Specific Objectives

- To assess the treatment outcome in newly diagnosed patients with CML in TASH, Addis Ababa, Ethiopia.
- To assess the level of adherence to Imatinib treatment in newly diagnosed patients with CML in TASH, Addis Ababa, Ethiopia.
- To determine predicting factors of treatment outcome in newly diagnosed patients with CML in TASH, Addis Ababa, Ethiopia.
- To identify factors associated with adherence to Imatinib treatment in newly diagnosed patients with CML in TASH, Addis Ababa, Ethiopia.

3. Methods

3.1. Study Setting

The study was conducted at the hematology clinic of TASH, which was established in 1972. It is the largest teaching hospital affiliated with College of Health Sciences, Addis Ababa University and serves as a training center for undergraduate and postgraduate medical, pharmacy and other health science students. It is also an institution where specialized comprehensive and clinical services that are not available in other public or private institutions are rendered to the whole nation, of which CML management is one of them. The hospital has around 465 physicians', 76 pharmacists, 992 nurses and 115 other health care professionals dedicated to providing health care services. It also has 950 administrative and support staff (College of health sciences human resource management, 2018). The various departments, faculty members and residents under specialty training in the School of Medicine provide patient care in the hospital. In addition, almost all regional and federal hospitals in Addis Ababa use this hospital as referral unit and training site.

The Hospital served more than 500,000 patients per year in its 20 outpatient specialty clinics, inpatient and emergency departments. Of the 20 outpatient specialty clinics; ambulatory hematology clinic is one of the largest units, which provides comprehensive specialty services, mainly for CML patients. On average, 3-5 new CML cases were diagnosed per week and a total of more than 50 CML patients visit the clinic per. In this clinic, there are a total of three hematologists, nine dedicated nurses and around 12 residents working in rotation. Outpatient services to CML patients were rendered in the clinic three times per week. All CML patients take Imatinib free of charge from the oncology pharmacy.

3.2. Study Design and Period

A prospective cohort study was conducted from 1 October 2016 to 30 November 2017. Each patient included in the study was followed for a total of 3- months and outcome variables were determined at the end of the follow-up.

3.3. Source and Study Population

All newly diagnosed CML patients who visited outpatient hematology clinic were considered as source population. All newly diagnosed CML patients that were kept on Imatinib and had regular follow up in the clinic during the study period formed the study population.

3.4. Sampling and Sample Size Determination

All newly diagnosed patients with CML and who started Imatinib treatment between October 1, 2016 to September 1, 2017 were enrolled for the follow-up study period.

3.5. Inclusion and Exclusion Criteria

Eligible patients include: (i) all newly diagnosed Ph chromosome positive (Ph +ve) CML patients; (ii) who regularly visiting outpatient hematology clinic to receive Imatinib treatment; and (iii) willing to participate. Exclusion criteria include: patients with any cognitive impairment, who did not start with Imatinib treatment due to being Ph chromosome negative (Ph -ve); and pregnant during study period.

Accordingly, among 152 study participants, 147 newly diagnosed eligible patients with CML were enrolled. Five patients fulfilling the exclusion criteria were (2-Ph chromosome negative, two women who were not started Imatinib treatment due to being pregnant at time of diagnosis and one patient who directly started Nilotinib). In addition, CHR and adherence status were not assessed for three patients due to lost to follow up (Figure 1).

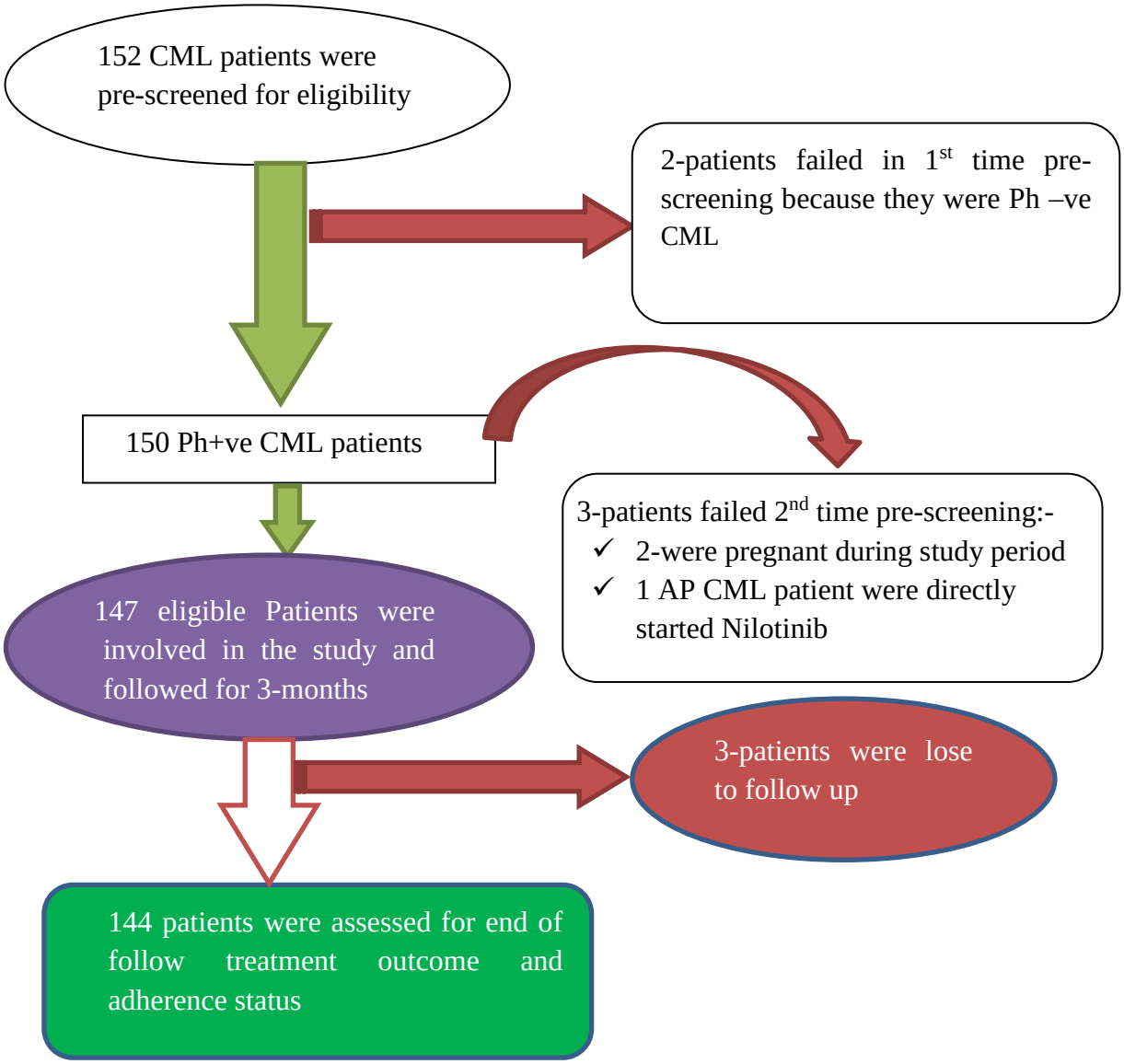

Figure 1: Diagrammatic scheme of study participant recruitment process

3.6. Study Variables

Independent Variables:

- Socio demographic variables (age, sex, educational level, monthly income, marital status, occupation, residence)
- Patient clinical characteristics at time of diagnosis (presence of co-morbidities, Prognostic scores based on EUTOS (Hasford *et al*., 2011), Sockal (Sokal *et al*., 1984) and Hasford

(Hasford *et al*., 1998) prognostic scoring system, clinical phase of CML, CBC, Ph chromosome percentage, PM and BM blast count)

- Treatment related characteristics (upfront hydroxyurea treatment and duration, daily dose of Imatinib treatment, difference between confirmed diagnosis and initiation of Imatinib treatment, adverse drug events of Imatinib)

Dependent variables:

- Treatment outcomes
- Adherence to Imatinib treatment,

3.7. Data Collection and Management

3.7.1. Data Collection Instruments and Techniques

A pre-tested, semi-structured questionnaire (Annex I) and data abstraction form (Annex II) were used to extract information from the patients and medical records, respectively. The questionnaire was used to ask their willingness to participate in the study and gather information on socio-demographic characteristics, 8-item Morisky medication adherence scale (MMAS-8) (Morisky *et al*., 2008), reasons for non-adherence to Iamtinib and encountered adverse drug events. The MMAS-8 is a 7 items with yes/no response options and 1 item with a 5-point Likert scale response option. MMAS-8 is a part of the World Health Organization case management adherence guideline assessment tools and mostly used to classify patients as "low", "medium" and "high" on motivation and knowledge domain. Patient reported reasons to medication non-adherence was collected for those patients whose MMAS-8 total score <8. Documented objective reasons for non-adherence and adverse effects encountered were also collected from patient chart.

The data abstraction form (Annex II) was designed to capture baseline and follow-up information. It had two parts. Part I was for all baseline findings at time of diagnosis and at initiation of Imatinib treatment. Part II was for follow-up findings. Information was categorized to those findings obtained at time of confirmed diagnosis, at initiation of Imatinib treatment and follow-up findings such as clinical characteristics, biochemical markers and upfront treatment

history. Prognostic scores were calculated by using online prognostic scoring calculators (BloodRef).

Furthermore, clinical characteristics, documented adverse drug events of Imatinib, dose or regimen change history with reasons, supportive treatments given, CHR rate and others were also collected at 2 weeks, 1, 2 and 3-months of follow-up. This part was designed based on the appointments given for the patients.

3.7.2. Data Collectors Recruitment and Training

Two nurses and one pharmacist were recruited as data collectors to collect data from patient charts and patient interview. A two-day training was given to all data collectors focusing on uniform interpretation of questions, strict use of study criterion, explanation of study objectives and getting verbal consents and assents from study participants, implementation of confidentiality of the collected data.

3.7.3. Data Quality Control

The data collection instruments were reviewed by senior experts of the area for clarity and comprehensiveness of its contents. Following that pre-testing of both data collection tools were done in ten selected patients with CML who had been taking Imatinib treatment for at least 3-months. Accordingly, all the necessary modifications and adjustments were done before implementing the main study. Throughout the data collection process close supervision was made by the principal investigator. The collected data were checked for completeness and accuracy. After data entry, data cleaning was performed and maximum effort was also done at the analysis and interpretation.

3.7.4. Data Analysis and Interpretation

Data were entered into Epi-Info Version-7.2.1.0 and analyzed by using SPSS version-21. Descriptive statistics including: frequency, median, range, mean and standard deviation were used to summarize socio-demographic data, clinical and treatment related characteristics and evaluate distribution of responses. Bivariate analysis was conducted to see the existence of association of adherence, CHR rate and physician led temporary cessation of Imatinib treatment

with independent variables. All variables with $p<0.25$ in the univariate binary logistic regression analysis were included in the multivariable binary logistic regression, which was performed to determine the potential predictors of non-adherence and treatment outcomes. p-value < 0.05 was considered as statistically significant.

3.8. Ethical Considerations

Ethical clearance and approval of the study protocols was obtained from the Ethical Review Board of School of Pharmacy. In addition, permission was sought from head of Department of Internal Medicine and hematology unit to conduct the study in the clinic. Prior to data collection, individuals were informed about the study and verbal assent was taken from parents for those study participants whose age was <18 years and verbal consent was obtained from the rest of the study participants. Each patient was informed about the objective of the study, procedures of selection and assurance of confidentiality. Individuals were informed that it is fully voluntary and they can withdraw from the study at any time and this would not affect the service they get from the hospital. They were also informed that they would not receive any monetary incentive for participating in the study. The collected data was secured in a lockable cabinet, no identifiers were used and data was analyzed in aggregate to maintain confidentiality and anonymity of information.

3.9. Operational Definitions

High adherent to Imatinib treatment: A patient who scored 8 for the MMAS-8 said to be adherent to medications.

Medium adherent to Imatinib treatment: A patient who scored <8 and ≥6 for the MMAS-8 said to be Medium adherent to medications

Low adherent to Imatinib treatment: A patient who scored <6 for the MMAS-8 said to be poor adherent to medications.

Suboptimal adherence: Either Medium adherent or poor adherent.

Treatment outcomes: CHR, No CHR and adverse drug events encountered after Imatinib initiation.

CHR: normalization of peripheral blood counts with no immature blood cells, WBC less than 10,000 cells/ mm^3, platelet count less than 450,000 cells/mm^3 and free of signs and symptoms with complete disappearance of splenomegaly. But if either of the criterion is missed, then it is considered as CHR failure (NCCN, 2018).

Adverse drug events: Any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment, i.e, an adverse outcome that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it (EFMHACA, 2014).

Grade III-IV Hematologic toxicity: **in CP-CML;** Neutropenia with ANC<1000 or thrombocytopenia with platelet count of $<50x10^3$ cells/ mm^3, and in AP-CML, neutropenia with ANC<500 or thrombocytopenia of platelet count of $10x10^3$ cells/mm^3. The rest are categorized in Grade I-II hematologic toxicity (Jabbour *et al*., 2011).

AP- CML: Patients with baseline peripheral blast count of 10-19% or with basophilia ≥20% in the peripheral blood or patients with persistent thrombocytosis (>1 million cells/mm^3) unresponsive to therapy or persistent thrombocytopenia (<100,000cells/mm^3) not related to therapy or detection of cytogenetic clonal evolution (e.g.del-9q chromosome)(WHO, 2016).

Blast crisis phase: Blasts ≥ 20% in the peripheral blood or bone marrow, extramedullary blast proliferation, apart from the spleen, large foci or clusters of blasts in the bone marrow biopsy (WHO, 2016).

Chronic phase CML: other than AP and BC phase criteria.

EUTOS score: low risk if it is ≤87 and high risk (>87)

Sockal Score: Low risk if it is <0.8, intermediate risk (0.8-1.2) and high risk (>1.2)

Hasford (Euro) Score: low risk for those with score <780, intermediate risk (780-1480), high risk (>1480).

4. Results

4.1. Socio-demographic Characteristics

A total of 147 eligible newly diagnosed patients with CML were enrolled during the study period. Their mean age was 37.8 years (SD=13.7) and median 36 years (Range 14-74); with most (96, 65.3%) of the patients being in the age group of less than 40 years. Majority of the patients were male (87, 59.2%), with male to female ratio of 1.45: 1 and married (101, 68.7%). Being employee (37, 25.2%), attended secondary education (43, 29.3%) and do not read and write (43, 29.3%) accounted the highest proportion. Virtually most patients (110, 74.8%) were out of Addis Ababa. Almost half (67, 45.6%) of the study participants were > 300km away from the Hospital. A significant proportion of the study participants (71, 48.3%) were in a very low or low level of monthly family income. A significant number (136, 92.5%) of patients diagnosed with CP-CML and only 11(7.5%) of patients diagnosed at advanced stage CML (Table 1).

Table 1: Socio-demographic characteristic of newly diagnosed patients with chronic myeloid leukemia at Tikur Anbessa Specialized Hospital from October 1, 2016- September 1, 2017

Variables	Phase of CML, N (%)		
	CP (n=136)	AP(n=11)	Total (n=147)
Age (in years)			
Median(Range), 36(14-74)			
Mean ± SD, 37.8 ± 13.7			
Sex			
Male	81(59.6)	6(54.5)	87 (59.2)
Female	55(40.4)	5(45.5)	60 (40.8)
Marital Status			
Single(single, divorced and widowed)	42(30.9)	4(36.4)	46(31.3)
Married	94(69.1)	7(63.6)	101(68.7)
Educational Status			
Can't read and write	41(30.1)	2(18.2)	43(29.3)
Primary Education	33(24.3)	4(36.4)	37(25.2)
Secondary Education	21(15.4)	1(9.0)	22(14.9)
Higher Education	39(28.7)	4(36.4)	43(29.3)
Can read and write but have no formal education	2(1.5)	0(0)	2(1.3)
Occupation			
Farmer	24(17.6)	1(9.1)	25(17.0)
Merchant/Trader	23(16.9)	3(27.3)	26(17.7)
Employed[a]	33(24.3)	4(36.4)	37(25.2)
House wife	21(15.4)	2(18.1)	23(15.6)
Retired	15(11.1)	0(0.0)	15(10.2)
Others*	20(14.7)	1(9.1)	21(14.3)
Residence, Region			
Addis Ababa	36(26.5)	1(9.1)	37(25.2)
Oromia	35(25.7)	2(18.1)	37(25.2)
Amhara	33(24.3)	2(18.1)	35(23.8)
SNNPR	13(9.6)	3(27.5)	16(10.9)
Tigray	11(8.0)	1(9.1)	12(8.1)
Others**	8(5.9)	2(18.1)	10(6.8)
Ava. distance between Patients home & TASH			
< 100km	42(30.9)	1(9.1)	43(29.2)
100-300km	33(24.3)	4(36.4)	37(25.2)
>300 km	61(44.8)	6(54.5)	67(45.6)
Monthly Family Income in ETB[$]			
Low and Very Low (≤1500)	68(50.0)	3(27.3)	71(48.3)
Average and Above Average (1501-5000)	53(39.0)	7(63.6)	60(40.8)
High (≥ 5001)	15(11.0)	1(9.1)	16(10.9)

[a] Having a job working for a company or another person for a monthly salary basis *Student, Daily laborer, Religious teachers and servants; **Afar, Harari, Ethiopian Somali, Diredawa, Benishangul; [$]Based on the Ethiopian Civil Service monthly salary scale for civil servants.

Regarding age distribution of newly diagnosed patients with CML, majority 42(28.6%) of them were in the 21-30 years age category; followed by 31-40 years (40, 27.2%) and 41-50 years (25, 17.0%) (Figure 2).

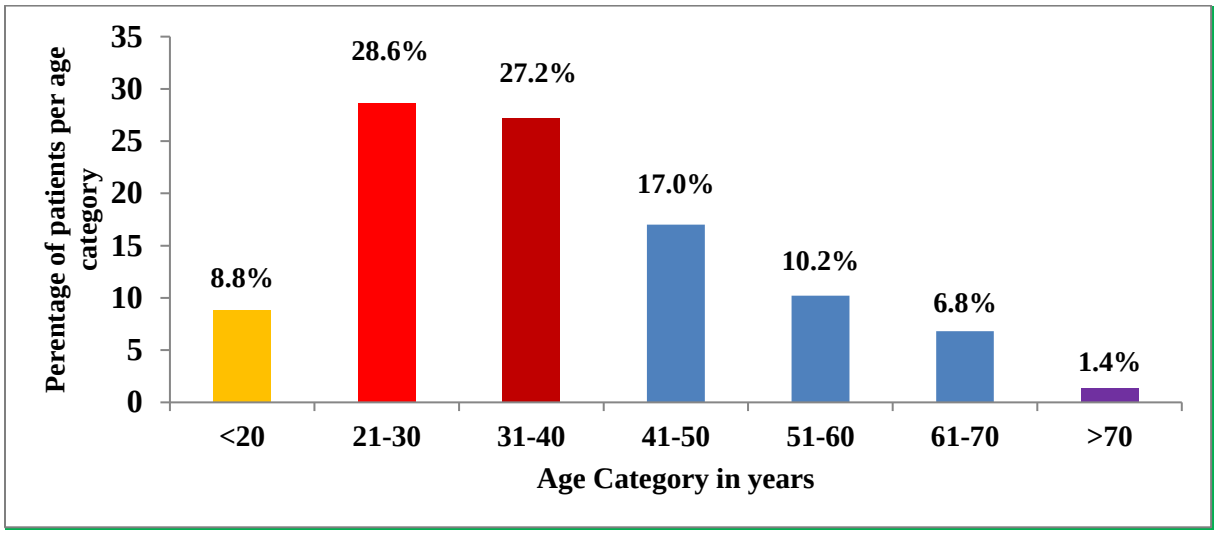

Figure 2: Age distribution of newly diagnosed patients with chronic myeloid leukemia in Tikur Anbessa Specialized Hospital from october 1, 2016-September 1, 2017

4.2. Baseline Clinical Characteristics of Patients at Diagnosis

Clinical characteristics of the study participants are depicted in Table 2. All patients had a Ph chromosome/BCR-Abl testing by RT-QPCR, FISH or classical karyotyping at diagnosis, of which (141, 95.9%) tests were quantitative with median percentage of 85% (Range: 1.12-100%). Most (136, 92.5%) patients were diagnosed as CP-CML and those diagnosed at advanced stage (AP-CML) (11, 7.5%) were found in the age group <40 years old (7, 63.6%). Staging of CML was made mainly based on peripheral blast count percentage. But there were also patients staged based on basophil (>20%), platelet count (> 1 million count) and detection of del-9q chromosome. Only 15 (10.2%) CML patients had other comorbid illnesses, of these human immune-deficiency virus infections (HIV) (5, 33.3%) accounted for the highest proportion followed by hypertension (4, 26.7%). Almost all (139, 94.6%) participants had organomegally, of which 70(47.6%) of them had hepatosplenomegaly, and 69(46.9%) had only splenomegaly. The median spleen size below right costal margin (BRCM) in centimeter (cm) was 16 (Range: 8-32). Baseline median (range) of WBC and platelet counts x 10^3 cells/ mm^3 were 310.6(47-1191) and 313(63-1753), respectively.

Table 2: Baseline clinical characteristics of newly diagnosed patients with chronic myeloid leukemia at Tikur Anbessa Specialized Hospital from October 1, 2016- September 1, 2017

Variables	N	%	Median (Ranges)	(Mean ± SD)
CML Phase at diagnosis				
Chronic phase	136	92.5		
Accelerated phase	11	7.5		
Presence of Co-morbid illnesses				
Yes	15	10.2		
No	132	89.8		
Type of comorbid illness				
HIV *	5	33.3		
Hypertension	4	26.7		
Others**	6	40.0		
Presence of Organomegally				
Splenomegaly only	69	46.9		
Both HSM***	70	47.6		
Spleen size, BRCM[a], cm			16 (8-32)	17.3 ±3.9
No Organomegally	8	5.4		
Baseline Complete blood count				
WBC count, x 10^3 cells/ mm^3			310.6 (47-1191)	341± 212.5
Basophil count, %			11.0 (0-33)	11.6± 6.1
Eosinophil, %			3.5(0.1-15.8)	4.5±7.3
Platelet count, x 10^3 cells/ mm^3			313 (63-1753)	377.4 ± 232.1
Hemoglobin count, g/dl			9.1 (5-17)	9.7 ± 2.2
Peripheral Blast count, %			5 (0-16)	4.9 ± 3.1
Bone marrow blast count, %			6(2-16)	5.6 ± 2.8
Ph chromosome/BCR-Abl %			85 (1.12-100)	66.7 ±33.1%

*Patients living with human immune-deficiency virus infection. **Type 2 diabetes mellitus 2(13.3%), congestive heart failure 2(13.3%), hypothyroidism 2(13.3%), Congenital Anomaly 1(6.7%). ***Hepatosplenomegaly

[a]Maximum distance below the right costal margin in centimeter, assessed by manual palpation measurement.

Majority (78, 53.0%) of the patients baseline WBC count at time of confirmed diagnosis was above 300x10^3 cells/mm^3 with most (49, 33.3%) of them in 301-500x 103 cells/mm^3 baseline WBC category. In addition, 56 (38.1%) patients had baseline abnormal platelet count, of which the high base line platelet count (>450 x 10^3 cells/ mm^3) accounted the highest percentage (43, 76.8%) (Figure 3).

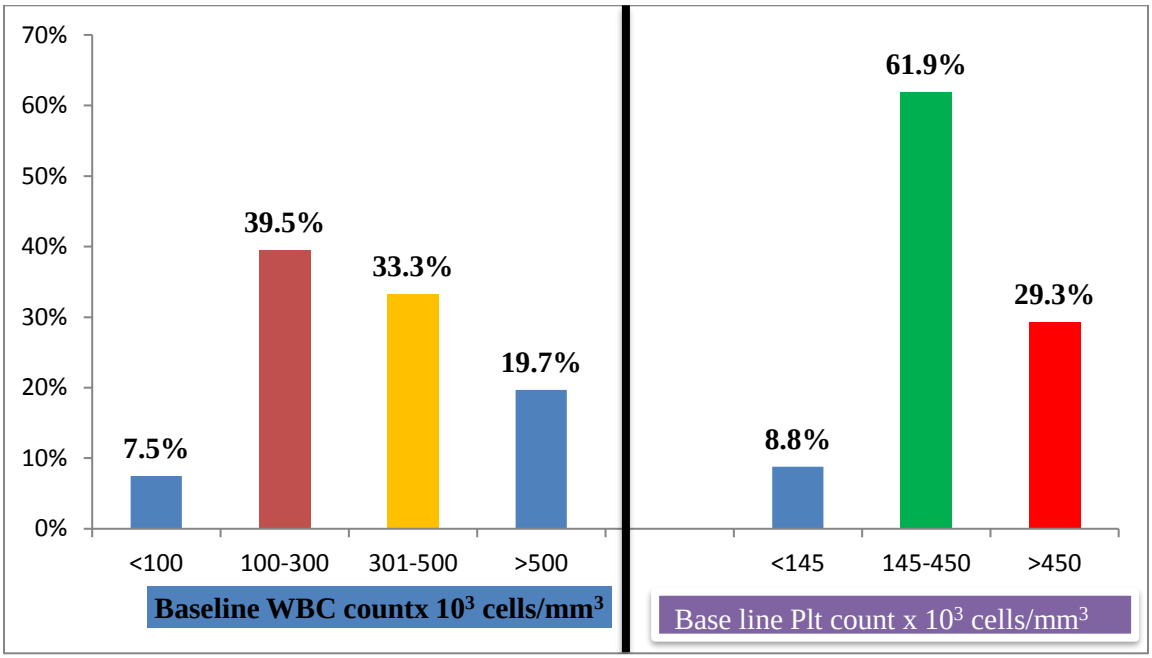

Figure 3: Baseline white blood cell and Platelet counts(x 10^3 cells/ mm^3) for newly diagnosed patients with chronic myeloid leukemia at Tikur Anbessa Specialized Hospital from October 1, 2016- September 1, 2017

Among 140 study participants, 110 (78.6%) and 78 (55.7%) of them were high risk based on EOUTS, and Sockal prognostic scoring system, respectively. But only one-third (46, 32.9%) of them were high risk based on Hasford prognostic scoring system (Table 3).

Table 3: Prognostic scores of newly diagnosed patients with chronic myeloid leukemia at Tikur Anbessa Specialized Hospital from October 1, 2016- November 30, 2017

Prognostic score system	**N**	**%**
EUTOS Score		
Low risk (≤ 87)	30	21.4
High Risk (> 87)	110	78.6
Sockal Score		
Low Risk (<0.8)	13	9.3
intermediate Risk (0.8-1.2)	49	35
High Risk (>1.2)	78	55.7
Hasford Score		
Low risk (<780)	15	10.7
Intermediate risk(780-1480)	79	56.4
High risk (>1480)	46	32.9

4.3. Treatment History

Median (range) of WBC and platelet count at Imatinib initiation was 43.1 (3.3- 644) $x10^3$ cells/ mm^3 and 311 (70-1508) $x10^3$ cells/ mm^3, respectively. Moreover, nearly, three-quarter (114) of the patients had organomegally, of which splenomegaly accounted for the highest percentage (96, 65.3%). Majority (136, 92.5%) of the patients had taken upfront hydroxyurea treatment for cytoreduction. Treatment duration of hydroxyurea ranged from 2-weeks to 9.5 months, with median treatment duration of 1-month. In addition, the latency for initiation of Imatinib treatment between suspected diagnosis of CML through bone marrow and confirmed diagnosis by cytogenetic test ranged from 2-weeks to 1-year with median period of 1.5 months. Nearly, all patients (141, 95.9 %) received 400 mg Imatinib as a daily dose and 36 (24.5%) of them also had taken HU and Imatinib combination for a maximum of 2-months and a minimum of 2-weeks, with median of 2-weeks duration (Table 4).

Table 4: Treatment history and baseline findings at initiation of Imatinib treatment for newly diagnosed patients with chronic myeloid leukemia at Tikur Anbessa Specialized Hospital from October 1, 2016- November 30, 2017

Base line Findings at Initiation of Imatinib			
Complete blood count	**Median (Ranges)**	**N**	**%**
WBC, x 10^3 cells/ mm^3	43.1 (3.3- 644)		
Basophil count, %	6.8 (0-39)		
Platelet count, x 10^3 cells/ mm^3	311.0 (70-1508)		
Hemoglobin count, g/dl	10.3(5.2-15.2)		
Presence of organomegally			
Splenomegaly only		96	65.3
Both Hepatosplenomegaly		18	12.2
No organomegally		33	22.4
Treatment History			
For Cytoreduction treatment			
HU**		136	92.5
No (directly started IM[a] treatment)		11	7.5
Duration of HU treatment, In months	1.0 (0-9.5)		
Latency of Initiation of IM therapy	1.5(0.5-12.0)		
Initial daily Dose (IM)			
400 mg		141	95.9
600 mg		6	4.1
IM + HU combination treatment			
Yes		36	24.5
No		111	76.5
Duration of combination, in months	0.5(0.5-2)		

* Hepatosplenomegaly, **Hydroxyurea [a] Imatinib

4.4. Imatinib Treatment Outcome

4.4.1. Treatment Response to Imatinib

Treatment response at each time line was also assessed based on appointment period given which was at 2 weeks, 1, 2 and 3-months. The median for total number of clinic visits during study period was 4-times (Ranged: 2-8 times). Among 127 patients visited hematology clinic after 2-weeks of Imatinib treatment, 29 (22.8%) of them achieved CHR, of which patients who had WBC count <50 x 10^3 cells/ mm^3 at time of initiation of Imatinib accounting for the highest proportion (27, 93.1%). WBC count after 2-weeks of Imatinib treatment was also increased from baseline in 14 (11.1%) of the patients. Majority of the patients who came after 1-month (n=121) and 2-months (n=118) of treatment achieved CHR: (73, 60.3%) and (93, 78.8%), respectively. From the 147 newly diagnosed patients, 3 (2%) of them were lost to follow up with unknown status. Overall, among the 144 study participants who completed follow up study, 132 (91.7%) of them achieved CHR at the end of 3-months. Majority of patients (7, 58.3%) who failed to achieve CHR at the end of follow-up were in the WBC count at initiation of Imatinib <50 x 10^3 cells/ mm^3 category. In the subgroup analysis most of patients (60, 74.1%) in the <50 x 10^3 cells/ mm^3 category were from country side (out of Addis Ababa). The median time for CHR attainment was 6 weeks (Ranged: 2-16weeks) (Table 5).

Table 5: Response status to Imatinib treatment among newly diagnosed patients' with chronic myeloid leukemia at Tikur Anbessa Specialized Hospital from October 1, 2016- November 30, 2017

Duration of Imatinib Treatment		**Response Status based on baseline WBC category*, n (%)**					
		≤50k	**51-100k**	**101-150k**	**≥151k**	**Total**	***p-value***
2 weeks	CHR	27(93.1)	0	2(6.9)	0	29(22.8)	
	No CHR	34(40.5)	23(27.4)	14(16.6)	13(15.5)	84(66.1)	
	WBC increased from baseline**	5(35.7)	6(42.9)	0	3(21.4)	14(11.1)	
	Total	66(52.0)	29(22.8)	16(12.5)	16(12.5)	127	***0.001***
1 month	CHR	50(68.5)	11(15.1)	7(9.6)	5(6.8)	73(60.3)	
	No CHR	18(37.5)	15(31.3)	5(10.4)	10(20.8)	48(39.7)	
	Total	68(56.2)	26(21.5)	12(9.9)	15(12.4)	121	***0.059***
2 months	CHR	52(55.9)	22(23.7)	9(9.7)	10(10.7)	93(78.8)	
	No CHR	10(40.0)	5(20.0)	5(20.0)	5(20.0)	25(21.2)	
	Total	62(52.5)	27(22.9)	14(11.9)	15(12.7)	118	***0.409***
3 months	CHR	74(56.1)	28(21.2)	14(10.6)	16(12.1)	132(91.7)	
	No CHR	7(58.3)	2(16.7)	3(25.0)	0	12(8.3)	
	Total	81(56.3)	30(20.8)	17(11.8)	16(11.1)	144	***0.320***

*White blood cell count x 10^3 cells/ mm^3 found at time of initiation of Imatinib treatment.
**White blood count increased as compared to the preceding complete count test findings and also are part of no CHR category

4.4.2. Safety of Imatinib and Management Trend

Safety of Imatinib

Significant number (59, 40.1%) of patients developed hematologic toxicity, such as thrombocytopenia (39, 26.6%), neutropenia (15, 10.3%) or bicytopenia (6, 4.2%), of which 1/3rd of them were grade III-IV hematologic toxicity. Based on organ system, the most common non-hematologic toxicities that patients experienced were gastrointestinal (GI) related adverse effects (65, 33.8%), of which dyspepsia accounted for the highest percentage (49, 75.6%) followed by nausea/vomiting (10, 16.1%). Among non-GI-related adverse drug events, fatigue (51, 39.8%) and headache (30, 23.4%) were the most common events (Table 6).

Table 6: Documented and patient reported adverse drug events of Imatinib and among newly diagnosed patients with chronic myeloid leukemia at Tikur Anbessa Specialized Hospital from October 1, 2016- November 30, 2017

Imatinib adverse drug events N=147	**Hematologic Toxicity, (N=59)**		
	Grade I/II hematologic toxicity, n(%)	**Grade III/IV hematologic toxicity, n(%)**	**Total, n(%)**
Thrombocytopenia	29(74.4)	10(25.6)	39(26.6)
Neutropenia	7(46.7)	8(53.3)	15(10.3)
Bicytopenia*	3(50)	3(50)	6(4.1)
Total	**38(64.4)**	**21(35.6)**	**59(40.1)**
	Non hematologic, (N=193)**		
GI-adverse drug events			**65(33.8)**
Dyspepsia			49(75.4)
Nausea/vomiting			10(15.4)
Diarrhea			6(9.2)
Non GI-related adverse drug events			**128(76.2)**
Fatigue			51(39.8)
Headache			30(23.4)
Edema			13(10.1)
Facial Puffiness			11(8.6)
Myalgia/Arthralgia			10(7.8)
Skin Rash			9(7.0)
Others[a]			8(6.3)

*Both thrombocytopenia and neutropenia, [a]Skin color change, dizziness, insomnia,

**Grading was not done due to lack of grading system and most were patient reported that also makes them very difficult.

Management Practices after Imatinib Initiation

Among 147 study participants, management was altered in 35 (23.8%) of the patients i.e. either treatment temporarily discontinued by physicians or due to stock out of Imatinib, dose of Imatinib decreased or increased (Figure 4).

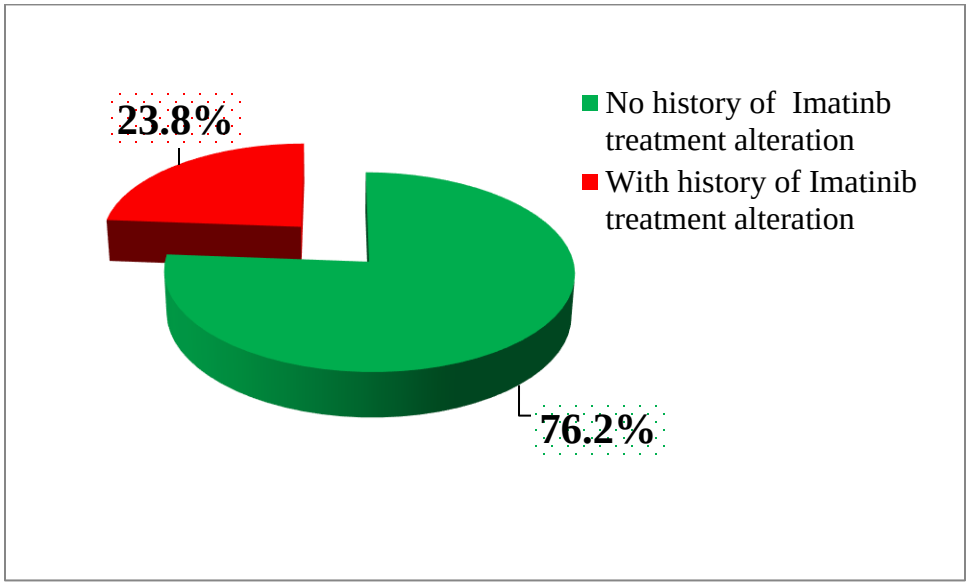

Figure 4: Proportion of Imatinib treatment alteration among newly diagnosed patients with chronic myeloid leukemia at Tikur Anbessa Specialized Hospital from October 1, 2016-November 30, 2017

Alteration was due to physician-led temporary discontinuation (25, 71.4%), decrement of daily dose due to intolerance (5, 14.3%), and increment of daily dose due to poor response (3, 8.6%). The median total duration of treatment discontinuation was 14 days (Range: 14–42 days). Furthermore, two patients had also skipped their treatment for two weeks due to stock out of the drug. Most of the physician led temporary treatment discontinuations were encountered within one month of therapy at median Imatinib treatment duration of 21 days (14-90 days). Almost all patients' (23, 92%) whose treatment temporarily discontinued had resumed treatment, except for two patients due to pregnancy at 2 and 2½ months of Imatinib treatment (Figure 5).

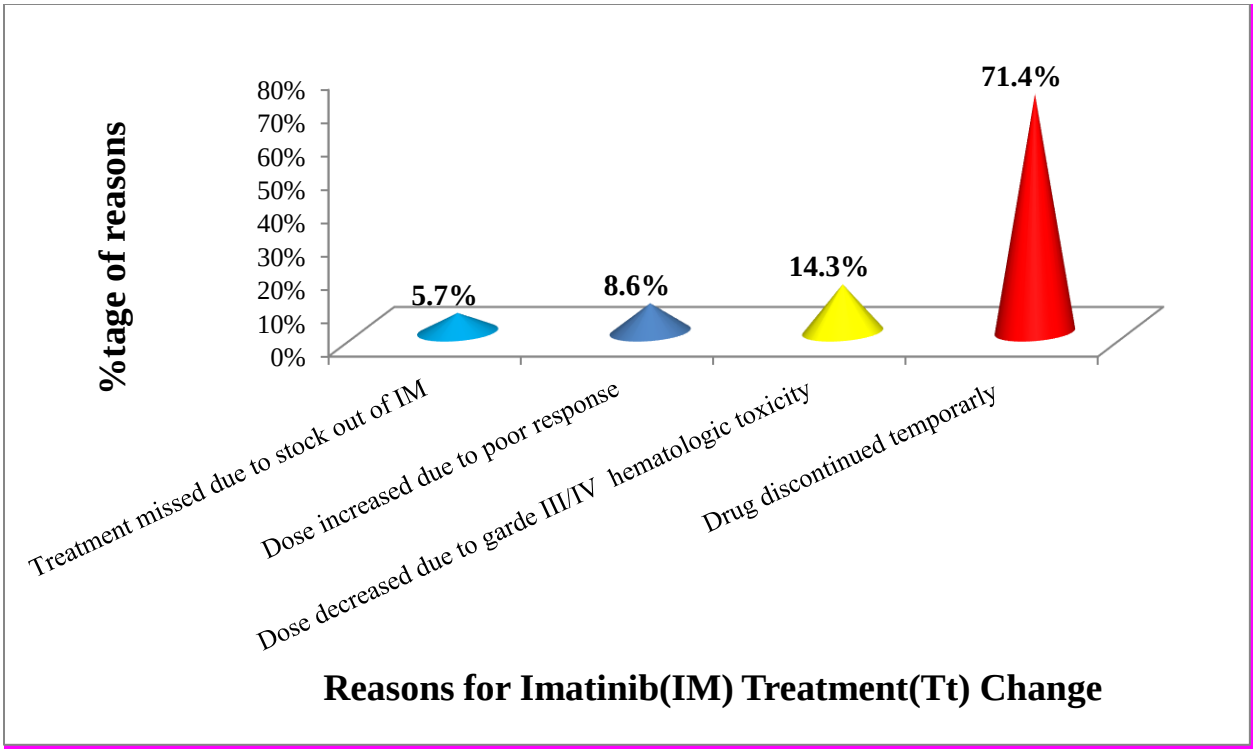

Figure 5: Reasons for Imatinib treatment change among newly diagnosed patients with chronic myeloid leukemia at Tikur Anbessa Specialized Hospital from October 1, 2016- November 30, 2017

Reasons for Temporary Discontinuation or Dose decrement

Among the 30 study participants who fulfilled temporary treatment discontinuation or dose decrement due to safety issue, grade III/IV Imatinib toxicity accounted for the highest proportion (28, 93.3%). Grade III/IV thrombocytopenia was the main reason (12, 40.0%) followed by neutropenia (7, 23.3%), bicytopenia (5, 16.7%) and skin rash (3, 10.0%). In addition, in two study participants, Imatinib was also temporarily discontinued due to grade III/IV thrombocytopenia though they didn't fulfill the criteria. The rest, (2, 6.7) and (1, 3.3) reasons were associated with being pregnant while on Imatinb treatment and severe arthralgia/myalgia, respectively (Figure 6).

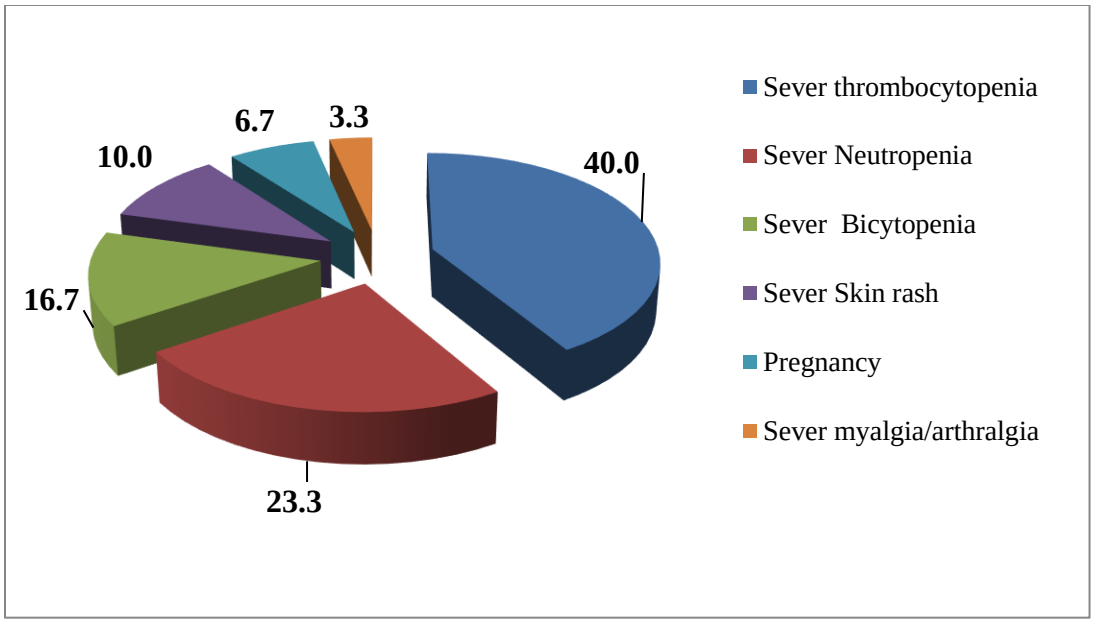

Figure 6: Reasons for temporary treatment discontinuation or dose decrement due to Imatinib safety among newly diagnosed patients with chronic myeloid leukemia at Tikur Anbessa Specialized Hospital from October 1, 2016- November 30, 2017

Types of Regimens used in Imatinib Toxicity Management

Among regimens prescribed as supportive management for Imatinib toxicity, proton pump inhibitors mainly omeprazole was the most widely used medication (38, 40.4%) followed by tramadol (12, 12.8%) and antihistamines (10, 10.6%). Blood transfusion and unspecified antibiotics were also the next common regimens used for supportive management of Imatinib toxicity. Other least commonly used medications were folic acid, diuretics, ranitidine, steroids and sun screen (Table 7).

Table 7: Types of regimens used in Imatinib toxicity management among newly diagnosed patients with chronic myeloid leukemia at Tikur Anbessa Specialized Hospital from October 1, 2016- November 30, 2017

Types of Regimens used in Imatinib Toxicity Management	N	%
Proton pump inhibitor(Omeprazole)	38	40.4
Tramadol	12	12.8
Antihistamines (chlorpheniramine)	10	10.6
Antibiotics	8	8.5
Blood Transfusion	8	8.5
H2 Blockers(Ranitidine)	5	5.4
Others*	13	13.8
Total	94	100.0

*Folic acid (4-patients), diuretics (3-patients), paracetamol (2-patients), steroids (2-patients) and sun screen (1-patient).

4.5. Adherence and Reason for Non- Adherence

Assessment of patients' responses to the 8-item Morisky Medication Adherence scale (MMAS-8) among those who completed a 3-months follow up showed that 80 (55.5%), 42 (29.2%) and 22 (15.3%) patients exhibited high, medium and low adherence to Imatinib treatment, respectively (Figure 7).

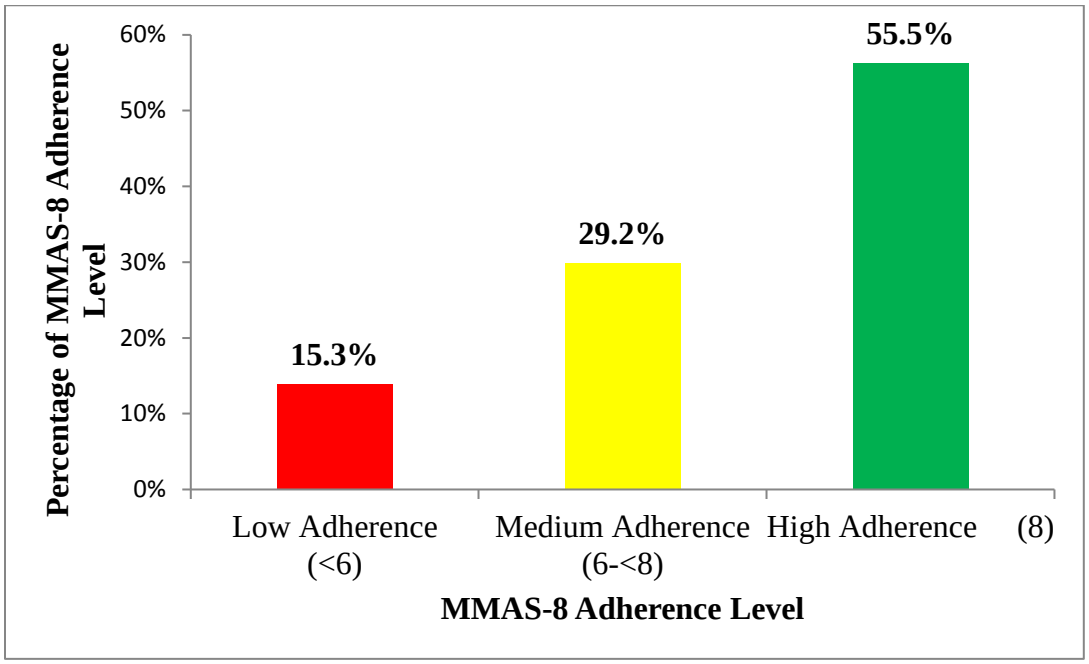

Figure 7: MMAS-8 rate of adherence to a 3-months Imatinib treatment follow up period from October 1, 2016 - November 30, 2017 among newly diagnosed patients with chronic myeloid leukemia in Tikur Anbessa Specialized Hospital

Up on evaluation of the reasons for CML patients' non-adherence to Imatinib treatment, it was identified that adverse effects of Imatinib was the main reason for their non-adherence (44, 68.8%). Furthermore, boredom of taking Imatinib daily, feeling well without treatment and lack of trust on efficacy of treatment due to religious beliefs accounted for 37.5%, 34.4% and 31.5% of medication non-adherence, respectively. Forgetfulness and inadequate information about the drug were, however, the least common reasons for non-adherence (Figure 8).

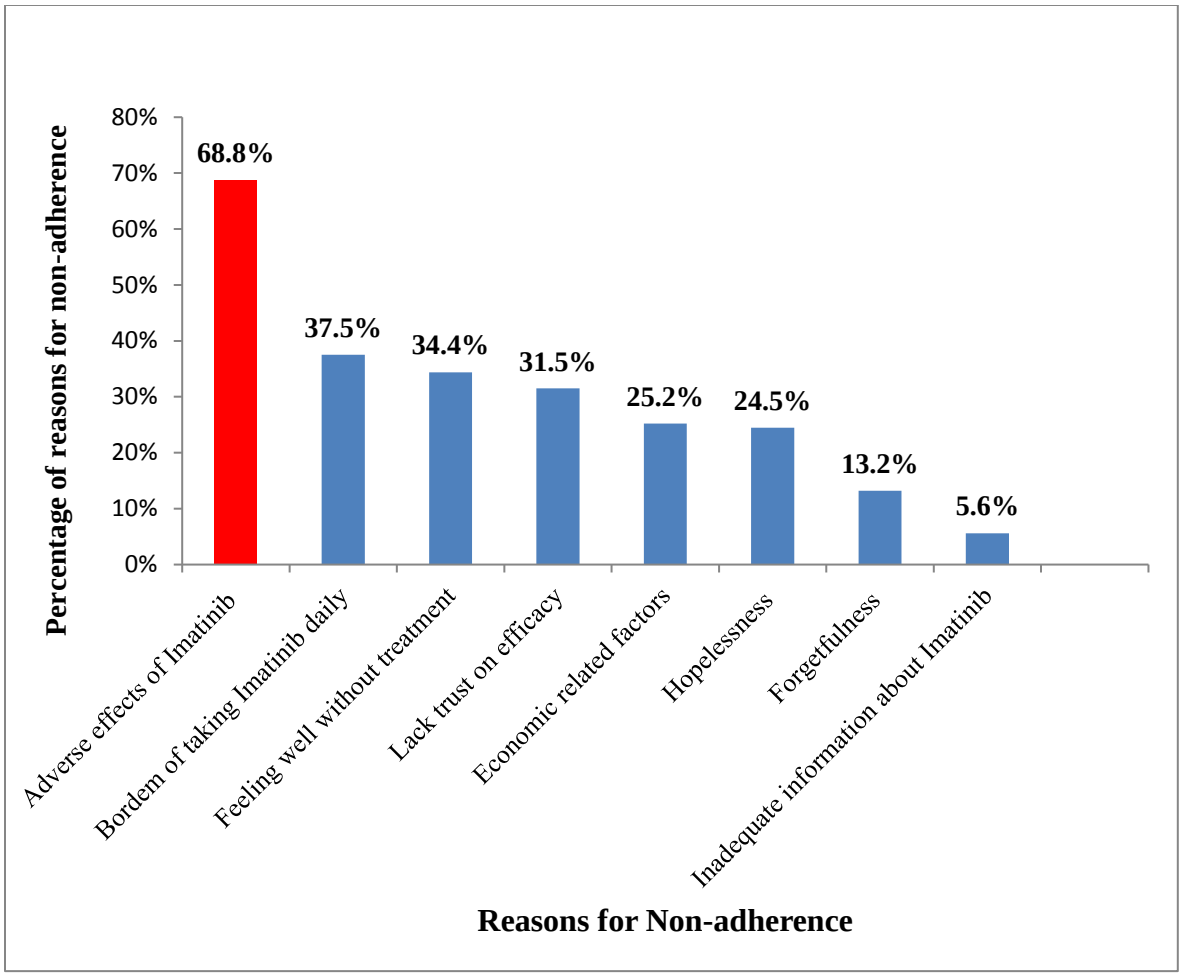

Figure 8: Reasons for non-adherence to Imatinib among newly diagnosed patients with chronic myeloid leukemia at Tikur Anbessa Specialized Hospital from October 1, 2016- November 30, 2017

4.6. Predicting Factors Associated with Treatment Outcome

4.6.1. Predicting Factors Associated with Complete Hematologic Remission to Imatinib

Of those nine variables (Table 8) included in multivariable logistic regression following univariate binary logistic regression analysis; only peripheral blast count, WBC count at Imatinib initiation and adherence status were significantly associated with CHR at the end of 3-months of Imatinib treatment.

The study found that having peripheral blast count <5% was a predictive for CHR success (AOR=0.33, 95% CI: 0.16-0.79). In other words, patients whose peripheral blast count ≥5% had a 67% less chance to achieve CHR than their counterparts. Moreover, patient adherence status was also examined for possible association with CHR and the result showed that as adherence level increased, the probability of CHR increased. Study participants who had Morisky high adherent and medium adherent score were about nine (AOR= 8.6, 95% CI: 4.32-11.1) and seven (AOR=6.9, 95% CI: 3.1-10.7) times more likely to achieve CHR than Morisky low adherent counter parts (Table 8).

Table 8: Univariate and multivariable binary logistic regression analysis of predictors of hematologic response status at the end of 3-months of Imatinib treatment

Variable	Response Status		COR, 95% CI	AOR, 95% CI
	CHR	No CHR		
Gender				
Male	77(58.3)	9(75.0)	1.00	1.00
Female	55(41.7)	3(25.0)	3.1(0.53, 0.99)*	3.8(0.29-6.3)
Age, in years				
≤40	86(65.2)	7(58.3)	1.00	1.00
41-60	36(27.3)	3(25.0)	0.8(0.19-3.38)	0.08 (0.003-2.06)
>60	10(7.5)	2(16.7)	0.26(0.06-0.92)*	0.06(0.001-2.93)
EUTOS score				
Low risk	26(20.0)	4(33.3)	1.00	1.00
High risk	104(80.0)	8(66.7)	0.31(0.039-2.6)	0.28(0.032-2.4)
Sockal Score				
Low risk(<0.8)	12(9.2)	2(16.7)	1.00	1.00
Intermediate risk(0.8-1.2)	50(38.5)	4(33.3)	2.01(0.17-24.9)	1.21(0.001-12.6)
High Risk (>1.2)	68(52.3)	6(50.0)	0.67(0.07-5.43)	0.49(0.003-3.88)
Peripheral blast count				
<5%	38(28.8)	1(8.3)	1.00	1.00
≥5%	94(71.2)	11(91.7)	0.13(0.06-0.51)*	0.33(0.16-0.79)*
CML phase				
CP	122(92.4)	11(91.7)	1.00	1.00
AP	10(7.6)	1(8.3)	1.1(0.13-4.5)	1.0(0.45-3.6)
WBC count at IM initiation				
<50x10^3 cells/mm^3	74(56.1)	7(58.3)	1.00	1.00
50-100 x10^3 cells/mm^3	28(21.2)	2(16.7)	1.32(0.26-6.76)	1.58(0.23-10.8)
≥100 x10^3 cells/mm^3	30(22.7)	3(25.0)	0.95(0.23-3.90)	0.54(0.09-3.25)
Presence of organomegaly				
Yes	101(76.5)	10(83.3)	1.00	1.00
No	31(24.5)	2(16.7)	0.74(0.32-7.38)	0.88(0.12-5.66)
Upfront HU treatment				
No	9(6.8)	2(16.7)	1.00	1.00
Yes	123(93.2)	10(83.3)	2.69(0.51-14.17)	3.6(0.36-9.1)
IM temporarily discontinued				
Yes	27(20.5)	2(16.7)	1.00	1.00
No	105(79.5)	10(83.3)	1.4(0.27-6.45)	3.9(0.61-13.9)
Adherence status				
Low (<6)	12(9.1)	9(75.0)	1.00	1.00
Medium(6-<8)	41(31.1)	2(16.7)	7.1(2.92, 11.8)*	6.9(3.1-10.7)*
High (8)	79(59.8)	1(8.3)	9.35(7.55, 16.6)**	8.6(4.32-11.1)**

COR=Crude odd ratio, AOR=Adjusted odd ratio,

*Statistically Significant at $P < 0.05$, **statistically significant at $p < 0.001$

4.6.2. Factors Associated with Temporary Imatinib Discontinuation or Dose Decrement

In the multivariable binary logistic regression analysis, only sex and baseline platelet count at initiation of Imatinib had significant association with temporary discontinuation of Imatinib treatment and dose decrement. In this regard, patients who had baseline platelet count < $100x10^3$ cells/mm^3 at Imatinib initiation were five (AOR= 5.3, 95% CI: 2.35, 8.7) times more prone for temporary discontinuation or dose decrement when compared with those having ≥ $100x10^3$ cells/mm^3. With regard to gender; females were about three (AOR= 2.82, 95% CI: 1.32, 4.94) times more likely to have temporary Imatinib discontinuation or dose decrement as compared to males (Table 9).

Table 9: Univariate and multivariable binary logistic regression analysis of predictors of temporary Imatinib discontinuation and Dose decrement due to adverse effect intolerance

Variables	Treatment change [a]		COR, 95% CI	AOR, 95% CI
	Yes	No		
Gender				
Male	10(33.3)	77(65.8)	1.00	1.00
Female	20(66.7)	40(34.2)	2.39(1.25, 3.89)*	2.82(1.32, 4.94)*
Age				
≤40	17(56.7)	78(66.7)	1.00	1.00
40-60	9(30.0)	28(23.9)	0.87(0.33, 2.32)	1.1 (0.39, 3.08)
≥60	4(13.3)	11(9.4)	0.44(0.13, 1.44)	2.19(0.61, 7.85)
Phase of CML				
CP	27(90.0)	109(93.2)	1.00	1.00
AP	3(10.0)	8(6.8)	1.54(0.38, 6.22)	1.68(0.39, 7.17)
WBC count at IM[$] initiation				
<50 x 10^3 cells/mm^3	15(50.0)	66(56.4)	1.00	1.00
50-100 x 10^3 cells/mm^3	10(33.3)	22(18.8)	1.88(0.72, 4.93)	1.65(0.58, 4.68)
>100 x 10^3 cells/mm^3	5(16.7)	29(24.8)	0.79(0.26, 2.37)	0.61(0.18, 2.09)
Plt count at IM[$] initiation				
≥100	18(60.0)	116(99.1)	1.00	1.00
<100	12(40.0)	1(0.9)	6.4(1.97, 9.7)*	5.3(2.35, 8.7)*

COR=Crude odd ratio, AOR=Adjusted odd ratio,

[a]Physician led temporary Imatinib discontinuation + dose decrement

*Statistically Significant at P < 0.05,

[$]Imatinib

4.7. Predicting Factors for Adherence to Imatinib Treatment

Based on the results of univariate binary logistic regression analysis, variables such as gender, age, occupation, residence, distance between patients home and institution, educational status, family average monthly income, presence of adverse drug events of Imatinib and comorbidities were included in the multivariable logistic regression analysis. After controlling different demographic and other factors through the use of multivariable logistic regression analysis, this study showed that only adverse drug events, residence, family monthly income, comorbidity and occupational status had significant association with Imatinib treatment adherence. Accordingly, patients who had no experience of any adverse drug events of Imatinib were about six (AOR= 6.12, 95% CI: 2.31, 14.3) times more likely to adhere as compared to those who encountered at least one grade I-IV adverse drug events of Imatinib other than physician led reasons for temporary cessation of treatment. Patients who had an average family monthly income (AOR= 3.43, 95% CI: 1.25-7.74) and high income (AOR=3.62, 95% CI: 1.09-6.61) were more likely to adhere as compared to those who had very low income.

The study also found that being merchant and employed had a significant association with their level of adherence, where they were about six (AOR=6.55, 95% CI: 1.98, 44.10) and four (AOR= 4.61, 95% CI: 1.31, 23.86) times more likely to adhere, respectively, as compared with patients who were house wife. Patients who had no comorbid illness were also 4.39 times more likely to adhere to their treatment when compared to those who had at least one comorbid illness (AOR= 4.39, 95% CI: 1.16, 16.64). On the other hand, patients who came from country side (AOR= 0.29, 95% CI: 0.02, 0.84) were less likely to adhere compared to those from Addis Ababa (Table 10).

Table 10: Univariate and multivariable binary logistic regression analysis of predictors of Imatinib treatment non-adherence among Ethiopian chronic myeloid leukemia patients

Variables	Adherence		COR, 95%CI	AOR, 95%CI
	Suboptimal Adherence	Adherent		
Gender				
Female	31(48.4)	28(35.0)	1.00	1.00
Male	33(51.6)	52(65.0)	1.63(0.83, 3.19)	1.02(0.71, 2.77)
Occupation				
House Wife	15(23.4)	8(10.0)	1.00	1.00
Farmer	13(20.3)	12(15.0)	1.44(0.46, 4.52)	1.63(0.37, 7.12)
Merchant/Trader	9(14.1)	17(21.3)	2.94(1.15, 9.42)*	6.55(1.98, 44.10)*
Employee	12(18.8)	25(31.3)	3.24(1.24, 9.60)*	4.61(1.31, 23.86)*
Retired	8(12.5)	7(8.8)	1.12(0.365, 5.07)	1.65(0.48, 5.38)
Others	7(10.9)	11(13.8)	1.71(0.52, 5.67)	2.76(0.56, 13.5)
Educational Status				
Can't read and write	22(34.4)	20(25.0)	1.00	1.00
Primary Education	18(28.1)	19(23.8)	1.22(0.51, 2.90)	1.41(0.2, 1.92)
Secondary Education	9(14.1)	13(16.2)	1.58(0.56, 4.46)	1.6(0.84, 2.54)
Higher Education	15(23.4)	28(35.0)	1.85(0.79, 4.35)	1.42(0.59, 1.86)
Family Income				
Low (<1500)	42(65.6)	26(32.5)	1.00	1.00
Average (1501-5000)	20(31.3)	40(50)	2.92(1.68, 4.82)*	3.43(1.25, 7.74)*
High (>5001)	2(3.1)	14(17.5)	3.01(1.25, 5.39)*	3.62(1.09, 6.61)*
Place of residence				
Addis Ababa	8(12.5)	29(36.3)	1.00	1.00
Out of Addis Ababa	56(87.5)	51(63.7)	0.42(0.19, 0.91)*	0.29(0.02, 0.84)*
Presence of Comorbidity				
At least One	9(14.1)	3(3.7)	1.00	1.00
None	55(85.9)	77(96.3)	2.72(1.21, 8.80)*	4.39(1.16, 16.64)*
Adverse effects				
At least one	56(87.5)	54(67.5)	1.00	1.00
None	8(12.5)	26(32.5)	4.34(1.35, 7.78)*	6.12(2.31, 14.3)*

COR=Crude odd ratio, AOR=Adjusted odd ratio, *Statistically Significant at $P < 0.05$

5. Discussion

This is the first prospective cohort study conducted to gain knowledge about adherence and treatment outcomes of Imatinib in newly diagnosed CML patients in Ethiopia. The findings could be used in informing treatment decisions, designing innervations to improve adherence of CML patients towards Imatinib and will also be used as baseline for other studies.

The median age of study participants at time of confirmed diagnosis was 36 years which is almost similar to Indian CML patients (39 years) (Unnikrishnan *et al*., 2016). But it was lower than other African and Asian countries that ranged from 42-48 years (Louw , 2012, Ali *et al*., 2014, Edesa and Abdel-malek , 2015, Al-Dewik *et al*., 2016, Entasoltan *et al*., 2017). Median age of European countries (60 years) (Hoffmann *et al*., 2015) and USA (64 years) (Miller *et al*., 2016) was also almost double to that of the present study participants. Probably this presentation at younger or productive age group may have huge economic impact in the country and therefore necessities further studies to explore the reason. Presentation in younger age in the present study was also one of the reasons in majority cases for more aggressive clinical presentation; which was explained by high cell count [WBC count, up to 1-million (Median: 310.6 x 10^3 cells/mm^3)], huge organomegally, Sockal and EUTOS high risk. Similar to the present study, high WBC count was also reported in the Algerian patients [median WBC count of 346 x 10^3 cells/mm^3] (Entasoltan *et al*., 2017) whereas significantly lower WBC counts were reported from studies done in other countries with median count ranged from 21- 150 x 10^3 cells/mm^3 (Hoffmann *et al*., 2015, Edesa and Abdel-malek, 2015, Ali *et al*., 2014, Liu *et al*., 2017, Talpaz *et al*., 2002).

At time of initiation of Imatinib treatment, the median WBC count was higher [43.1(3.3- 644) x 10^3 cells/mm^3 than what is recommended by the NCCN (2018) and European Leukemia Net (Baccarani *et al*., 2013) guidelines [WBC count is <20 x 10^3 cells/mm^3 cells/ mm^3 or at least with adequate control for better outcome]. The reason for initiation of Imatinib with this high cell count, up to 644 x 10^3 cells/mm^3, was mainly due to stock out of HU from the hospital during majority time of the study period and on the other hand, majority of the patients couldn't afford to procure it from abroad. It was also not easily accessible for those who could afford to buy due to absence of legal suppliers in the country other than Pharmaceutical fund and supply agency of Ethiopia. The fact that unaffordability is a huge concern can be seen from the observation that 64

(43.5%) patients were followed for more than two months after diagnosis by bone marrow, peripheral morphology and clinically before initiation of Imatinib treatment as 50(78.1%) of them couldn't afford for the chromosome testing that costs up to 5000 birr per patient. This is also explained by majority of the patients in the present study were in very low or low monthly income category (48.3%).

The present study found CHR rate of 91.7% with 6 weeks median time for achievement of the CHR. The CHR rate finding was in line with several studies done elsewhere, which ranged from 90%–100% (Kantarjian *et al*., 2002, Deshmukh *et al*., 2005, de Lavallade *et al*., 2008, Doval *et al*., 2013, Edesa and Abdel-malek, 2015) but higher than a study conducted in Algeria (83%) (Entasoltan *et al*., 2017). The lower CHR rate in Algeria could be due to brand difference of Imtinib. The median time for achievement of CHR was slightly higher than the Indian study (4.3 weeks) (Doval *et al*., 2013) and this difference might be due to Initiation of Imatinib treatment at high cell count which was also significantly associated with CHR failure in this study. In addition; WBC count after 2-weeks of Imatinib treatment was increased from baseline in 14-patients and then decreased thereafter in all of them. Backward analysis was done to see probable reason for this and found that for majority of them (in 10-patients) were because HU was discontinued without dose tapering. Since discontinuation of HU without dose tapering causes relapse of cell proliferation that acts directly by inhibiting DNA synthesis through ribonucleotide reductase inhibition so is blockage of proliferation is very high as compared to Imatinib which acts differently by inhibiting TK-enzymes and then subsequently down regulation of cell proliferation and differentiation (Hochhaus *et al*., 2017). But in the rest of patients, they were not taking the drug regularly mainly due to GI adverse effect of the drug.

Similar to other studies (Kantarjian *et al*., 2012, Ibrahim *et al*., 2011, Ganesan *et al.,* 2011, Marin *et al*., 2010); CHR failure was significantly associated with adherence and baseline peripheral blast count. In this study, adherent patients were 8.6 times more likely to achieve CHR than their counterparts, though Cytogenetic response was not assessed due to absence of RT- QPCR testing service in the study hospital. In line with this, a meta-analysis by DiMatteo *et al* (2002) reported that adherence reduces the risk for null or poor treatment outcomes by 26% and 3 times as probable to have good treatment outcomes compared with non-adherent patients. Similarly, being non- adherent to Imatinib treatment is major cause of CCgR and MMR failure (Noens *et*

al., 2009, Santoleri *et al*., 2016). Moreover, non-adherence was associated with increasing treatment cost and hospital stay (Halpern *et al*., 2009). Peripheral blast count ≥5% were also associated with 0.67 times less likely to achieve CHR than their counter parts, which mirrors with a study done by Kantarjian *et al* (2012) and Sawyers *et al* (2002). Contrastingly, even if most of the study participants were in EUTOS high risk group (76.4%) compared with only small proportion of the European, Algerian and Egypt CML patients 11.8%, 24.5% and 25%; respectively (Hoffmann *et al*., 2015, Entasoltan *et al*., 2017, Edesa and Abdel-malek, 2015), there was no statistically significant association between CHR and EUTOS prognostic score in the present study. In contrary; though the present study didn't assess CgR and MR, EUTOS score was considered a predicative factor for these outcomes (Hoffmann *et al*., 2013, Breccia *et al*., 2012).

Among 11 patients diagnosed as AP-CML, five of them took Imatinib 400mg as a daily dose, though international guidelines recommended Imatinib 600mg or 800mg as daily dose for confirmed AP-CML which was also employed in case of poor response or treatment failure (Steegmann *et al*., 2016, Hochhaus *et al*., 2017, NCCN, 2018). Though these patients took daily dose against the international recommendations, almost all (n=10) of them achieved CHR except one who already on Imatinib 600mg PO daily failed to achieve CHR and this patient found to be resistant to Imatinib due to T315A mutated gene. The probable reason for this unintentional dose against the recommendation might be due to information gap of resident physicians' practicing in the unit by rotation. On the contrary, the justifiable reason for good outcome irrespective of recommendations might be difference in definition of AP-CML between the present study which followed WHO definition and the ELN definition, since only five of them fulfilled the definition of ELN (Baccarani *et al*., 2012).

Though Imatinib was found to be the most effective and safe as compared to previous treatment modalities of CML (Kantarjian *et al*., 2002), several studies identified that hematological, musculoskeletal and GI systems were the commonly affected systems due to Imatinib drug-related toxicities (O'Brien *et al*., 2003, Thanopoulou and Judson, 2012, Kekäle *et al*., 2015, Francis *et al*., 2015, Jabbour *et al*., 2011). Concurrently, the present study revealed that hematologic toxicities, thrombocytopenia or neutropenia, were found to be the most commonly encountered adverse drug events. Like a study conducted in India (Francis *et al*., 2015); large

proportion of them were grade III-IV hematologic toxicities and also the key reasons for physician led temporary discontinuation of Imatinib treatment and dose decrement in 16.3% of the study participants. On the contrary, treatment was temporarily discontinued only in 11(2%) of study participants in the International STI571 CML Study Group (Kantarjian *et al*., 2002) and no study participants in the a study done in Italy (Breccia *et al*., 2008) and Iraq (Al-Awad and Al-Sharifi, 2016) due to ADEs. This difference might be due to difference in pharmacokinetic and pharmacodynamics properties of the drug, which still needs further study. Furthermore; grade III-IV hematologic toxicities and sever skin rash were also major reasons for frequent clinic visit although there were also patients who were against physicians' appointment period mainly due to financial reason associated with distance. Accordingly, the most common non-hematologic toxicities that patients experienced were GI- adverse effects, like that of the Finland study (Kekäle *et al*., 2015), though in the present study grading was not done for non-hematologic toxicities due to difficulty of grading for such toxicities and most of them were patient reported that make it very difficult. But in the Finland study diarrhea and vomiting were most predominant GI related adverse effects unlike the present study that dyspepsia was the most common one. This probably in the present study, patients might took their medication without food that may aggravate dyspepsia. Joint pain/muscle cramp and edema were also other most common adverse effects reported in the Finland (Kekäle *et al*., 2015) and Algerian (Entasoltan *et al*., 2017) study, though the Algerian study reported only Grade III-IV non-hematologic toxicity's. However in the present study these adverse effects were the least reported. Skin rash was also the other most common adverse effect reported in the present study similar to other studies(O'Brien *et al*., 2003, Entasoltan *et al*., 2017).

This study revealed that, being female was three times more at risk of having temporary treatment discontinuation or dose decrement than males which is similar with a study conducted in Iraq (Matti *et al*., 2013). This might be due to females are more sensitive to the myelosuppressive effect of Imatinib than males at the same standard dose, because females can achieve higher serum concentration than males (Belsey *et al*., 2017). Also, patients who had baseline platelet count $<100x10^3$cells/mm^3 at initiation of Imatinib were five times more prone to temporary treatment discontinuation or dose decrement compared to their counterparts. This is in

fact, in the present study grade III-IV thrombocytopenia was a major reason for temporary treatment discontinuation.

Like general perceptions of physicians about patient adherence to Imatinib treatment is a major issue, in this study adherence to Imatinib treatment was observed in 55.6% of the study participants. This finding is comparable with previous studies conducted in India (45%) (Unnikrishnan *et al*., 2016) and Qatar (61%) (Al-Dewik *et al*., 2016). On the contrary, adherence rate was considerably lower in the present study as compared to the Swedish (97%)(Jönsson *et al*., 2012) and meta-analysis (75.2%)(DiMatteo, 2004) studies. The lowest adherence rate in the present study probably due to presence of single institution for the whole country, frequent experience of adverse effects especially GI related as the present study participants explained of a major hindering reason for their medication and also the present study only includes MMAS-8 high adherence score as adherent.

Though, being Imatinib given as free for all the present study participants, its tolerability profile as compared to other anti-cancer drugs, the high efficacy, the mortality and morbidity of CML before the advent of Imatinib and the convenience of oral administration which are convincing reasons for patients with CML to be highly adherent, still adherence is also a problem for patients treated in TASH, Addis Ababa, Ethiopia. Hence, more efforts are needed to increase the treatment adherence of these patients so that they could realize the full benefits of prescribed therapies.

Our study revealed that, the odds of being adherent in patients who didn't experienced any adverse effect of Imatinib were about 6-times more likely to adhere to their medication than those experienced at least one adverse effect of Imatinib and this implies patients who experienced adverse effects of Imatinib were found to be less likely to adhere to their medications. This finding is in line with a qualitative study conducted in Taiwan (Chen *et al*., 2014) and the other study in India (Kapoor *et al*., 2015) demonstrated that Imatinib-related adverse effects were the most common reason for participants hindering to take their medications as prescribed. Numerous literatures support this finding, as adverse effects had a significant inverse association with Imatinib treatment adherence (Geissler *et al*., 2017, Lim *et al*., 2017, Kvarnström *et al*., 2018). Moreover, in the present study residence had significant association

with Imatinib adherence. Patients who live in Addis Ababa were more likely to engage in adherence compared to those who were from countryside. This could probably be due to the fact that Imatinib treatment for CML patients is only given in TASH located in Addis Ababa. Hence, residents from countryside should travel long distance with extra expenses though Imatinib is given free of charge for all patients and; also they might have lower awareness about the disease and importance of adherence than those from Addis Ababa. On the other hand, monthly family income was significantly associated with medication adherence as the family income increased, patients were found to be more likely to adhere to their medications. This finding is in line with previous meta-analysis, which reported that economic status had a significant association with Imatinib adherence (Geissler *et al*., 2017). On the contrary, according to a study done in India economic status was not associated with adherence, though majority of patients in the Indian study took Imatinib as free like all Ethiopian CML patients or at highest subsidized rate (Unnikrishnan R *et al*., 2016). This probably in fact that unlike Ethiopia; CML is treated at different hospitals in India. Likewise, occupation had significant association with Imatinib treatment adherence. Patients who were Merchant/trader and employee were more likely to adhere to their treatment compared to those who were housewives. This could probably be due to the fact that housewives might be less aware of their disease and the importance of medication adherence which might be due to little contact with others; and also they are dependent on their husband for any type of expense when compared with merchants and employees and thus more likely to be non-adherent. Last but not least, the present study also revealed that presence of comorbid illness is significantly a predictive of non-adherence, which is similar to other studies (Noens L *et al*., 2009, Kapoor J *et al*., 2015, Geissler J *et al*., 2017). This could be due to pill burden and specifically for this study being HIV infection is the most comorbid illness in which pill burden is very high and may also depressed or lose hope about their treatment.

In this study, patients with poor adherence reported several reasons for not adhering to their medication. Like other studies (Kekäle *et al*., 2015, Unnikrishnan *et al*., 2016, Geissler *et al*., 2017); the most common reasons were found to be adverse drug events of Imatinib, boredom of taking Imatinib daily, feeling well without treatment and perceived lack of trust on the effectiveness of treatment**.** Similarly, according to a two qualitative studies done by Chen *et al* (2014) and Mortensen and Mourek (2017) revealed that adverse effects were identified as the

main obstacle for medication adherence. Forgetfulness and inadequate information about the drug were, however, the least common reasons for non-adherence. As discussed before adherence was found to be a major determinant of CML treatment success. Nonadherence should be examined as a possible reason for patient non- or reduced response to Imatinib before considering such patients to be Imatinib-resistant and switching them to next-line treatment with the new second-generation TKIs. Non-adherence to Imatinib must be ruled out as a possible cause of lack of optimal response, which also had a significant association CHR success in this study. Hence Identifying specific barriers for each patient and adopting suitable techniques to overcome them will be necessary to improve medication adherence. Health care professionals such as physicians, pharmacists and nurses have significant role in their daily practice to improve patient medication adherence (Jimmy and Jose, 2011).

6. Limitations of the Study

In this study, though CHR status is comparable to most international study findings, due to financial constraint and unavailability of the tests in the institution this study couldn't address cytogenetic response and molecular response status which are very crucial for proper clinical decision in the management of CML. Also, the present study followed patients for 3-months only, because at 6, 12 and 18 months outcome assessment requires cytogenetic and molecular tests. There were also patients who were evaluated after 3-months of Imatinib up to maximum of 4-months because evaluation was mainly depend on the appointment periods given which can possibly affect CHR rate. Adherence was self-reported, and the results may underestimate patients' real non-adherence status as compared to any objective test, e.g., measurements of Imatinib plasma concentration or pill counts or electronic medication monitors. On the other hand, the quantitative nature of the data could not properly highlight the reasons for non-adherence from the patients' perspective. Thus, longitudinal studies that take into account qualitative assessments should be conducted to investigate the reasons for medication non adherence and design strategic plan to solve the problems. Since self-report was used for the assessment of adherence, the present study was dependent on the assumption that patients who claimed to adhere to Imatinib treatment be actually adhered. Finally; the sample size was small because of time constraint which may affect the power of the study.

7. Conclusion

This study showed that most patients with CML were presented at younger age with more aggressive clinical presentation, as compared to other countries. The CHR was found to be 91.7% and it was significantly associated with treatment adherence and baseline peripheral blast count. Imatinib 400mg PO once daily was found to be effective in achieving CHR for those patients who fulfilled the WHO criteria for AP-CML although they didn't fulfill ELN criteria. Grade III-IV hematologic toxicities were major reasons for physician led temporary treatment discontinuation in 19(12.9%) and dose decrement in 5(14.3%) of patients. Imatinib adherence (55.1%) was found to be suboptimal. Income, place of residence, patient reported adverse drug events and presence of comorbidity were significantly associated with patient adherence to Imatinib. Patients believed that adverse drug events, lack of trust in efficacy, economic related factors, and boredom of taking Imatinib on daily basis and feeling well without taking the medication were the most important reasons for their non-adherence.

8. Recommendations

- ✓ Monitoring cytogenetic, molecular response and doing gene mutation analysis should be practiced as per widely accepted international CML treatment guidelines. For this necessary equipment, laboratory reagents and manpower must be fulfilled.
- ✓ Physician led temporary treatment discontinuation of Imatinib was found to be very common as compared to other studies and also had statistically significant association with being female, which warrants pharmacogenomics studies.
- ✓ Temporary discontinuation of Imatinib treatment recommendation during study period had some inconsistencies especially in case of grade III-IV hematologic toxicities. Hence, unit specific guideline has to be developed to standardize the practice.
- ✓ Since adherence is still a problem, health care providers practicing in hematology clinic and dispensing pharmacists are urged to promote medication adherence with more emphasis on how to manage adverse drug events which was reported as the main reason for medication non-adherence.
- ✓ Efforts should be made to make Imatinib accessible to other parts of the country as this study revealed that being from the country side and low income were predictors of poor adherence.
- ✓ Other studies are recommended to explore why CML is common at younger age in Ethiopia.
- ✓ Prospective study of treatment outcome using cytogenetic and molecular tests is recommended.

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Annexes

Annex I: Structured Questionnaire

Part I: English Version of Information Sheet

Dear participant, Good Morning/Afternoon

Introduction

My name is _____. I am a member of the study that is carried out at Tikur Anbessa Specialized Hospital, Ambulatory Hematology Clinic; Addis Ababa, Ethiopia entitled "Treatment Outcome and Adherence to Imatinib among newly diagnosed CML patients".

Objective

The main purpose of this study is to assess treatment outcome and adherence to Imatinib among newly Diagnosed CML patients at TASH, Addis Ababa, Ethiopia. Your input will be extremely valuable as the information will be used to assess the medication use and adherence to identify gaps in treatment outcome.

Expected Outcomes and/or Benefits

At the end of the study, the treatment outcome and adherence will be evaluated. Therefore, the study will identify and investigate the main gaps and challenges associated with adherence and treatment outcome and will propose the feasible recommendations and may benefit you directly or indirectly by improving the epilepsy treatment in the hospital.

Thank you so much in advance.

Part II: English Version of Informed Consent Form

Everything from your information and records would be completely confidential to the research and the data are stored without your name and only used for the purpose of this study. None of this would affect the care you receive from Hematology Ambulatory clinic of TASH, but will help in future planning for the hospital. No identifying names or characteristics will go into my report, so you may share your thoughts openly. Additionally, taking part in this study is completely voluntary. It is your choice whether to participate or not. You may skip any questions that you do not want to answer. Please ask me to stop as we go through the information and I will take time to explain. I would be grateful if you could sign the attached form to say you have no objections to our accessing any records and interviewing you. Would you be willing to assist me by having a 10-15 minutes'?

If the interviewee responds "Yes", Please proceed and let him/her to sign or replies "No" gratitude him/her and quit the interview. If you have any questions concerning the study, please call Atalay Mulu (+251) 23295462.

_____ _____

Signature of respondent **Signature of interviewer**

Date: _____ (Day/month/year)

Principal Investigator: Atalay Mulu

Addis Ababa University, CHS, School of Pharmacy, Department of

Pharmacology and Clinical Pharmacy

Email: atalay.mulu@aau.edu.et

Part III: Data Collection form from Patient Interview

Socio-Demographic Characteristics
Age:_____(in years)
Sex: ❑ Male ❑ Female
Marital Status ❑ Single ❑ Married ❑ Divorced ❑ Widowed/er
Educational Level ❑ Can't read & write ❑ Can read and write without formal education ❑ Primary Education(1-8) ❑ Secondary Education(9-12) ❑ Diploma and Above ❑ Others
Place of Residence ❑ Addis Ababa ❑ Out of Addis Ababa
Region: _____(Write in words where they are from)
Occupation ❑ Unemployed ❑ House wife ❑ Student ❑ Farmer ❑ Daily laborer ❑ Employed ❑ Merchant ❑ Retired ❑ Other(s) [Specify]
Monthly Income (ETB): _____ (Write in number) ❑ Very Low (≤ 860 Birr) ❑ Above average (3001-5000 Birr) ❑ Low (861-1500 Birr) ❑ High (≥5001 Birr) ❑ Average (1501-3000Birr)
Substance Use ❑Alcohol ❑Smoking ❑Chewing Khat ❑ Others ❑ Nothing

Part IV: Adherence Assessment Tool

Morisky Medication Adherence scale (8-item)

You indicated that you are taking medication(s) for your chronic myelogenous leukemia. Individuals have identified several issues regarding their medication-taking behavior and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with your chronic myelogenous leukemia medication. (Please check your response below.

	Response Yes=1, No=0	
1. Do you sometimes forget to take your chronic myelogenous leukemia medication(s)?		
2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your chronic myelogenous leukemia medication(s)?		
3. Have you ever cut back or stopped taking your medication(s) without telling your doctor, because you felt worse when you took it?		
4. When you travel or leave home, do you sometimes forget to bring along your chronic myelogenous leukemia medication(s)?		
5. Did you take your chronic myelogenous leukemia medication(s) yesterday?		
6. When you feel like your chronic myelogenous leukemia is under control, do you sometimes stop taking your medication(s)?		
7. Taking medication(s) every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your chronic myelogenous leukemia treatment plan?		

8. How often do you have difficulty remembering to take all your medication(s)? **(Please tick the correct answer)**

❑ Never/rarely (1) ❑ Usually (0.25)

❑ Once in a while (0.75) ❑ All the time (0)

❑ Sometimes (0.5**)**

MMAS-8 Adherence Scale

❑Low (<6) ❑ Medium (6-<8) ❑High (8)

Part V: Reasons for Non-Adherence

If the finding for the above MMAS-8 score is <8 (or any suspicion of things which affects adherence to treatment), what do you think are the factors?

❑ Unintentional (forgetfulness, carelessness)

❑ Intentional, due to lack of trust on the treatment (personnel beliefs about taking medication such as cultural beliefs)

❑ Costs other than medication price (transport cost, cost for home and bed accommodation while coming for medication refill)

❑ Hopelessness (consider taking medication lifelong while it is not cured)

❑ Lack of support from family or friend

❑ Lack of support from health professionals

❑ Distance from AA or hospital

❑ Others, specify_____

Part VI: Safety of Imatinib

What are the adverse effects you faced due to your medication or review on patient chart?

❑Edema/Fluid retention ❑ Headache ❑ Nausea/Vomiting

❑Fatigue ❑ Muscle pain ❑ Epigastric pain/Burning sensation

❑Rash ❑ Diarrhea ❑ Skin rash

❑ Facial Puffiness ❑ Skin color change ❑ Others_____

Based on answers provided in above, do the above adverse events affect your medication taking behavior? ❑ Yes ❑ No

If yes in question 3.4; how often did you miss your dose?

❑Never ❑Rarely ❑ Sometimes ❑ Often

Annex II: Data Abstraction format from Patient Chart

Part I: Presence of Co-morbid Illnesses

1. Are there any Co-morbid conditions other than CML? ❑ Yes ❑ No
2. If yes for question number 1, what type of co-morbid condition/s is this/are they? _____
3. Is there any medications taken by the patient? Please list all the medications _____

Part II: Baseline Laboratory and clinical findings other than comorbid illness

I. CBC	Range	Test Result	Remark
WBC			
Basophils			
Eosinophil			
Neutrophils			
Platelet count			
RBC			
Hgb			

II. What was initial blast count (Myeloblast percentage): _____

III. Stages of Disease at diagnosis

❑ Chronic Phase ❑ Accelerated Phase ❑ Blast Crisis Phase

IV. Cytogenetic/BCR-ABL/ Ph chromosome test

❑ Was BCR-ABL(RT-PCR) test done?

❑ If yes what type of CML was it?_____

❑ Ph chromosome Percentage: _____

❑ If the test was not done, why?_____

V. Clinical Findings

1. Presence of splenomegaly: ❑Yes ❑No

2. If yes, Spleen size below right costal margin: _____
3. Presence of hepatomegaly: ❑ Yes ❑ No

VI. Prognosis based on

1. Sockal Prognostic Scoring system

   ❑ Low risk (<0.8) ❑ Intermediate risk (0.8-1.2) ❑ High risk (>1.2)

2. EUTOS prognostic system

   ❑ Low risk (≤87) ❑ High risk (>87)

3. Hasford Prognostic System

   ❑ Low risk (<780) ❑ Intermediate risk (780-1480) ❑ High risk (>1480)

VII. Treatment History

1. Did the Patient take hydroxyurea? ❑ Yes ❑No
2. If yes for Qn no 1; dose, frequency and duration of treatment:-

   _____

3. Difference between confirmed diagnosis of CML and initiation of Imatinib, in weeks: _____
4. **Daily dose of Imatinib:**

   ❑ 300mg ❑ 400mg ❑ 600mg ❑ 800mg

Part III. Documented Baseline and follow up laboratory and clinical findings at and after Initiation of Imatinib treatment.

Date: _____

1. **Base line findings**

CBC	Normal Range	Lab findings	Remark
WBC count x 10^3 cells/ mm^3			
Basophils, %			
Eosinophil, %			
Neutrophils, %			
Lymphocyte, %			
Platelet count x 10^3 cells/ mm^3			
RBC count x 10^6 cells/ mm^3			

Hct, %			
Hgb, g/dl			
Clinical findings	Yes	No	
Splenomegaly			
Hepatomegaly			
Are/is there other clinical findings? If yes Specify			

2. Follow up findings

CBC	At 2wks	At 1month	At 2-month	At 3-month
WBC x 10^3 cells/ mm^3				
Neutrophil, %				
ANC				
Lymphocyte, %				
Basophils, %				
Platelet count x 10^3 cells/ mm^3				
RBC x 10^6 cells/ mm^3				
HCT, %				
Hgb, g/dl				
Clinical Findings				
Splenomegaly (Yes/No)				
Hepatomegaly (Yes/No)				
CHR status(Yes/No)				
Are/is there other clinical findings? If yes Specify				

3. **About Regimen/dose change History**

   I. Was the dose/ regimen changed? ❑ **Yes** ❑ **No**

   II. **If yes to Qn No I,**

   When (after initiation of Imatinib in weeks)_____

   Why?

   a. Dose decreased, because the patient responds to the initial dose and changed to maintenance treatment.

   b. Dose decreased, because the patient didn't tolerate

   c. Dosed increased, because the patient didn't respond to current treatment

   d. Drug discontinued because patient fulfills for Imatinib discontinuation.

4. **If the answer is "d", Reasons for temporary treatment discontinuation**

   _____

5. **For how long, treatment discontinued (In weeks)_____**

6. **Supportive managements given for the patient**

   1. **_____**

   2. **_____**

   3. **_____**

7. **End of follow up Findings**

   a. Disease status: ❑ Primary ❑ Relapse

   b. Disease Phase:

   ❑Chronic phase: ❑ Accelerated phase: ❑ Blast Crisis phase:

   c. Current Disease parameters

   i. **Current clinical status:**

   ❑ Improved: ❑ The same: ❑ Worsened:

   ii. Was Complete Hematologic response achieved?

   ❑**Yes** ❑ **No** ❑ **Not Known**

Annex III: የአማርኛ መጠይቅ ቅፅ

ቅጽ 1: የጥናቱ መረጃ ቅጽ

ቀን፦_____

ውድ የቃለ መጠይቅ ተሳታፊ፤ እንደምን አደሩ/ዋሉ? የጥናቱ መግቢያ ስሜ _____ ይባላል። በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል ሄማቶሎጅ ክፍል ዉስጥ በተመላላሽነት እንደ አዲስ Imatinib (Gleevec) የተባለዉን መድኃኒት ለጀመሩ የCML ህሙማን ስለ መድሀኒት አወሳሰድ እና የህክምና ዉጤት ሁኔታ የ 3-ወር የክትትል የድህረ ምረቃ ጥናት " ሲሆን የጥናቱም አባልም ነኝ። በተለይ የእርስዎ የመድኃኒት አጠቃቀም በጥናቱ ላይ በደንብ ከሚጠኑ ነጥቦች አንዱ ነዉ።

የጥናቱ አላማ፦-

የዚህ ጥናት ዋና አላማው Imatinib(Gleevec) የህክምናዉ ዉጤት ምን እንደሚመስል ፡ መድኃኒት እንዴት እንደሚጠቀሙት፣ በታዘዘው መሰረት በአግባቡ እንዴት መድኃኒትዎን እንደሚወሰዱት እና መድኃኒትዎን ሁል ጊዜ እንዳይወሰዱ የሚያደርጉ ዋና ዋና ክፍተቶችን በመለየት፤ የመፍትሄ ሀሳቦችን ማቅረብ ነው።

ከጥናቱ የሚጠበቁ ውጤቶች/ጥቅሞች

በዚህ ጥናት ላይ የእርስዎ የሚጥል መድኃኒቶች በታዘዘው መሰረት በአግባቡ የአወሳሰድና የአጠቃቀም ክህሎት በድንብ ይጠናሉ። መድኃኒትዎን ሁል ጊዜ እንዳይወሰዱ የሚያደርጉ ዋና ዋና ክፍተቶችን በመለየት፤ የመፍትሄ ሀሳቦችን ማቅረብ ነው።በተጨማሪም ከጥናቱ በሚገኙ ግኝቶች የሚጥል ህክምና ዉጤትን በተወሰነ መልኩ ለማሻሻል እንደሚቻል በመገመት፤ እርስዎ የጥቅሙ ተቋዳሽ ይሆናሉ ብለን እናምናለን። ስለዚህ የእርስዎ ቅንና ሓቀኛ መረጃ ለጥናቱ እጅግ በጣም ወሳኝ ነው።

የተከበረ ጊዜዎ ስለሰጡን እጅግ በጣም እናመሰግንዎታለን።

ቅጽ 2፡ በቃለ መጠይቅ ለመሳተፍ የፈቃደኝነት ቃል መቀቢያ ቅጽ

በCML ታካሚዎች ዉጤት እንዲሁም ተያያዥ ጉዳዮች ላይ ያጠነጠነ እና ከመድሃኒቱ አወሳሰድ እንዲሁም ከህክምናዉ ጋር ተያይዘዉ ያሉ ችግሮችን በመቅረፍ የበሽታዉን የህክምና ዉጤት ለማሻሻል አላማ አድርጎ የተነሳ ጥናት ነው። መሰብሰቢያ ቅፁም ይህንኑ አላማ አድርጎ የተዘጋጀ ነዉ። በመሆኑም ከእርስዎ፡ ከእርስዎ ካርድ ላይ እና ከሀኪምዎ መረጃ ለመውሰድ እንፈልጋለን።በዚህ ጥናት ለመሳተፍም ሆነ ላለመሳተፍ መወሰንዎ በሆስፒታሉ ዉስጥ ለሚያገኙት ማንኛዉም አገልግሎት ላይ ምንም አይነት ተጽዕኖ የማይኖረዉ ሲሆን ተሳትፎዉንም በማንኛዉም ሰዓት ማቻረጥ ወይም ጥያቄዎችን አለመመለስ ይችላሉ። በዚህ ጥናት የእርስዎ መረጃ ሙሉ በሙሉ በምስጥር የተጠበቀና ለምርምሩ አላማ ብቻ የሚዉል ነው። በተጨማሪም የእርስዎ ተሳታፊነት በፈቃደኝነት የተመሠረተ ነው። የጥናቱ አላምውን ተረድተውና ጊዜዎን ሰውተው፤ ከ 10-15 ደቂቃዎች ለሚፈጅ ቃለ-መጠይቅ እውተኛው መረጃ ለመስጠት ፍቃደኛ በመሆንዎ በቅድሚያ አመሰግናለሁ። አዎ ከሆነ፣ ያስፈርሙ እና ይቀጥሉ፤ ካልሆነ ወደሚቀጥለዉ ተጠያቂ ይሂዱ።

_____ _____

የቃለ መጠይቅ የቀረበለት ሰው ፊርማ **የቃለ መጠይቅ አቅራቢ ፊርማ**

በየትኛው ጊዜ ጥያቄ ካለዎት አታላይ ሙሉ ብለው በ ስ.ቁ. (+251) -92295462 ወይም በ ኢ-ሜይል atalay.mulu@aau.edu.et ይጠይቁን።

የተከበረ ጊዜዎን ስለሰጡን እጅግ በጣም እናመሰግንዎታለን።

ዋና አጥኚ: አታላይ ሙሉ

አዲስ አበባ ዩኒቨርሲቲ፣ ጤና ሳይንስ ኮሌጅ፤ ፋርማሲ ት/ቤት፤ ፋርማኮሎጅና ክሊኒካል ፋርማሲ ትምህርት ክፍል

ኢ-ሜይል: atalay.mulu@aau.edu.et

ስ/ቁ፡ 09 23 29 54 62

Socio-Demographic Characteristics

እድሜ:_____(በዓመት)

ፆታ:

❑ወንድ ❑ሴት

የጋብቻ ሁኔታ

❑ያላገባ/ች ❑ያገባ/ች ❑አግብታ/ቶ የፈታ/ች ❑ ባል/ሚስት የሞተባት/ችበት

የትምህርት ደረጃ

❑ ማንበብም ሆነ/መፃፍ የማይችል ❑ ማንበብም እና መፃፍ የሚችል ያለ ዘመናዊ ትምህርት

❑ የመጀመሪያ ደረጃ (1-8) ❑ ሁለተኛ ደረጃ (9-12)

❑ ድህረ ምረቃ የጨረሰ/ች ❑ ሌሎች _____

የሚኖሩበት ቦታ

❑ አዲስ አበባ ❑ ከአዲስ አበባ ውጭ

የመጡበት ክልል: _____(በፅሁፍ ይፃፍ)

ስራ

❑ ስራ አጥ ❑ የቤት እመቤት ❑ ተማሪ

❑ አርሶ/አርብቶ አደር ❑ የቀን ሰራተኛ ❑ ተቀጣሪ(ወርኃዊ ተከፋይ)

❑ ነጋዴ ❑ ጡረተኛ ❑ ሌሎች [ይገለፀ] _____

ወርሀዊ የቤተሰብ ገቢ (በብር): _____ (በቁጥር ይጻፍ)

❑ በጣም ዝቅተኛ (≤ 860 ብር) ❑ ከአማካይ በላይ (3001-5000 ብር)

❑ ዝቅተኛ (861-1500 ብር) ❑ ከፍተኛ (≥5001 ብር)

❑ አማካይ (1501-3000ብር)

ማህበራዊ ልማዶች

❑አልኮል መጠጣት ❑ማጨስ ❑ ጫት መቃም

❑ ሌሎች _____ ❑ ምንም አልጠቀምም

Part 1: **ሞሪስኪ" መድኃኒትን በታዘዘው መሰረት በአግባቡ ስለመውሰድ" መለኪያ- 8**

እርስዎ እነደነገሩን/ እነደሚታወቀዉ ለCML ማከሚያ የሚሆን Imatinib የሚባል መድሀኒት እየወሰዱ ይገኛሉ፡፡ ነገር ግን ይህንን ወይም ሌላ መድሀኒት የሚወስዱ ብዙ ሰዎች ከሚያጋጥማቸዉ እና ካላቸዉ ልምድ ሥለ መድሃኒት አወሳሰዳቸዉ ባህሪ ብዙ ነገር ስለሚሉ እኛ ደግሞ የእረስዎን ማለትም የImatinib መድሀኒት አወሳሰድ ባህሪ ለማወቅ እንፈልጋለን፡፡ ስለዚህ እባክዎትን እርስዎ የሚሰማዎትን ትክክለኛ ነገር በሚቀጥሉት መጠይቆች መሰረት ይንገሩን፡፡

	ሞሪስኪ" መድኃኒትን በታዘዘው መሰረት በአግባቡ ስለመውሰድ" መለኪያ- 8	አ ዎ	አይደ ለም
	ጥያቄዎች	(0)	(1)
1	አንዳንድ ጊዜ መድኃኒትዎን ረስተው ሳይወሰዱ ቀርተው ያውቃሉ?		
2	ሰዎች አንዳንድ ጊዜ ከመርሳት ውጪ ባሉት የተለያዩ ምክንያቶች መድኃኒታቸውን ሳይወስዱ ይቀራሉ፡፡ ባለፉት ሁለት ሳምንታት፣ መድኃኒትዎን ሳይወስዱ የቀሩበት ቀናቶች ነበሩ'?		
3	ሐኪምዎን ሳይነግሩ፣ መድኃኒትዎን እየወሰዱ ህመምዎ ሲባባስ፣ መድኃኒትዎን አቋርጠው ያውቃሉ?		
4	በጉዞ ምክንያት ወይም ከቤትዎ አርቀው ሲጓዙ፣ አንዳንድ ጊዜ መድኃኒትዎን (ወደጉዞው) ረስተውት ሳይወስዱት ያውቃሉ?		
5	በትላንትናው ዕለት ሁሉንም መድኃኒትዎን ወስደውታል?		
6	ህመምዎ ሲሻልዎት (የህመምዎ ስሜቶች ሲጠፉ) አንዳንድ ጊዜ መድኃኒትዎን አቋርጠው ያውቃሉ?		
7	በየቀኑ መድኃኒት መውሰድ፣ ለአንድ አንድሰዎች ምቾት አይሰጣቸውም፡፡ እርስዎ በየቀኑ፣ እንድሁም አንድም ሰዓት ሳያዛንፉ መድኃኒትዎን መውሰድዎ፣ የመሰላቸት ስሜት ተሰምቶት ያውቃል?		

8	መድኃኒትዎን አስታውሰው ለመውሰድ ምንያክል ይቸገራሉ? ❑ ጭራሽ ተቸግሬ አላዉቅም(1) ❑ ዕለታት አንድ ጊዜ እቸገራለሁ (0.75) ❑ አልፎ አልፎ እቸገራለሁ (0.5) ❑ አብዛኛው ጊዜ እቸገራለሁ (0.25) ❑ ሁል ጊዜ እቸገራለሁ (0) ❑Low (<6) ❑ Medium (6-<8) ❑High(8)		

Part 2: መድሀኒትን በታዘዙት መሠረት/በትክክለኛዉ መንገድ እንዳይወስዱ ያደርጋሉ ተብለዉ የታሰቡ ችግሮችን ማወቂያ

2.1. በሞርስኪ-8 መጠይቅ መልስ መሰረት Adherence level ከ8-በታች ላሉት ታካሚዎች የሚጠየቅ ጥያቄ፡ ከሚከተሉት የመድሃኒት አወሳሰድን ያዉካሉ ተብለዉ ከተቀመጡ ምርጫዎች መካከል እርስዎን በታዘዙት መሰረት እንዳይወስዱ ያስቸገርዎት የትኞቹ ናቸዉ (ከአንድ በላይ መልስ ይቻላል)፡፡

❑ በመርሳት	❑ ተስፋ በመቁረጥ
❑ በቸልተኝነት/በግዴለሽነት	❑ ሁሌ መድሀኒት መዉሰድ ስለሚሰለቸኝ
❑ባህላዊ እና ኃይማኖታዊ በሆኑ ምክንያቶች ተጨማሪ ህክምና በመፈለግ፡ ህክምናዉን ሙሉ በሙሉ ስለማላምንበት	❑ ህክምና ቦታ ያሉት የጤና ባለሙያዎች ድጋፍ ስለማያደርጉሊኝ
❑ ቤተሰቦቼ/ጓደኞቼ በተለያዩ ነገሮች ድጋፍ ስለማያደርጉሊኝ	❑ በመድኃኒቱ የጎንዮሽ ምክንያት
❑ የምመጣበት አካባቢ ሩቅ ስለሆነ በቀጠሮየ ቀን ለመምጣት ገንዘብ ስለሚቸግረኝ	❑ ሌሎች ካሉ በዕሁፍ ይገለፅ _____ ___

2.2. Imatinib የተባለዉን መድሀኒት ሲወሰድ ያጋጥማሉ የተባሉ የጎንዮሽ ጉዳቶችን ማወቂያቅፅ፡

2.2.1. እባክዎትን መድሀኒቱን ሲወስዱ ወይም መዉሰድ ከጀመሩ በኋላ ያጋጠምዎትን ችግሮች ይንገሩን(ከአንድ መልስ በላይ መልስ መመለስ ይቻላል)።

- ❑ የሰዉነትዎት እብጠት
- ❑ የማቅለሽለሽ ስሜት/ ማስታወክ
- ❑ ድካም
- ❑ ተቅማጥ
- ❑ ሰዉነትን ማሳከክ?
- ❑ የ ጨ ጓ ራ / የ ሆ ድ ህ መ ም
- ❑ ራስ ምታት
- ❑ ሰዉነት ማሳከክ
- ❑ የመገጣጠሚያ ህመም
- ❑ የቆዳ ቀለም መቀየር
- ❑ የፊት ቆዳ ማፈግፈግ
- ❑ ሌሎች_____

2.2.2. ከላይ በሰጡን መልስ መሰረት፡ የዘረዘሯቸዉ የጎንዮሽ ጉዳቶች የመድሀኒት አወሳሰድዎትን አዉከዎት/በታዘዙት ትክክለኛ አወሳሰድ እንዳይወስዱ አድርጎዎት ነበር?

❑ አዎ ❑ የለም

2.2.3.ከላይ በ2.2.2. የሰጡት መልስ አዎ ከሆነ፡ ምን ያህል ጊዜ መድሀኒትዎትን ሳይወስዱ ቀርተዋል/ዘለዋል

- ❑ ምንም አልዘለልኩም
- ❑ አንዳንድ ጊዜ
- ❑ከዕለታት አንድ ጊዜ
- ❑ አብዛኛው ጊዜሁል ጊዜ