

Adherence to Glivec (Imatinib Mesylate) Therapy Amongst Patients with Chronic Myeloid Leukaemia in Nigeria

Charles Erhinyodavwe Origbo, Rahman A. Bolarinwa¹, Anthony A. Oyekunle¹, Temitope O. Afolabi², Benedict Nwogoh³, Muheez A. Durosinmi¹

Department of Haematology, Federal Medical Centre, Asaba, Delta State, ¹Department of Haematology and Blood Transfusion, Obafemi Awolowo University and Teaching Hospital Complex, ²Department of Community Health, Obafemi Awolowo University, Ile-Ife, Osun State, ³Department of Haematology and Blood Transfusion, University of Benin Teaching Hospital, Benin City, Edo State, Nigeria

Abstract

Background: Adherence to Imatinib (Glivec®) is of critical importance in achieving optimal treatment outcomes in patients with chronic myeloid leukemia (CML). **Objective:** This study aims to investigate adherence to therapy and factors that could influence patient adherence to Glivec®. **Methods:** This is a prospective cohort study conducted at the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife. Seventy consenting newly diagnosed CML patients in the chronic phase were counseled on adherence to therapy and administered 400 mg/day dose of Glivec. Six months after commencement, they were evaluated for adherence using two structured self-administered questionnaires. The first one to evaluate adherence (Morisky Medication Adherence Scale) and the other was administered to identify factors known to influence adherence to therapy. Data were analyzed using SPSS version 21.0 Statistical package (2012, IBM Corp, Armonk, NY, USA.). **Results:** The study participants had a mean age of 38.4 ± 12.7 years. The male-to-female (male:female) ratio was 1.7:1. Thirty-three (47.1%) of the patients were classified as adherent. Family support was significantly associated with adherence ($P = 0.012$). The distance of >200 km away from the point of drug collection, OAUTHC, Ile-Ife was significantly associated with nonadherence to Glivec therapy ($P = 0.008$). **Conclusion:** This study found that adherence in patients on Glivec® therapy was $<50\%$. Distance of >200 km and family support were significant determinants of adherence in this study.

Keywords: Adherence, chronic myeloid leukemia, glivec, imatinib mesylate, Nigeria

Received: 06-02-20 Revised: 25-04-20 Accepted: 15-07-20 Published on: ****

INTRODUCTION

Imatinib Mesylate, a tyrosine kinase inhibitor is a targeted therapeutic agent currently used as the first-line medication for the management of chronic myeloid leukemia (CML).^[1] CML is a clonal hematopoietic disorder characterized by the malignant expansion of bone marrow stem cells of myeloid lineage with maturation. The disease is typified by a chromosomal translocation between chromosomes 9 and 22 t (9;22) (q34;q11). The affected chromosome 22 is referred to as the Philadelphia chromosome and it is positive (Ph+) in over 95% of cases.^[2,3] This translocation results in a novel fusion gene product *BCR-ABL*, which encodes a deregulated tyrosine kinase protein that underlies the disease pathogenesis.^[3]

Imatinib mesylate revolutionized the treatment of CML, transforming the once lethal disease with a postdiagnostic

survival of a few years to a chronic illness with life expectancy comparable to the general population.^[1] Imatinib is an adenosine triphosphate (ATP) analog that selectively inhibits the enhanced tyrosine kinase activity of the BCR-ABL oncoprotein by occupying the ATP binding site of the BCR-ABL oncoprotein.^[4] This interaction prevents the transfer of phosphate groups to tyrosine residues on substrate molecules involved in downstream signal transduction pathways, thus, causing selective blockage of cellular proliferation and induces apoptosis in Ph/BCR-ABL positive hematopoietic cells. It can

Address for correspondence: Dr. Charles Erhinyodavwe Origbo,
Department of Haematology, Federal Medical Centre, Asaba,
Delta State, Nigeria.
E-mail: drchaori@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Origbo CE, Bolarinwa RA, Oyekunle AA, Afolabi TO, Nwogoh B, Durosinmi MA. Adherence to glivec (imatinib mesylate) therapy amongst patients with chronic myeloid leukaemia in Nigeria. *Ann Trop Pathol* 2020;XX:XX-XX.

Access this article online

Quick Response Code:



Website:
www.atpjournals.org

DOI:
10.4103/atp.atp_4_20

induce complete and/or major cytogenetic remission in all phases of the disease.^[4]

Imatinib is remarkably an effective therapy for the management of CML.^[5] However, adherence to therapy is critical to achieving good treatment outcomes. Poor adherence has been reported in CML patients on Imatinib mesylate, but this has not been adequately investigated in our environment. This study is designed to evaluate adherence and factors that influence adherence to Imatinib mesylate therapy among Nigerians on Glivec.

METHODS

This is a prospective cohort study conducted at the Department of Haematology, Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, Osun State, Nigeria. The institution is the host of the Glivec international patient-assistance program (GIPAP). The center serves as a referral center for Nigerians diagnosed with CML. Through the GIPAP program, patients with established CML Ph⁺ and/or BCR-ABL positive are provided with Glivec (Imatinib mesylate) at no cost to the patients to support their care. The GIPAP program commenced in June 2003 and OAUTHC has remained the only referral center in Nigeria where the Glivec intervention is provided.

Newly diagnosed CML patients with Ph⁺ chromosome and/or BCR-ABL transcript were recruited for the study. Following diagnosis, the patients were counseled on adherence. Consenting patients were administered with the adherence assessment questionnaire during their follow up visit at 6 months postcommencement of therapy. Study inclusion criteria include: positivity of Philadelphia chromosome and/or BCR-ABL positivity; chronic phase disease; on a standard Glivec[®] dose of 400 mg, and gave voluntary informed consent. Those who were on cytotoxic drugs other than Glivec and those who had received hemopoietic stem cell transplant were excluded.

After recruitment, subjects received medication for 4 weeks; in the second visit, 8 weeks medication were given to them and at the third visit, they were given medications for 12 weeks. Adherence was evaluated on the fourth visit after the commencement of Glivec[®]. An interviewer-administered questionnaire was used to obtain data on adherence and factors influencing adherence to therapy.

Adherence was assessed using the nine-item Morisky Medication Adherence scale (MMAS), a self-reported medication-taking adherence scale with scores that ranges from 1 to 13. A Morisky score of 11 and above was considered as adherent, while patients with a score of <11 were classified as nonadherent.^[6] Cronbach $\alpha > 0.7$ was used as an indicator for acceptable internal consistency reliability.^[7-9]

Predefined follow-up questions were asked to identify factors known to influence adherence to therapy, such as adverse effects of medication, knowledge about CML, social support, and feeling about the disease. The study was conducted between January 2014 and November 2015.

The study was approved by the Research and Ethics Committee of OAUTHC, Ile-Ife. Data was analyzed using SPSS version 21.0 statistical package (2012, IBM Corp, Armonk, NY, USA).

RESULTS

A total of 70 participants were recruited for the study. The study population had a mean age (standard deviation) of 38.4 (12.7) years. They included 44 (62.9%) males and 26 (37.1%) females (male:female = 1.7:1). The majority of the study population, 49 (70%) were married at the time of the study, a significant proportion 38 (54.3%) had tertiary level of education, while a few 3 (4.3%) had no formal education [Table 1].

The MMAS score of study participants ranged from 5 to 13, with a median score of 10. A total of 37 (52.9%) had a score of <11, while 33 (47.1%) had scores of 11 and above. Thus the estimated adherence in the study was 47.1%.

Table 2 compares the sociodemographic parameters between adherent and nonadherent participants. Age ($P = 0.21$), sex ($P = 0.64$), marital status ($P = 0.57$), and educational status ($P = 0.98$) were not associated with adherence to therapy. Reported reasons for nonadherence include traveled without medication in 30%, missed taking medication due to act of carelessness 27%, forgetfulness 24%, drug interruption when feeling worse 13%, and drug interruption when perceived that the disease is under control in 6% [Figure 1].

Sixty-three (90.0%) of the study participants received support from their family members, while seven (10%) did not. Thirty-three (52.4%) that received family support were adherent and this was statistically significant ($\chi^2 = 6.93$,

Table 1: Sociodemographic characteristics of the study population

Variable	Total, n (%) 70 (100)
Age at presentation (years)	
Mean±SD	38.4±12.7
Age group	
<20	5 (7.1)
20–39	32 (45.7)
40–59	30 (42.9)
60 and above	3 (4.3)
Gender	
Male	44 (62.9)
Female	26 (37.1)
Marital status	
Single	21 (30.0)
Married	49 (70.0)
Level of education	
None	3 (4.3)
Primary	6 (8.6)
Secondary	23 (32.9)
Tertiary education	38 (54.3)

SD: Standard deviation

Table 2: Comparison of demographic parameters between adherent and nonadherent participants

Variable	Adherent, n (%)	Nonadherent, n (%)	P
Mean age	36.3±13.0	40.2±12.3	0.210
Gender			
Male	17 (38.6)	27 (61.4)	0.640
Female	16 (61.5)	10 (38.5)	
Marital status			
Single	11 (52.4)	10 (47.6)	0.565
Married	22 (44.9)	27 (55.1)	
Education			
None	2 (66.7)	1 (33.3)	0.858*
Primary	2 (33.3)	4 (66.7)	
Secondary	11 (47.8)	12 (52.2)	
Tertiary	18 (47.4)	20 (52.6)	

*Fisher's exact test

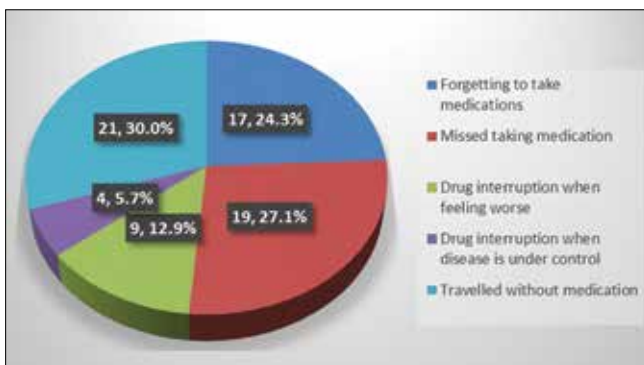


Figure 1: Pie chart showing frequency distribution of reasons for nonadherence

$P = 0.008$). Thirty-eight (54.3%) reported they had support from friends; of these, 21 (55.3%) belonged to the adherent group while 17 (44.7%) were in the nonadherent group.

To determine the influence of distance to the drug collection site on adherence, we classified the subjects according to whether they live >200 km away from the hospital or not. Thirty-five (50%) of the participants live >200 km away from the hospital. Twenty four (64.9%) of those living >200 km compared to 13 (35.1%) of those living within 200 km from the hospital were nonadherent, and this was statistically significant ($P = 0.008$) [Table 3].

DISCUSSION

Lack of adherence to oral medication for chronic disease is a well-recognized barrier to the success of an intervention program.^[10,11] Despite free Glivec availability in resource-poor countries, adherence is still a major obstacle to achieving optimal treatment outcome.^[12] The adherence rate of CML patients on Glivec therapy in this study was 47.1%, despite adequate counseling and free drug supply. Varying rates of adherence to medication have been reported in various studies, with rates ranging from 50% to 75% in Western nations.^[12,13] The findings of this study are supportive of previous findings

that reported suboptimal adherence in CML patients on Imatinib therapy.^[14] However, some other studies reported optimal adherence in these group of patients.^[6,15] A Swedish cohort study involving 38 CML patients, reported an adherence rate of 97.4%.^[6] However, the latter finding was based on phone call interviews by an independent research nurse, and there is a likelihood of social desirability bias unlike in the index study where the patients and their relatives were interviewed directly in person by the attending physician.

In an effort to understand the factors that influence patients' medication-taking behaviors, researchers differentiated between two types of nonadherence (intentional and unintentional).^[16,17] Intentional nonadherence is described as an active process whereby patients choose to deviate from the prescribed therapy while unintentional nonadherence is a passive process whereby patients fail to adhere to prescribing instructions through forgetfulness, carelessness, or circumstances beyond their control such as their level of health literacy. Nonadherence in 24% and 27% of the study population were due to forgetfulness and carelessness, respectively. Some researchers have suggested forgetfulness to taking medications as an insight to reduce motivation, having doubts about the prescribed therapy, or having low perceived need for the medication.^[18-20] Gadkari and MacHorney,^[21] in their work on unintentional nonadherence to chronic medication prescriptions reported 62% and 23% of their study participants to be forgetful and careless about taking their medication and therefore concluded that the importance of unintentional nonadherence may lie in its potential prognostic significance for future intentional nonadherence. In a previous study on adherence to Imatinib, the main reason for intentional nonadherent was to minimize side effects.^[22] Studies have also shown that patients could, and often exhibit both intentional and unintentional nonadherence.^[22,23]

This study found that family support was significantly associated with adherence to medication. Previous works on adherence had shown that social support was associated with adherence in patients with HIV and hypertension.^[24,25] Efficace *et al.* were the first to report that social support was a key issue in patients with CML.^[26] Two broad types of social supports, including structural and functional, been investigated in previous adherent studies.^[27] Efficace and his team of researchers focused on the functional aspect of social support, by measuring the strength and quality of patients' relationship with family and friends.^[26,27] They found that functional social support indeed proved to be a predictor of adherence to therapy in CML patients. Patients with stronger social networks are more likely to be reminded to take their medications and gain psychological support, which will ultimately promote patients' coping with the disease burden as well as the burden of a lifelong therapy.^[27] This study found that distances of > 200 km away from the hospital were significantly associated with nonadherent to Glivec medication. This may reflect effects of the physical stress of traveling over such distance, cost of transportation, and poor economic status that may impact on their capacity to come for their medications. Thus patient may

Table 3: Factors influencing adherence in the study participants

Variable	Frequency (%)			P
	Non-adherent	Adherent	Total	
Medication for other illness				
Yes	3 (8.1)	1 (3.1)	4 (5.8)	0.618*
No	34 (91.9)	31 (96.9)	65 (94.2)	
Like taking drug orally?				
Yes	29 (78.4)	26 (78.8)	55 (78.6)	1.000
No	8 (21.6)	7 (21.2)	15 (21.4)	
Knowledge about CML				
Little	33 (89.2)	25 (75.8)	58 (82.9)	0.205
Much	4 (10.8)	8 (24.2)	12 (17.1)	
Family support				
Yes	30 (81.1)	33 (100)	63 (90.0)	0.012
No	7 (18.9)	0	7 (10.0)	
Friend support				
Yes	17 (45.9)	21 (63.6)	38 (54.3)	0.157
No	20 (54.1)	12 (36.4)	32 (45.7)	
Feeling about disease				
Depressed	2 (5.4)	2 (6.3)	4 (5.8)	0.292*
Sad	5 (13.5)	1 (3.1)	6 (8.7)	
Happy	30 (81.1)	28 (87.5)	58 (84.1)	
Indifferent	0	1 (3.1)	1 (1.4)	
Taking drug when fasting				
Before fasting	0	1 (3.0)	1 (1.4)	0.806*
After fasting	17 (47.2)	15 (45.5)	32 (46.4)	
I don't fast	19 (52.8)	17 (51.5)	36 (52.2)	
Side effect to medication				
Yes	30 (81.1)	28 (87.5)	58 (84.1)	0.527
No	7 (18.9)	4 (12.5)	11 (15.9)	
Distance to hospital (km)				
Distance ≥200	24 (64.9)	11 (33.3)	35 (50.0)	0.008
Distance <200	13 (35.1)	22 (66.7)	35 (50.0)	

*Fisher's exact. CML: Chronic myeloid leukemia

decide to ration their medication and spread it to cover till such a time they anticipate they may be able to come to the hospital.

There is conflicting evidence in the literature on the influence of patient age and gender on adherence in CML patients. An adherence study of 87 patients by Marin *et al.*^[28] showed that adherence was lower in younger patients, unlike in this study, in which age had no influence adherence. Darkow *et al.*^[29] in another adherence study conducted on 276 CML patients reported a significant association with gender. The females were reported to have a significantly higher nonadherence. In the index study and in a similar work by Kapoor *et al.*^[15] on Indians with CML, gender seems not to have any influence.

Concomitant drug burden has been reported to be associated with adherence to imatinib therapy in CML patients.^[15] On the

contrary, out of four patients on concomitant drugs in this study, only one patient was found to be adherent. A qualitative study by Eliasson *et al.*^[22] reported that adherent patients referred to taking imatinib as being part of their daily routine, hence it could be speculated that patients who are already taking medication for other diseases might integrate Imatinib into their regular overall medication-taking schedule. However, there was a relatively lower rate of concomitant drug use in this study compared to Eliasson *et al.*^[22] study probably owing to the relatively young age of our CML patients who are yet to develop chronic illnesses associated with advanced age and high pill burden for other age-associated diseases.^[30]

The majority of our patients had side effects with the use of imatinib, and these adverse effects were relatively common to both study groups. Mild to moderate and tolerable adverse drug effects were not found to influence adherence in the study participants though, 6% of patients in the nonadherent group admitted to drug interruption due to side effects. Studies have reported that simple actions such as informing the patient about the characteristics of the disease, risks and benefits of treatment, expected side effects, and correct use of medication can improve adherence.^[31,32]

The major limitation was that adherence was evaluated based on patient report and pill count. No objective biomarker was used to confirm reported adherence.

CONCLUSION AND RECOMMENDATION

This study found that a higher proportion of patients with CML were nonadherent to Imatinib (Glivec®) therapy. Distance of more than 200 km away from the hospital was significantly associated with nonadherent to Glivec therapy. Family support was a significant determinant of adherence in this study; and therefore, increase advocacy for family and social support will improve patient's adherence to medication. Future studies should consider the effect of distance as a barrier to patient adherence.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Noens L, Hensen M, Kucmin-Bemelmans I, Lofgren C, Gilloteau I, Vrijens B. Measurement of adherence to BCR-ABL inhibitor therapy in chronic myeloid leukemia: Current situation and future challenges. *Haematologica* 2014;99:437-47.
- Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N, *et al.* Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 2006;355:2408-17.
- Dos Reis SR, Quixadá AT, Nunes ST, Cid DM, de Souza JH, da Costa CM, *et al.* Adherence to treatment with imatinib in chronic myeloid leukemia: A study of the first decade of responses obtained at a Brazilian hospital. *Rev Bras Hematol Hemoter* 2013;35:174-9.
- Goldman JM, Melo JV. Chronic myeloid leukemia--advances in biology and new approaches to treatment. *N Engl J Med* 2003;349:1451-64.

5. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, *et al.* Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003;348:994-1004.
6. Jönsson S, Olsson B, Söderberg J, Wadenvik H. Good adherence to imatinib therapy among patients with chronic myeloid leukemia – A single-center observational study. *Ann Hematol* 2012;91:679-85.
7. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986;24:67-74.
8. Södergård B, Halvarsson M, Lindbäck S, Sönerborg A, Tully MP, Lindblad ÅK. Differences in adherence and motivation to HIV therapy—two independent assessments in 1998 and 2002. *Pharm World Sci* 2006;28:248-56.
9. Bland JM, Altman DG. Statistics notes: Cronbach's alpha. *BMJ* 1997;314:572.
10. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487-97.
11. Partridge AH, Wang PS, Winer EP, Avorn J. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. *J Clin Oncol* 2003;21:602-6.
12. DiMatteo MR. Variations in patients' adherence to medical recommendations: A quantitative review of 50 years of research. *Med Care* 2004;42:200-9.
13. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: Three decades of research. A comprehensive review. *J Clin Pharm Ther* 2001;26:331-42.
14. Noens L, van Lierde MA, De Bock R, Verhoef G, Zachée P, Berneman Z, *et al.* Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: The ADAGIO study. *Blood* 2009;113:5401-11.
15. Kapoor J, Agrawal N, Ahmed R, Sharma SK, Gupta A, Bhurani D. Factors influencing adherence to imatinib in Indian chronic myeloid leukemia patients: A cross-sectional study. *Mediterr J Hematol Infect Dis* 2015;7:e2015013.
16. Lehane E, McCarthy G. An examination of the intentional and unintentional aspects of medication non-adherence in patients diagnosed with hypertension. *J Clin Nurs* 2007;16:698-706.
17. Lehane E, McCarthy G. Intentional and unintentional medication non-adherence: A comprehensive framework for clinical research and practice? A discussion paper. *Int J Nurs Stud* 2007;44:1468-77.
18. Kim E, Gupta S, Bolge S, Chen CC, Whitehead R, Bates JA. Adherence and outcomes associated with copayment burden in schizophrenia: A cross-sectional survey. *J Med Econ* 2010;13:185-92.
19. Proulx M, Leduc N, Vandelaer L, Grégoire JP, Collin J. Social context, the struggle with uncertainty, and subjective risk as meaning-rich constructs for explaining HBP noncompliance. *Patient Educ Couns* 2007;68:98-106.
20. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res* 1999;47:555-67.
21. Gadkari AS, McHorney CA. Unintentional non-adherence to chronic prescription medications: How unintentional is it really? *BMC Health Serv Res* 2012;12:98.
22. Eliasson L, Clifford S, Barber N, Marin D. Exploring chronic myeloid leukaemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed. *Leuk Res* 2011;35:626-30.
23. Rees G, Leong O, Crowston JG, Lamoureux EL. Intentional and unintentional nonadherence to ocular hypotensive treatment in patients with glaucoma. *Ophthalmology* 2010;117:903-8.
24. Gordillo V, del Amo J, Soriano V, González-Lahoz J. Sociodemographic and psychological variables influencing adherence to antiretroviral therapy. *AIDS* 1999;13:1763-9.
25. DiMatteo MR. Social support and patient adherence to medical treatment: A meta-analysis. *Health Psychol* 2004;23:207-18.
26. Efficace F, Baccarani M, Rosti G, Cottone F, Castagnetti F, Breccia M, *et al.* Investigating factors associated with adherence behaviour in patients with chronic myeloid leukemia: An observational patient-centered outcome study. *Br J Cancer* 2012;107:904-9.
27. Lett HS, Blumenthal JA, Babyak MA, Strauman TJ, Robins C, Sherwood A. Social support and coronary heart disease: Epidemiologic evidence and implications for treatment. *Psychosom Med* 2005;67:869-78.
28. Marin D, Bazeos A, Mahon FX, Eliasson L, Milojkovic D, Bua M, *et al.* Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol* 2010;28:2381-8.
29. Darkow T, Henk HJ, Thomas SK, Feng W, Baladi JF, Goldberg GA, *et al.* Treatment interruptions and non-adherence with imatinib and associated healthcare costs: A retrospective analysis among managed care patients with chronic myelogenous leukaemia. *Pharmacoeconomics* 2007;25:481-96.
30. Durosini MA. *A Design Handbook of Haemato-Oncology Therapy for Medical Practitioners and Students*. 3rd ed.. Lagos Nigeria: Amkra and Allied Services Ltd; 2013. p. 15-7.
31. Richardson JL, Shelton DR, Krailo M, Levine AM. The effect of compliance with treatment on survival among patients with hematologic malignancies. *J Clin Oncol* 1990;8:356-64.
32. Moon JH, Sohn SK, Kim SN, Park SY, Yoon SS, Kim IH, *et al.* Patient counseling program to improve the compliance to imatinib in chronic myeloid leukemia patients. *Med Oncol* 2012;29:1179-85.