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Clinical Importance of Drug Adherence during Tyrosine Kinase Inhibitor Therapy for Chronic Myelogenous Leukemia in Chronic Phase

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Abstract

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm constituting approximately 15% of newly diagnosed leukemia in adult patients. Development of tyrosine kinase inhibitors (TKIs) have dramatically improved outcomes in patients with chronic CML in chronic phase. However, adverse drug events (ADEs) associated with TKI therapy have influenced drug adherence, resulting in adverse clinical outcomes and a decline in the quality of life (QoL). In this study, we carried out a unique questionnaire survey to evaluate ADEs, which comprised 14 adverse events. We compared drug adherence rates between patients using imatinib and those who switched from imatinib to nilotinib, a second-generation TKI. Following the switch, the total number of ADEs decreased considerably in most cases. Simultaneously, better QoL was observed in the nilotinib group than in the imatinib group. Drug adherence was measured using Morisky's 9-item Medication Adherence Scale (MMAS). MMAS increased significantly after switching to nilotinib in all cases. Drug adherence is a critical factor for achieving molecular response in patients with CML. In fact, our results showed a strong inverse correlation between clinical outcome [international scale (IS)] and adherence (MMAS), with a stronger tendency in the nilotinib group than in the imatinib group. In conclusion, low occurrence of ADEs induced a high level of QoL and a good clinical response with second-generation TKI nilotinib treatment.

Introduction

Chronic myeloid leukemia (CML) is a clonal disease of the hematopoietic stem cells and is characterized by the Philadelphia chromosome and its oncogene *BCR-ABL1*. The treatment of CML has dramatically changed over the last decade with the development of targeted therapy using tyrosine kinase inhibitors (TKIs). Furthermore, TKIs have dramatically improved outcomes in patients with CML in chronic phase [1]. Several adverse drug events (ADEs) related to TKI in CML patients are common, including general edema, nausea, fatigue, and musculoskeletal symptoms, which occur at varying frequencies depending on the TKIs. Patients who reported that ADEs had a negative

influence on their daily quality of life (QoL) perceived more ADEs than those who did not experience a negative influence. However, new ADEs developed once imatinib (IM) was switched to nilotinib (NILO); therefore, early and successful management of ADEs is required for the acquisition of tolerance to treatment [2]. The ADEs (peripheral edema, muscle spasm, and eruption) that occurred at the beginning of IM treatment disappeared after switching to NILO [3].

Adherence is compliance with a medication regimen and is based on patient understanding, decision-making, and therapeutic cooperation. Adherence is defined by various factors including awareness of taking medication, awareness of illness and medicines, life rhythm, character, relationship of trust with the doctor or pharmacist, and use of medicine information leaflets. Evaluation of medication adherence status revealed that patients with poor adherence most frequently forgot to take their medicines after lunch and between meals. Drug adherence has been reported as a critical factor for achieving molecular response in patients with CML [4-7], and non-adherence to TKI therapy may influence the disease outcome [5]. In this study, we evaluated drug adherence using the 9-item Morisky Medication Adherence Scale (MMAS) [8,9]. We compared drug adherence rates between patients using IM and those who switched from IM to NILO, a second-generation TKI. The 9-item MMAS showed that drug adherence improved significantly in the NILO group compared to that in the IM group. Moreover, switching to the second-generation TKI improved drug adherence in a time-dependent manner. Guérin et al. [10] reported that among the patients treated with second-line TKIs, those treated with NILO had a significantly higher adherence compared to patients treated with dasatinib. However, Trivedi et al. reported that among the second-line TKI-treated CML patients, dasatinib patients had significantly higher adherence and lower discontinuation rates compared with those receiving second-line nilotinib [11]. Chen et al., however, raised some questions about the results described above [12]. In general, social, disease-related, treatment-related, and patient-centered factors contribute to improved adherence [5,13]. However, no significant differences in adherence, hospitalization, or emergency room visits have been reported among patients initiating a second *vs* first-generation TKI [14]. Marin et al. reported that no complete molecular

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responses were observed when adherence was ≤ 90%, and no major molecular responses were observed when adherence was ≤ 80%; the adherence rate for each patient was defined as the dose taken according to the microelectronic monitoring systems (MEMS) reading and expressed as a percentage of the dose prescribed during the total duration of the study [5]. We, therefore, examined the relationship between clinical outcome using the international scale (IS) for *BCR/ABL* and clinical adherence determined by MMAS. This study aimed to evaluate patient-reported ADEs during TKI treatment and their influence on adherence and QoL in CML patients in chronic phase.

Patients and Methods

Patient population

Twenty patients with CML, who received TKIs at the National Hospital Organization Osaka Minami Medical Center, were selected for this study. All study participants provided informed consent, and the study design was approved by the appropriate ethics review board.

Adverse events

All patients were questioned using an interview form (Fig. 1). Patient-reported ADEs were assessed during the interview using a structured questionnaire (Fig. 1). Fourteen ADEs were included in the form.

Quality of life (QoL)

QoL was judged on a scale of 1 to 5 during IM treatment in the past and during NILO treatment in the present (Fig. 2).

Assessment of adherence and clinical outcome

Patient adherence was measured using the 9-item Morisky Medication Adherence Scale (MMAS) [8,9]., with scores ranging from 1-13, where 13 indicates perfect adherence. MMAS is composed of nine questions that explore the adherence behavior based on forgetfulness, negligence, interruptions in drug intake, and the restart of drug intake. Patients with an MMAS score of 11 or above were classified as adherent [21].

Statistical Analysis

Statistical analysis was performed using GraphPad Prism v6 software (GraphPad software Inc. La Jolla, CA). Unpaired student *t* test (Mann-Whitney test) was used comparison between two groups. P value of ≤0.5 was considered significant.

Results

Comparison of ADEs between IM and NILO treatments

A questionnaire survey (Fig. 1), which included 14 adverse events, was carefully carried out by calculating system. After switching from IM to NILO, the total number of AEs decreased in most cases, except in 2 (Fig. 3). New AEs developed upon switching to NILO; however, tolerance was gradually acquired by management of AE.

Improved symptoms after switching from imatinib to nilotinib

We investigated the type of ADEs that improved upon switching to NILO. As shown in Fig. 4, ADEs such as facial edema, peripheral edema, lids edema, general fatigue, depression, nausea, muscle pain and muscle cramp, were reduced significantly. These results indicated that fluid retention, digestive symptom, and muscle symptom induced by IM improved upon switching to NILO.

Alteration in QoL upon switching from imatinib to second-generation TKI

As the ADEs induced by IM was reduced by NILO administration, change of QoL was examined by a questionnaire study (Fig. 2). The QoL score was significantly decreased, indicating an improved QoL upon NILO administration (Fig. 5).

Relationship between clinical outcome (IS) and drug adherence (MMAS) in the NILO group compared to that in the IM group

We compared the drug adherence rates and clinical outcome. Drug adherence was measured using MMAS and clinical outcome was evaluated based on IS. A significant relationship between clinical outcome and drug adherence was found in the NILO group ($p = 0.0002$) (Fig. 6A) than in the IM group ($p = 0.0024$) (Fig. 6B).

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Discussion

Several ADEs related to TKI in CML during chronic phase, including general edema, nausea, fatigue, and musculoskeletal symptoms, occur at varying frequencies depending on the TKIs. We created a specific questionnaire survey that included 14 ADEs and was carefully conducted by calculating severity scores. After switching from IM to NILO, the total number of ADEs decreased in most cases. Although new ADEs developed initially after switching to NILO, tolerance was acquired by management of ADEs [3,15]. In particular, fluid retention, digestive symptoms, and muscle symptoms including facial edema, peripheral edema, lids edema, general fatigue, depression, nausea, muscle pain and muscle cramps induced by IM were reduced significantly (Fig. 4). Kekäle et al. reported that they were unable to find a clinical correlation between these symptoms and patient adherence although, they did find a significant correlation between higher number of symptoms and a negative impact on the patient's QoL [16]. Furthermore, they reported that intentional non-adherence was more common in women than in men (37 and 24%) and in patients receiving dasatinib and NILO than in patients receiving IM (44%, 44% *vs* 26%, respectively) [16]. However, Rychter et al. reported that there were no differences in adherence among patients treated with imatinib, dasatinib, and nilotinib ($p = 0.249$) [17]. In our study, the QoL score was significantly decreased in most patients who switched to NILO, which might be the result of fewer ADEs. Previously, we reported that statistically significant differences in adherence, defined by an MMAS score of ($p = 0.0011$), were observed between the IM and NILO groups [18]. It has been reported that adherence is the most critical factor for achieving clinical response and ultimately for improving survival in patients with CML receiving TKI therapy [4,14]. Winn et al. reported that, in a multivariate analysis, individuals with cost-sharing subsidies, younger age, lower comorbidity, and later year of diagnosis were significantly more likely to initiate TKIs [19]. We also compared drug adherence rates and clinical outcomes. Clinical outcomes were evaluated using the IS for major *BCR/ABL* gene expression. Significant relationships between clinical outcome and drug adherence

rates were found in the IM (p = 0.0024) and NILO (p = 0.0002) groups, with a more significant tendency in the NILO group. These results might be due to the difference in drug adherence between the TKI groups. It has been reported that the Morisky high adherence was positively associated with complete hematologic remission in the chronic phase of CML [15,20]. Drug adherence has been reported as a critical factor for achieving molecular response in patients with CML [4-7], and non-adherence to TKI therapy may influence the disease outcome [5].

Conclusion

Various factors have been assessed for their impact on drug adherence. Among the factors, ADEs of TKI have significant influence on drug adherence results, leading to poorer outcomes during the clinical course and a decline in the QoL. Management of ADEs associated with TKI treatment is the most important strategy to maintain a high-drug adherence. Furthermore, drug adherence has been reported to be a critical factor for achieving molecular response in patients with CML. In fact, our results showed a strong inverse correlation between clinical outcome and adherence.

Abbreviations

CML: Chronic myeloid leukemia; TKI: Tyrosine kinase inhibitors; ADE: Adverse drug events; QoL: Quality of life; MMAS: Morisky Medication Adherence Scale; IM: imatinib; NILO: nilotinib.

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Ethics Committee Approval and Patient Consent

All study participants provided informed consent. The study design was approved by the appropriate ethics review board.

Competing Interests

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The authors declare that they have no competing interests.

References

1. Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, Cervantes F, Deininger M, Gratwohl A, Guilhot F, Hochhaus A, Horowitz M, Hughes T, Kantarjian H, Larson R, Radich J, Simonsson B, Silver RT, Goldman J, Hehlmann R. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol. 2009; 27: 6041–6051.

2. O'Dwyer M, Atallah E. Practical considerations for the management of patients in the tyrosine kinase inhibitor era. Semin Hematol. 2009; 46: S16–S21.

3. Rosti G, Castagnetti F, Gugliotta G, Palandri F, Baccarani M. Physician's guide to the clinical management of adverse events on nilotinib therapy for the treatment of CML. Cancer Treat Rev. 2012;38: 241–248.

4. Santoleri F, Sorice P, Lasala R, Rizzo RC, Costantini A. Patient adherence and persistence with Imatinib, Nilotinib, Dasatinib in clinical practice. PLoS One. 2013; 8(2): e56813.

5. Marin D, Bazeos A, Mahon FX, Eliasson L, Milojkovic D, Bua M, Apperley JF, Szydlo R, Desai R, Kozlowski K, Paliompeis C, Latham V, Foroni L, Molimard M, Reid A, Rezvani K, de Lavallade H, Guallar C, Goldman J, Khorashad JS. 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: 2381–2388.

6. Hochhaus A. Educational session: managing chronic myeloid leukemia as a chronic disease. Hematology Am Soc Hematol Educ Program. 2011; 2011: 128-135.

7. Guilhot F, Coombs J, Szczudlo T, Zernovak O, Paolantonio M, Bender C, Macdonald NJ, Shapiro A. The patient journey in chronic myeloid leukemia patients on tyrosine kinase inhibitor therapies: qualitative insights using a global ethnographic approach. Patient. 2013; 6: 81–92.

8. 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: 679–685.

9. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens. 2008; 10: 348–354.

10. Guérin A, Chen L, Wu EQ, Ponce de Leon D, Griffin JD. A retrospective analysis of therapy adherence in imatinib resistant or intolerant patients with chronic myeloid leukemia receiving nilotinib or dasatinib in a real-world setting. Curr Med Res Opin. 2012; 28:1155–1162.

11. Trivedi D, Landsman-Blumberg P, Darkow T, Smith D, McMorrow D, Mullins CD. Adherence and persistence among chronic myeloid leukemia patients during second-line tyrosine kinase inhibitor treatment. J Manag Care Spec Pharm. 2014; 20: 1006-1015.

12. Chen L, Wu EQ. Adherence and Persistence Among Chronic Myeloid Leukemia Patients During Second-Line Tyrosine Kinase Inhibitor Treatment. J Manag Care Spec Pharm. 2015;21: 1088

13. de Almeida MH, Pagnano KB, Vigorito AC, Lorand-Metze I, de Souza CA. Adherence to tyrosine kinase inhibitor therapy for chronic myeloid leukemia: a Brazilian single-center cohort. Acta Haematol. 2013; 130: 16–22.

14. Ward MA, Fang G, Richards KL, Walko CM, Earnshaw SR, Happe LE, Blalock SJ. Comparative evaluation of patients newly initiating first-generation versus second-generation tyrosine kinase inhibitors for chronic myeloid leukemia and medication adherence, health services utilization, and healthcare costs. Curr Med Res Opin. 2015; 31: 289–297.

15. Cortes JE1, Apperley JF2, DeAngelo DJ3, Deininger MW4, Kota VK5, Rousselot P6, Gambacorti-Passerini C7. Management of adverse events associated with bosutinib treatment of chronic-phase chronic myeloid leukemia: expert panel review.
J Hematol Oncol. 2018; 11(1):143.

16. Kekäle M, Peltoniemi M, Airaksinen M. Patient-reported adverse drug reactions and their influence on adherence and quality of life of chronic myeloid leukemia patients on

per oral tyrosine kinase inhibitor treatment. Patient Prefer Adherence. 2015; 9: 1733–1740.

17. Rychter A, Jerzmanowski P, Hołub A, Specht-Szwoch Z, Kalinowska V, Tęgowska U, Seferyńska I, Kołkowska-Leśniak A, Lech-Marańda E, Góra-Tybor J. Treatment adherence in chronic myeloid leukaemia patients receiving tyrosine kinase inhibitors. Med Oncol. 2017; 34(6):104.

18. Maeda Y, Okamoto A, Kawaguchi SI, Konishi A, Yamamoto K, Eguchi G, Kanai Y, Yamaguchi T. Improved Drug Adherence in Patients with Chronic Myeloid Leukemia in the Chronic Phase by Switching to Second-Generation Tyrosine Kinase Inhibitors. Acta Haematol. 2017;138(3):140-142.

19. Winn AN, Keating NL, Dusetzina SB. Factors Associated with Tyrosine Kinase Inhibitor Initiation and Adherence Among Medicare Beneficiaries With Chronic Myeloid Leukemia. J Clin Oncol. 2016; 34(36): 4323-4328.

20. Mulu Fentie A, Tadesse F, Engidawork E, Gebremedhin A. Prevalence and determinants of non-adherence to Imatinib in the first 3-months treatment among newly diagnosed Ethiopian's with chronic myeloid leukemia. PLoS One. 2019; 14(3): e0213557.

21. 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(1): e2015013.

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Figure legends

Figure 1.

Figure 1.

<Questionnaire for changing AE>

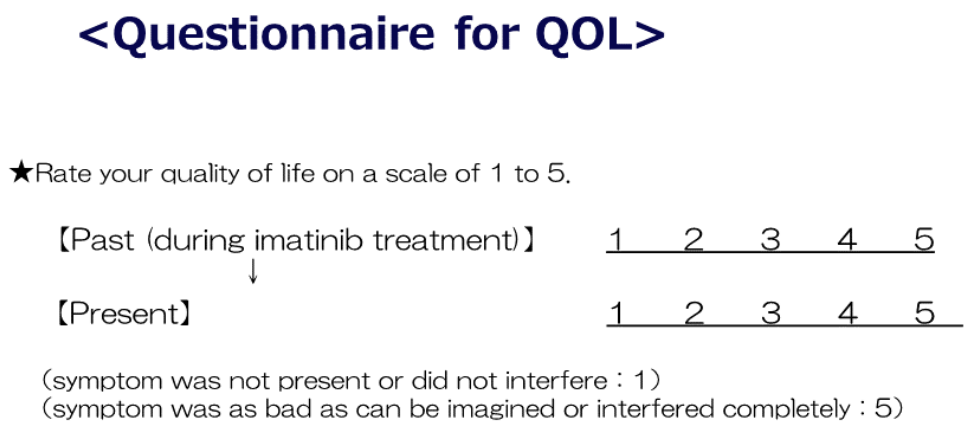
★Please fill in check mark in the place to apply to it.

	Severity score							
	During imatinib treatment				Present			
	No AE	Low	Intermediate	High	No AE	Low	Intermediate	High
Face Edema								
Peripheral Edema								
Lids Edema								
Chest Discomfort								
Headache								
Genaral Fatigue								
Depression								
Diarrhea								
Constipation								
Nausea								
Muscle Pain								
Muscle Cramp								
Eruption								
Pruritus								
Oher( )								

An interview form for ADEs was prepared for all patients. Patient-reported adverse events (ADEs) were assessed during the interview using a structured questionnaire.

Figure 2.

Figure 2.



An interview form for QoL was prepared for all patients. QoL was judged on a scale 1 to 5 during IM treatment (in the past) and during NILO treatment (in the present).

Figure 3.

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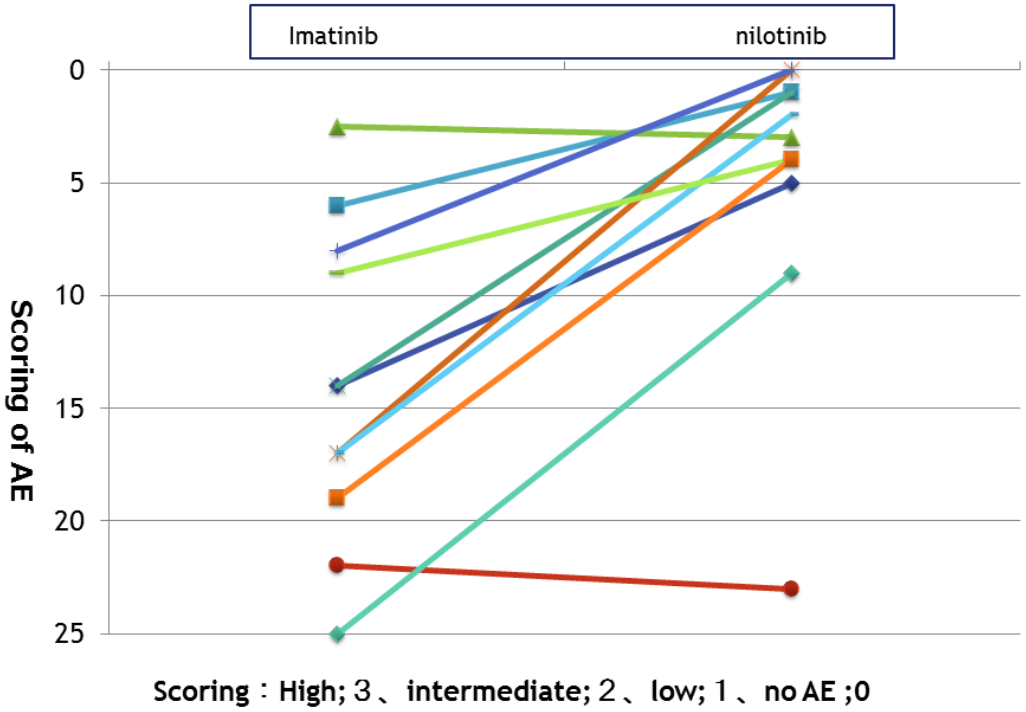
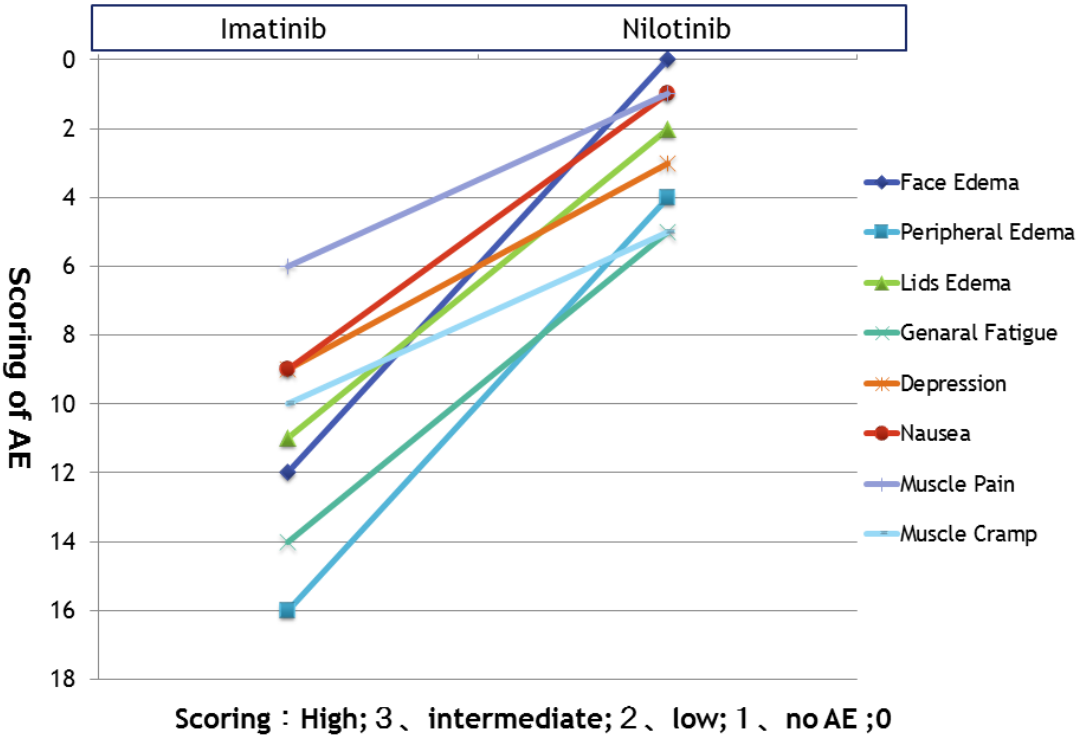
Figure 3.



A unique questionnaire survey including 14 ADEs was carefully conducted by calculating the severity score. Comparison of the ADE scores between IM group and NILO group.

Figure 4.

Figure 4.



The ADEs which improved by switching to NILO are indicated. ADEs described below including facial edema, peripheral edema, lids edema, general fatigue, depression, nausea, muscle pain and muscle cramp improved.

Figure 5.

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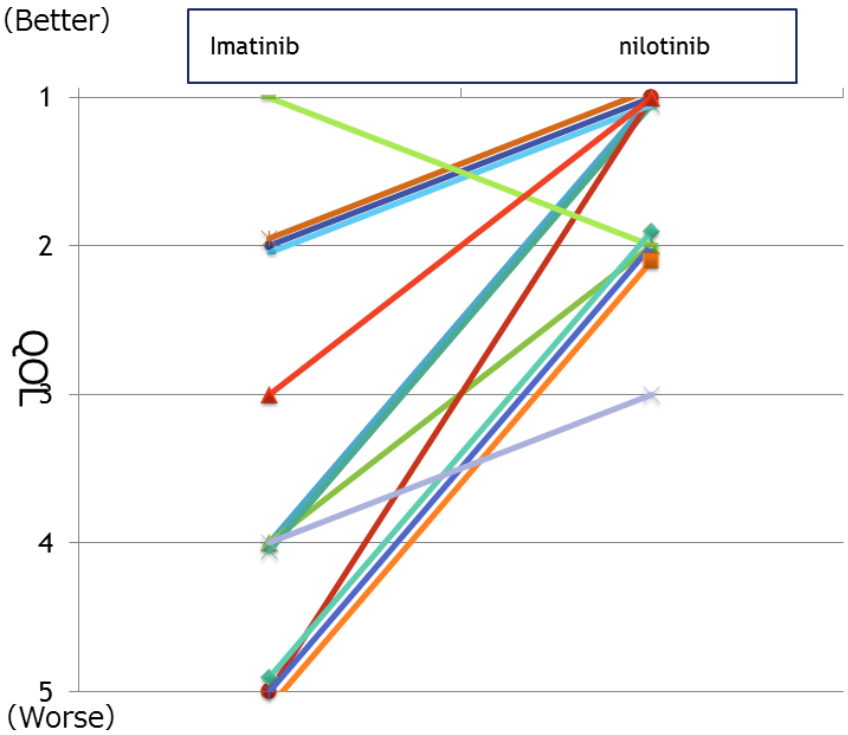
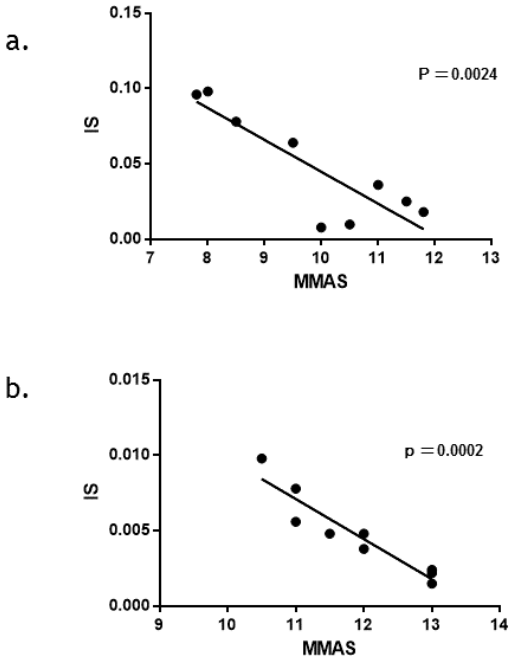
Figure 5.



An interview form for QoL was prepared for all patients. Comparison of QoL score between IM group and NILO group.

Figure 6.

Figure 6.



Relationship between drug adherence rates and clinical outcome determined with IS. Drug adherence was measured by Morisky's 9-item Medication Adherence Scale (MMAS). A more significant relationship between those evaluated parameters was found in the NILO group (p = 0.0002) (Fig. 6A) than in the IM group (p=0.0024) (Fig. 6A).