Quality of Life and Adherence to Therapy in Patients With Chronic Myeloid Leukemia Treated With Nilotinib as a Second-Line Therapy: A Multicenter Prospective Observational Study

Tomasz Sacha,[1] Joanna Góra-Tybor,[2] Ewa Wąsak-Szulkowska,[3] Sławomira Kyrcz-Krzemień,[4] Ewa Mędraś,[5] Rafał Becht,[6] Grażyna Bober,[4] Aneta Kotowska,[3] Joanna Wącław,[1] Andrzej Hellmann[7]

Abstract

To evaluate quality of life (QOL) and adherence to nilotinib used as second-line therapy in 177 chronic myeloid leukemia patients in chronic phase, a multicenter, prospective, observational study was conducted. The QOL was very good and adherence to the treatment was high. Study results could be taken into consideration in the process of tyrosine kinase inhibitor treatment choice.

Introduction: The aim of this study was to evaluate quality of life (QOL) and adherence to the therapy in patients with chronic myeloid leukemia in chronic phase treated with nilotinib as second-line therapy. **Patients and Methods:** A multicenter, prospective, observational trial with 6 time points was conducted; 177 patients were recruited in 23 centers in Poland who were treated with nilotinib as second-line therapy because of the ineffectiveness or intolerance of their previous therapy. QOL was evaluated with the standard European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire. Adherence to the therapy was assessed using the 4-item Morisky Medication Adherence Scale by patients and their physicians. **Results:** The average QOL in patients who completed the study was significantly higher during the last visit (69.4 $\pm$ 17.4) than at the start of the study (59.1 $\pm$ 18.8; $P < .001$). At their first visit, 120 (83.2%) patients assessed themselves as highly compliant and 135 (93.4%) at the fifth visit. Low-compliance patients represented 3 (1.7% of the total) during visit 1; none of the patients self-assessed as low compliance since the fourth visit. At the first visit 151 (85.3%) patients were categorized by their physicians as highly compliant and 138 (96.0%) during the last 3 visits. Patients' and their physicians' assessments were significantly correlated. **Conclusion:** The QOL among patients receiving nilotinib administered as second-line therapy was very good and adherence to the treatment was high. The efficacy and safety of the drug were confirmed in the real-life setting.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 17, No. 5, 283-95
Keywords: CML, Drug compliance, Second generation tyrosine kinase inhibitor treatment, Therapy outcome on doctor's perspective, Therapy outcome on patient's perspective

Introduction

Chronic myeloid leukemia (CML) accounts for approximately 15% of all leukemias in adults.[1] The advent of imatinib, the first tyrosine kinase inhibitor (TKI), has completely changed the landscape of the disease.[2] CML has transformed from a fatal illness to a chronic one, with estimated 5-year overall survival of 89%.[3] Introduction of dasatinib and nilotinib, second-generation TKIs, provided even more options to effectively treat CML patients.

[1]Department of Hematology, Jagiellonian University Hospital, Kraków, Poland
[2]Institute of Hematology and Transfusion Medicine, Warszawa, Poland
[3]Novartis Poland, Warszawa, Poland
[4]Department of Hematology and Bone Marrow Transplantation, Silesian Medical University, Katowice, Poland
[5]Department of Hematology, Malignant Blood Diseases and Bone Marrow Transplantation, Wroclaw Medical University, Wrocław, Poland
[6]Department of Hematology, Pomeranian Medical University in Szczecin, Szczecin, Poland
[7]Department of Hematology and Transplantology, Gdansk Medical University, Gdańsk, Poland

Submitted: Dec 23, 2016; Accepted: Jan 3, 2017; Epub: Jan 10, 2017

Address for correspondence: Tomasz Sacha, MD, PhD, Klinika Hematologii UJCM, 31-501 Kraków, ul, Kopernika 17, Poland
E-mail contact: sachatom@gmail.com

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2017.01.001

The survival of CML patients treated with TKIs is not significantly different from that of the general population. However, adverse effects of TKI treatment, although usually mild or moderate, are still an important issue. It has been reported that therapy with TKIs might have an adverse effect on quality of life (QOL). Most of the research on QOL among patients taking TKIs for CML has focused on imatinib, although studies on second-generation TKIs have also been published.[4,5] Patient adherence or compliance, defined by the World Health Organization as the extent to which a person's behavior corresponds with the agreed recommendations of a health care provider, is crucial to achieve good outcomes with TKI therapy.[6,7] Correlations between poor adherence to imatinib therapy and reduced failure-free survival and increased health care costs have been shown among CML patients in clinical trials and real-world settings.[8-11]

Nilotinib is a potent inhibitor of breakpoint cluster region - abelson 1 tyrosine kinase, an oncoprotein that drives pathogenesis of CML.[12] The drug has been approved as therapy for chronic and accelerated phases of CML in patients resistant and/or intolerant to imatinib as well as in newly diagnosed patients with CML in chronic phase (CML-CP).[13,14] The recommended dose of nilotinib in second-line treatment is 400 mg twice daily. The method of drug administration might be more challenging for the patients compared with other TKIs. Nilotinib should be taken twice daily approximately 12 hours apart and must not be taken with food. No food should be consumed 2 hours before and at least 1 hour after the drug is administered.[15]

Recent studies that compared adherence to second-line CML treatment with nilotinib and dasatinib reported conflicting results.[16,17] To date, no prospective studies on patient QOL and adherence to nilotinib treatment have been published. The aim of this study was to obtain data on QOL and adherence in patients with CML-CP treated with nilotinib as well as to determine factors that influence them within a prospective multicenter observational trial.

Research Question and Objective

The primary end point of the study was to assess the QOL in CML-CP patients treated with nilotinib (Tasigna; Novartis) as a second-line therapy at the start of observation and after 1, 3, 6, 9, and 12 months of observation with the use of the European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire (EORTC QLQ-C30). The secondary end points included the evaluation of drug compliance from patient's and from treating physician's perspective assessed using the Morisky Medication Adherence Scale (MMAS) at 1, 3, 6, and 9 months and at the completion of the observation, analysis of correlation between QOL and drug compliance, analysis of correlation between physicians' and patients' drug compliance assessment at 1, 3, 6, and 9 months, and at the completion of the study, evaluation of the relationship between drug compliance and dosing schedule (twice daily, once daily), and analysis of correlations between patient age, educational and marital status, satisfaction with medical care, and QOL as well as drug compliance.

Methods

Design and Sample

This study was designed as a multicenter prospective, observational trial. The enrollment period for observation within the study lasted from June 2010 to June 2012. The duration of observation of an individual patient was 12 months. Nilotinib in a first-line therapy of CML is not reimbursed in Poland, therefore eligible for the study were male and female patients, at least 18 years old, diagnosed with CML-CP, for whom the treating physician had made an independent decision to change previous treatment because of its ineffectiveness or intolerance to nilotinib within the approved label. The assignment of patients to treatment with nilotinib followed current clinical practice and was not decided in advance according to a trial protocol. The administration of the medicine was clearly separated from a decision to include a patient in the study. Excluded were patients in the accelerated phase or blast crisis of CML, patients treated with nilotinib for longer than 7 days before inclusion in the study, patients with contraindications to nilotinib as in the Summary of Product Characteristics, patients who were unable to independently fill out the questionnaires used in the study, or who were currently participating in another, interventional clinical study. Observation of a patient within the study was terminated before the end of 12 months if nilotinib was discontinued because of any reason.

Ethic committee approval was not required for this non-interventional study. Written informed consent was obtained from all patients. The patients could withdraw consent for filling out the study questionnaires at any time during the observation period, which resulted in termination of a patient's observation in the study.

Patient Characteristics

A total of 177 patients were recruited by the physicians treating CML in 23 centers in Poland. All patients were white, Caucasian. The mean age was 57.8 (±12.8 years). Most of the patients were female (50.8%; n = 90) and with medium education (58.2%; n = 103), followed by basic education (24.9% ; n = 44). Nearly two-thirds of the patients were either pensioners or received social support (65.5%; n = 116), employed persons accounted for almost 30% (n = 52). Most patients lived with family (52.5% ; n = 93) or partners (39% ; n = 69); 8.5% (n = 15) declared that they resided alone at home.

The mean time from the diagnosis of CML was 4.5 years (±4.6 years); 174 (98.3%) patients recruited in the study had been previously treated with imatinib, which had been preceded with a therapy with hydroxycarbamide in 157 (88.7%); 62 (35.0%) patients had received dasatinib as a second-line TKI treatment. Concomitant diseases affected 74 study participants (41.8%). The most frequent comorbidities were hypertension in 76 (43.2%), followed by diabetes mellitus in 19 (10.8%), and chronic ischemic heart disease in 19 (10.8%). Of the study population, 94 (53.1%) used long-term concomitant drugs. Nilotinib was administered as the second-line, and third-line TKI therapy in 114 (64.4%) and in 57 (32.2%) of patients, respectively. Of the patients in whom nilotinib was started because of a failure of a previous treatment (n = 124; 70.0%), in 43 (24.3%) because of intolerance, and in 4.5% (n = 8) previous therapy failure and intolerance coexisted. At the start of the study nearly all of the patients were given nilotinib at the dose of 800 mg/d. Of the remaining patients, 6 (3.4%) were given 600 mg/d and 4 (2.3%) received doses of 400 mg/d (Table 1). Doses of 800 mg/d and 600 mg/d were administered twice daily, whereas lower doses of 400 mg/d and 200 mg/d were administered once daily.

Methodology of Observation Within the Study

Observation within the study had 6 time points: baseline (enrollment visit) and follow-up in the first, third, sixth, ninth, and

Table 1 Patients Demographic Characteristics and Clinical Status at the Time of the Enrollment Visit

Patient Demographic Characteristic	Value
Age Range (Mean ± SD), Years	24-86 (57.8 ± 12.8)
Sex, %	
Male	49.2
Female	50.8
Education, %	
Basic	24.9
Medium	58.2
Higher	16.4
Socioeconomic Status, %	
Living with family	52.5
Living with partner	39.0
Living at home alone	8.5
Pensioners/social support beneficiaries	65.5
Employed	29.9
History of CML and Treatment	
Years since CML diagnosis, mean ± SD	4.5 ± 4.6
Previous CML Therapies, Percentage of All Patients	
Imatinib	98.3
Dasatinib	35.0
Hydroxycarbamide	88.7
Interferon-α	9.6
Busulfan	1.1
Comorbidities, Percentage of All Affected Patients	
Cardiovascular	49.7
Endocrine/metabolic	14.1
Gastrointestinal	6.7
Musculoskeletal and skin/connective tissue	6.7
Concomitant Medications, Percentage of All Nilotinib Therapy	53.1
Reasons for Starting Nilotinib Treatment, Percentage of All Patients	
Previous treatment failure	70.6
Previous treatment intolerance	24.3
Previous treatment failure and intolerance	4.5
Nilotinib Starting Dose, %	
800 mg/d	94.4
600 mg/d	3.4
400 mg/d	2.3

Abbreviation: CML = chronic myeloid leukemia.

12th month. The visit schedule reflected the frequency of follow-up examinations performed as a part of routine medical care, clinical practice, and standards of CML treatment established according to European Leukemia Net recommendations.[18]

During the first visit, after obtaining the patient's consent for the observation in the study, the treating physician documented the patient's data (including sex, age, and socioeconomic and family status) and information on a course of disease (including date of diagnosis of CML, previous therapy and its outcome, indications for starting nilotinib, comorbidities, and concomitant medications used long-term by a patient). The patients were asked to fill out the baseline QOL questionnaire as well as a compliance self-assessment questionnaire regarding previous treatment and a questionnaire on satisfaction with medical care. The patients were asked to fill out the aforementioned questionnaires during each follow-up visit. The treating physician assessed the patients' compliance according to his/her own perspective during each visit by asking a patient the specific set of questions (the same as in the questionnaire filled out by the patient).

The efficacy of nilotinib treatment was evaluated by testing hematologic, cytogenetic, and/or molecular response as a part of a routine medical practice.

Quality of Life

Quality of life was evaluated using the standard EORTC QLQ-C30, version 3.0. The EORTC QLQ-C30 is designed to measure health-related QOL in cancer patients.[19,20] It includes 5 functional scales (physical, role, emotional, social, and cognitive), 3 symptom scales (fatigue, nausea and vomiting, and pain), a global health status/QOL scale, as well as 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).[21] The Polish language version of the EORTC QLQ-C30, previously proven to be reliable, was used in the study.[22]

Adherence

Patient-reported adherence (experienced adherence) was assessed using 4-item MMAS.[23] The MMAS is a structured questionnaire used for a wide variety of medical conditions. It has already been used in published CML adherence studies.[24,25] The scale consists of 4 items with a scoring scheme of "Yes" = 0 and "No" = 1. Total point value of 0 is classified as high compliance with physician recommendations; 1-2 points are classified as medium compliance, and 3-4 as low compliance. The Polish language version of the MMAS was used. A treating physician assessed a patient's compliance according to his/her own perspective on the basis of questions from the MMAS as well.

Satisfaction With Medical Care

Patients rated their satisfaction with medical care on a visual analogue scale converted of 1 (very low satisfaction) to 7 (great satisfaction).

To ensure objectivity of a patient's answers, after filling out the questionnaires, a patient inserted them into sealed envelopes, which were placed in the anonymous Case Record Form.

Statistical Analysis

Basic descriptive statistics, such as arithmetic mean (average) and median were used to present results of the study. Distribution of observations was presented as either quantiles: minimal and maximal values, 25th, 50th (median), and 75th percentile (lower and upper quantile, respectively), or standard deviation of the mean.

The differences between groups were analyzed using statistical tests. In case of categorical data comparisons Pearson χ^2 test was used. In cases for which χ^2 test assumptions were not met Fisher exact test was used.

Mann–Whitney *U* test was used to test if observed differences of median values between 2 compared groups (such as median values

of QOL parameters in patients with high and low compliance) were statistically significant.

Statistical dependence (correlation) between 2 numeric variables, such as Morisky scale adherence assessed by patients versus that determined by physicians, were tested using a nonparametric Spearman rank correlation coefficient test. For all statistical calculations, the significance level α was set at 0.05 or lower.

Results

Of 177 patients who were recruited by the physicians treating CML in 23 centers in Poland to participate in this study, 144 (81.4%) completed all 6 visits. The remaining 33 patients (18.6%) were either withdrawn from the study (16.9%; 30 persons; the early termination group) or were lost from observation (1.7%; 3 patients). Causes of early termination encompassed insufficient response to nilotinib (including treatment failure, suboptimal response, disease progression; 17 patients); adverse events (8 patients); death during the treatment period (1 patient), and other (4 patients).

During the study period, nilotinib dose was changed in 20 patients (13.9%) who had completed the trial. However, 36.7% of patients from the early termination group were receiving a reduced dose during their last study visit, compared with the 800 mg/d initial dose.

Of the study patients 29.4% had temporary drug interruptions. Such interruptions were twice as common in the early termination group (46.7%) than among the patients who had completed the whole trial (25.0%). This difference was found to be statistically significant (Table 2).

Table 2 Changes of Nilotinib Dose and Termination Causes Within the Study

Changes of Nilotinib Dose Between Baseline and Last Follow-Up for Patients Who Completed the Study, Percentage of 144 Patients	
Dose reduced	12.5
Dose increased	1.1
Changes of Nilotinib Dose Between Baseline and Last Follow-Up for Patients From the Early Termination Group, Percentage of 30 Patients	
Dose reduced	36.7
Dose increased	0.0
Causes of Early Termination, n	
Insufficient response to treatment	17
Adverse events	8
Death	1
Other	4
Lost to follow-up	3

Quality of Life Outcomes

The study participants experienced an improvement in all 5 functional areas evaluated in the EORTC QLQ-C30 and a decrease in symptom burden (Table 3). No significant differences were observed in an average QOL expressed as the QL2 parameter between patients who had completed the study and those who had to terminate early. The average values of 8 of 15 parameters evaluated using the EORTC QLQ-C30 were significantly better ($P < .002$) at visit 6 than at visit 1. The average QL2 value for patients who had completed the study was significantly higher during visit 6 (69.4 ± 17.4) than at the start of the study (average was 59.1 ± 18.8; $P < .001$; Figure 1). During all visits male patients tended to have higher level of life quality, expressed as the QL2 parameter, than female patients. During the first visit the average QL2 value in the group of male participants was 61.9 (±18.3), and in the group of female participants 54.8 (±20.4). At the final sixth visit averages of QL2 were 71.2 (±17.2) and 67.8 (±17.6) in male and female patients, respectively. Younger patients (55 years old or younger) had higher averages of the QL2 parameter. During the first visit the average QL2 value was 63.7 (±19.2) for younger patients and 54.7 (±19.1) for older patients (older than 55 years old). On the last visit the averages were 73.0 (±17.0) and 66.8 (±17.2), respectively.

Adherence to Nilotinib Therapy

Patient-Reported Outcomes. In general, most of the patients were scoring themselves during their first visit as low on the Morisky scale, which placed them in the high compliance group (n = 120; 83.2% of total). This percentage increased during following visits, reaching a peak during visit 5 (n = 135; 93.4%). Three patients who scored themselves high on the Morisky scale (low compliance group) represented 1.7% of all of the patients during visit 1. Since the fourth visit none of the patients self-assessed as belonging to the low compliance group (Figure 2). Patients who completed the whole study reported a very good adherence. At the start of the trial 149 (83.9%) of patients from this group considered themselves highly compliant with physician recommendations. This percentage increased over the course of the study reaching 93.1% (n = 134) during the fifth and 92.4% (n = 133) during the final visit. One in 5 (22.2%) patients from the early termination group assessed themselves as medium compliance during the first visit. During following visits the percentage of patients with medium compliance to the drug decreased from 15.0% (n = 27) at visit 1 to 7.6% (n = 14) at visit 6. The proportion of patients who scored their adherence as low also decreased during the study period from 1.7% (n = 3) to 0% at the end of observation.

Physician-Reported Outcomes. At the start of the study 85.3% of patients were categorized as highly compliant. This percentage was increasing, reaching a value >96.0% (n = 209) within the last 3 visits. Meanwhile, only 1 (at visits 1, 5, and 6) or 2 patients (at visits 2 and 3) were categorized as low compliant (Figure 3). Patients who completed all 6 visits were evaluated as equally adherent to the treatment compared with the whole patient population. Among patients in the early termination group, during each visit at least 90% were assessed as highly compliant.

Correlation Between Patient- and Physician-Reported Outcomes

Patients' own assessment and that of their physicians were in excellent agreement. This was confirmed by testing correlation with the Spearman method. In all cases correlation was found to be highly significant (Table 4).

Association of Adherence With QOL, Drug Administration Schedule, Satisfaction With Medical Care, and Demographic Data

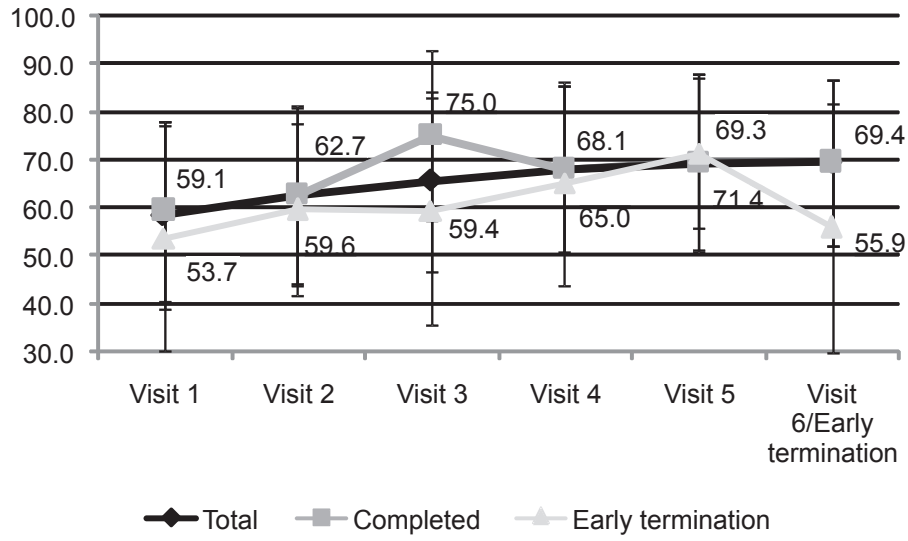
Four parameters (including role functioning, dyspnea, appetite loss, and diarrhea) evaluated in the EORTC QLQ-C30 proved

Table 3 Average Values of EORTC QLQ-C30 Parameters for All Participants Over Course of Visits 1 to 6

	Visit 1		Visit 2		Visit 3		Visit 4		Visit 5		Visit 6	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Global Health Status/QOL												
QL2	58.4	19.6	62.5	18.5	65.5	18.8	67.8	17.5	69.5	18.4	69.4	17.4
Functional Scales												
Physician functioning												
PF2	77.8	22.3	80.4	18.0	80.4	19.0	81.6	18.8	81.4	18.8	81.3	18.5
Role functioning												
RF2	79.7	24.9	82.5	22.7	81.6	23.2	82.2	21.9	82.0	22.7	80.4	21.6
Emotional functioning												
EF	75.6	20.7	78.6	20.6	78.1	22.9	78.6	20.7	78.3	22.5	78.2	22.2
Cognitive functioning												
CF	84.7	19.3	86.8	17.7	85.3	19.8	85.3	18.7	84.2	19.4	85.0	19.9
Social functioning												
SF	82.7	22.3	84.4	20.6	85.3	22.0	85.7	19.9	83.1	21.0	83.2	21.6
Symptom Scales/Items												
Fatigue												
FA	33.8	22.6	29.6	22.2	27.2	21.7	27.3	21.2	26.4	20.9	26.6	22.2
Nausea and vomiting												
NV	6.9	12.0	3.1	8.1	2.4	7.6	2.9	8.0	3.0	9.2	2.2	6.7
Pain												
PA	24.6	27.2	19.7	23.5	16.8	24.4	16.3	23.5	16.1	22.8	16.0	22.5
Dyspnea												
DY	18.6	24.7	11.6	19.3	12.7	21.2	11.1	19.1	11.6	21.1	11.3	21.3
Insomnia												
SL	25.3	30.0	18.9	25.1	18.9	24.6	23.1	25.5	19.6	24.1	21.1	24.3
Appetite loss												
AP	13.5	22.1	11.4	19.9	8.4	17.4	10.2	17.6	7.9	15.2	7.5	17.0
Constipation												
CO	10.9	22.4	10.4	22.1	9.9	20.8	10.6	22.3	10.5	21.8	10.5	21.6
Diarrhea												
DI	9.0	18.3	2.8	9.9	2.6	8.9	3.2	10.5	2.0	7.9	1.4	6.7
Financial difficulties												
FI	20.2	27.8	14.8	22.9	15.6	24.7	12.4	22.1	13.9	23.8	15.0	23.3

Abbreviations: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire; QOL = quality of life.

Figure 1 Changes of Quality of Life Expressed as a QL2 Parameter in Patients During the Study



to be significantly (negatively) correlated with adherence to nilotinib (Table 5).

No significant differences in drug adherence, measured using the MMAS, and the drug administration schedule (once daily vs. twice daily) were found in all of the patients as well as in subgroups. However, the total percentage of patients receiving nilotinib once daily was only 2.3% (n = 4) at the start of the trial and never reached more than 10.7% (n = 19).

No correlations between satisfaction with medical care and drug compliance were found.

Men were less likely to follow physicians' directions regarding drug use. Close to one-quarter of them (23.6%; n = 42) were classified as being in the medium or low compliance group at the first visit. For women this percentage was 10.3% (n = 18) (Fisher test; $P < .05$). During visits 2 and 3 the difference diminished but on visit 4, men were 3 times more likely (13.0%; n = 23) than women (3.6%; n = 6) to be in the medium compliance group (χ^2 test; $P < .05$). At the fifth visit only 2.5% of women (n = 2) were not highly compliant, whereas among men this percentage was 11.1% (n = 10) (Fisher test; $P < .05$; Figure 4). No significant relationship between patient age and adherence was observed.

Figure 2 Changes of Self-assessed Drug Compliance in All of the Patients (Percentage of 177)

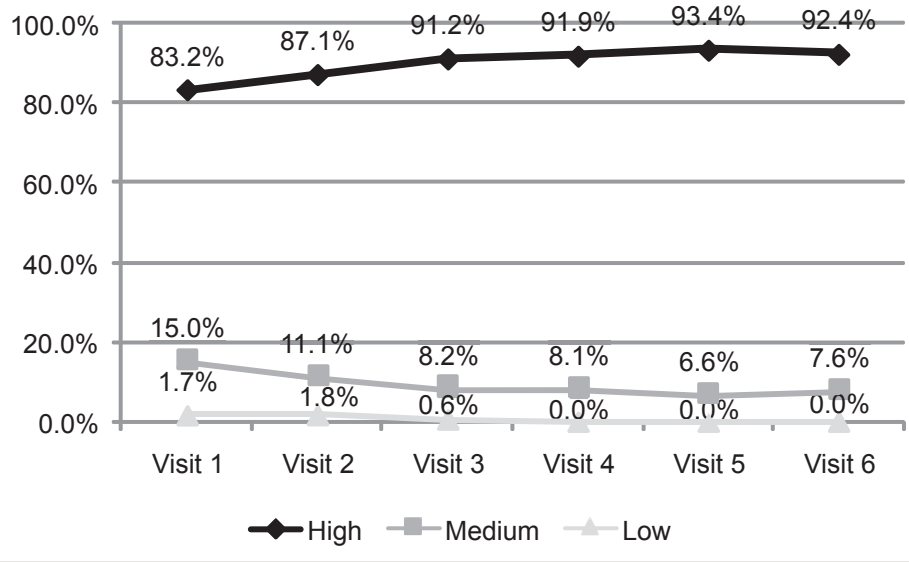
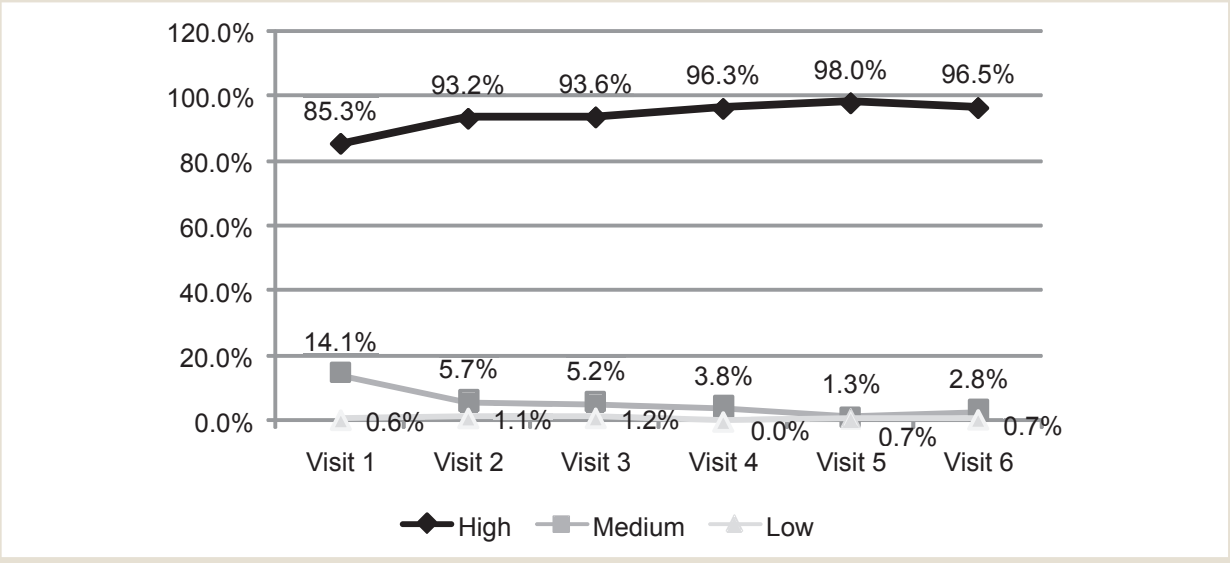


Figure 3 Changes in Drug Compliance Assessed by Physicians in All of the Patients (Percentage of 177)



In general, patients living with family were more likely to follow physician orders regarding drug use. The percentage of highly compliant patients in this group was 89.2% (n = 83) at visit 1, and increased to 96.7% (n = 90) at visit 3. None of the patients living with family were in the low compliance group. The compliance improved in the remaining 2 groups of patients (living with partner and living alone) as well (Figure 5). Of patients living with partner 20.9% (n = 13) and 3.0% (n = 2) were in the medium and low compliance group, respectively, at the start of the trial (Fisher test, $P < .05$) and 16.2% (n = 10) and 1.5% (n = 1) in the medium and low compliance group, respectively, at visit 3 (Fisher test, $P < .05$). At the first visit 76.9% of patients (n = 12) who lived alone were in the high compliance group, 15.4% (n = 2) in the medium compliance group, and 7.7% (n = 1) in the low compliance group. At the third visit, all patients who lived alone were highly compliant. Level of education did not play any significant role in determining medical adherence, with the exception of visit 3, when the population of patients with basic education had a higher percentage of highly compliant people (97.6%; n = 43) than those either with medium or higher education (n = 91; 88.0%) and (n = 28; 92.9%), respectively; Fisher test, $P < .05$).

An average level of satisfaction with medical care over the course of the trial was high (mean value of 6.1 ± 0.7) and similar for patients who completed and for those who terminated early the study. There was no significant difference between perceived level of satisfaction at the beginning and at the conclusion of the trial either for patients who completed or for those who terminated their participation early. No correlations between satisfaction with medical care and drug compliance were found (Figure 6).

Treatment Efficacy and Safety

Nilotinib therapy proved to have good efficacy during the observation period. Complete hematologic response was maintained in 97.7% (n = 173) of patients who completed the study. At the end of observation the cytogenetic response improved in 55 (31.1%) patients compared with the first visit, whereas in 4 (2.3%) the response worsened. Similarly, 74 participants (41.8%) experienced improvement in molecular response whereas only 5 (2.8%) experienced worsening. There were no new signals of nilotinib safety profile and only a few patients discontinued the study because of adverse events (n = 9; 5% of all participants; Tables 6 and 7).

Table 4 Correlation Between Morisky Score Assessed by Patients and Their Physicians

	Total		Completed		Early Termination	
Visit	Correlation Coefficient	*P*	Correlation Coefficient	*P*	Correlation Coefficient	*P*
1	0.479	2.5E-11	0.513648	5.36E-11	0.425	.027
2	0.489	1.1E-11	0.449294	2.04E-08	1	0
3	0.556	3.6E-15	0.519266	2.59E-11	1	0
4	0.546	1.0E-13	0.49884	2.29E-10	1	3.9E-103
5	0.561	5.8E-14	0.561513	2.45E-13	NA	NA
6	0.388	1.6E-06	0.387758	1.57E-06	NA	NA
Early Termination	NA	NA	—	—	NA	NA

Table 5 Statistically Significant Correlations Between Medical Adherence (Morisky Score) and Parameters of EORTC QLQ-C30 (N = 177)

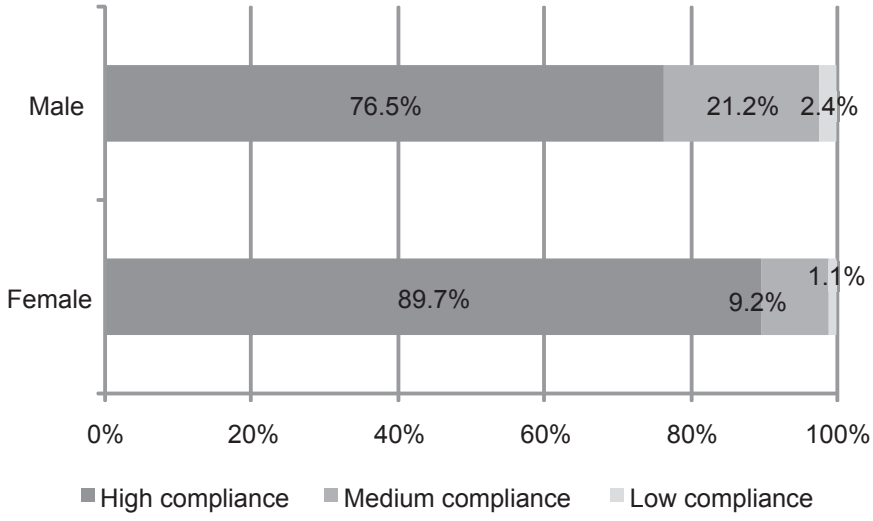
Visit	EORTC QLQ-C30 Parameter		*P*	Correlation Coefficient
2	Role functioning	RF2	.0397	.158
3	Dyspnea	DY	.0317	.165
5	Appetite loss	AP	.0208	.187
6	Diarrhea	DI	5.79E-05	.331

Abbreviation: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire.

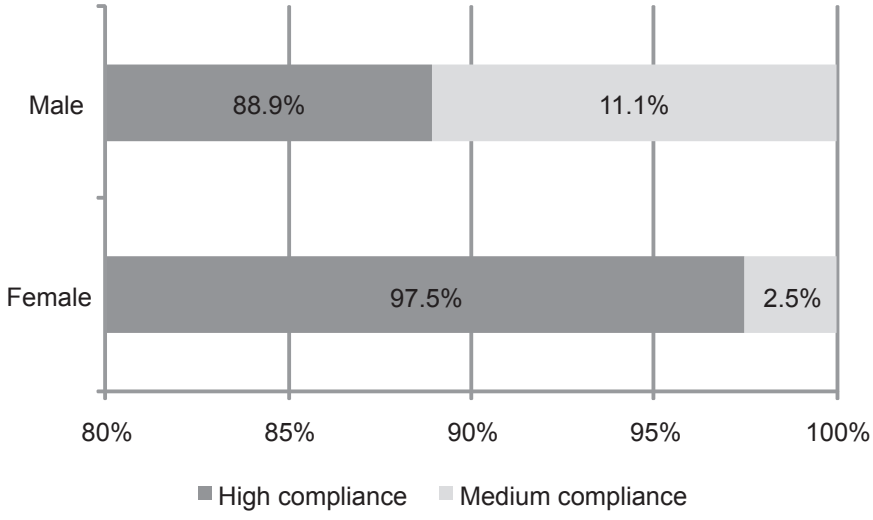
Discussion

The introduction of TKIs in the treatment of chronic myelogenous leukemia has changed the perception of CML from a potentially lethal disease to a chronic disorder. Patients are treated for many years with one or more TKIs and they have to take their medication every day. In this context a good QOL is one of the essential issues that should be considered when reaching important milestones during the CML therapy. The primary objective of this study was to assess QOL during 12 months of observation in patients with CML-CP who were switched to nilotinib therapy because of intolerance and/or resistance to previous treatment. The study population consisted of patients treated with nilotinib as the

Figure 4 Relationship Between Sex and Drug Compliance in All Patients During Visit 1 and 5

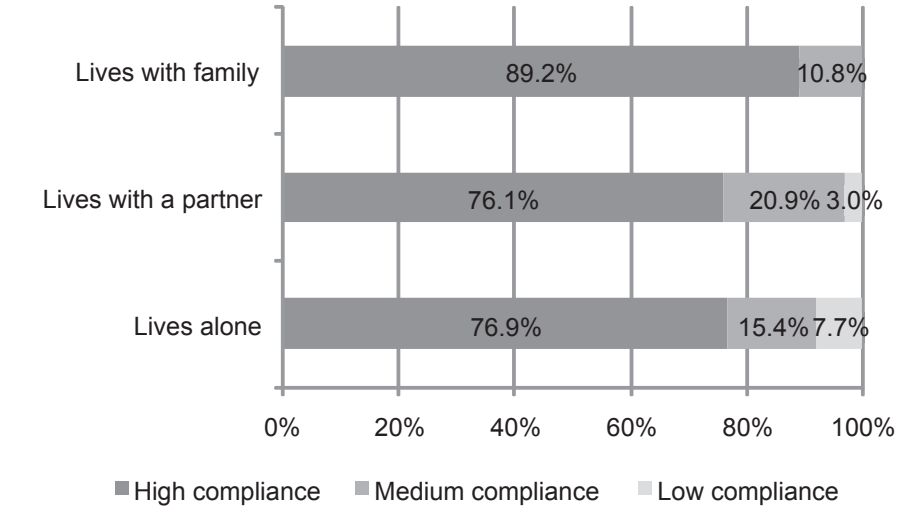


Visit 1.

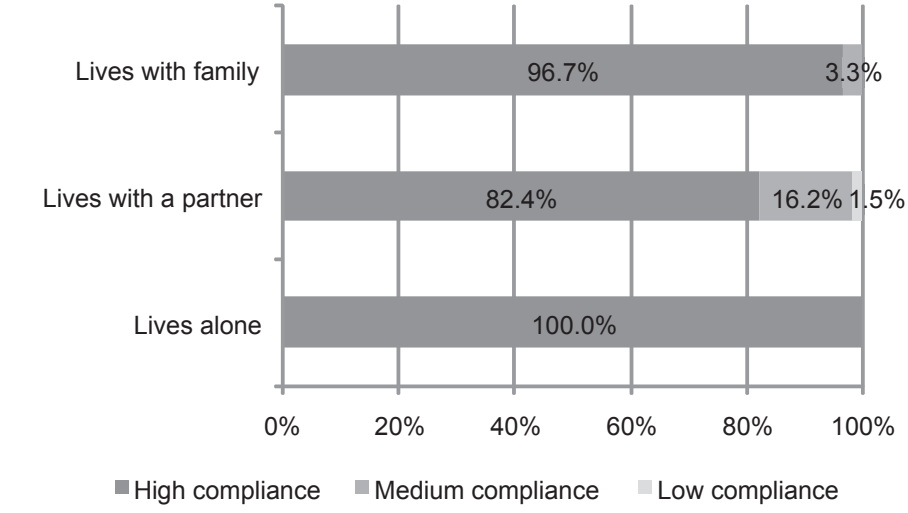


Visit 5

Figure 5 Relationship Between Family Status and Drug Compliance in all Patients at Visit 1 and 3



Visit 1



Visit 3

second- or third-line therapy indicated for resistance to previously used TKI in 133 patients (75.1%). An average time since the diagnosis to the switch of therapy and the start of participation in the study was long (4.5 years). The patients were switched to nilotinib, a drug with a different toxicity profile, dosage, and administration schedule. It could be supposed therefore, that such a group of patients would not experience a very good QOL because of many negative aspects of their disease course. However, the average baseline value of QOL measured according to the QL2 parameter at the beginning of the trial was 58.4. During the study this value increased gradually from visit 1 to the end of the trial, reaching a value of 69.4 at the last visit. The difference between the baseline and the end values was statistically significant ($P < .001$). Moreover, no significant differences were observed in average QOL expressed as the QL2 parameter at the end of observation between patients who completed the study and those who had to terminate early, suggesting that the QOL was not the primary and most important cause of trial discontinuation. Analysis of individual items included in the EORTC QLQ-C30 shows that the scores of all functional parameters (physical, role, emotional, cognitive, and social functioning) increased and symptom parameters (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea) decreased during the observation period. Because there are no data on QOL from nilotinib registration trials we found these results valuable and important especially in the context of factors that should be taken into consideration when choosing a

Figure 6 Satisfaction With Medical Care During the Whole Period of the Trial

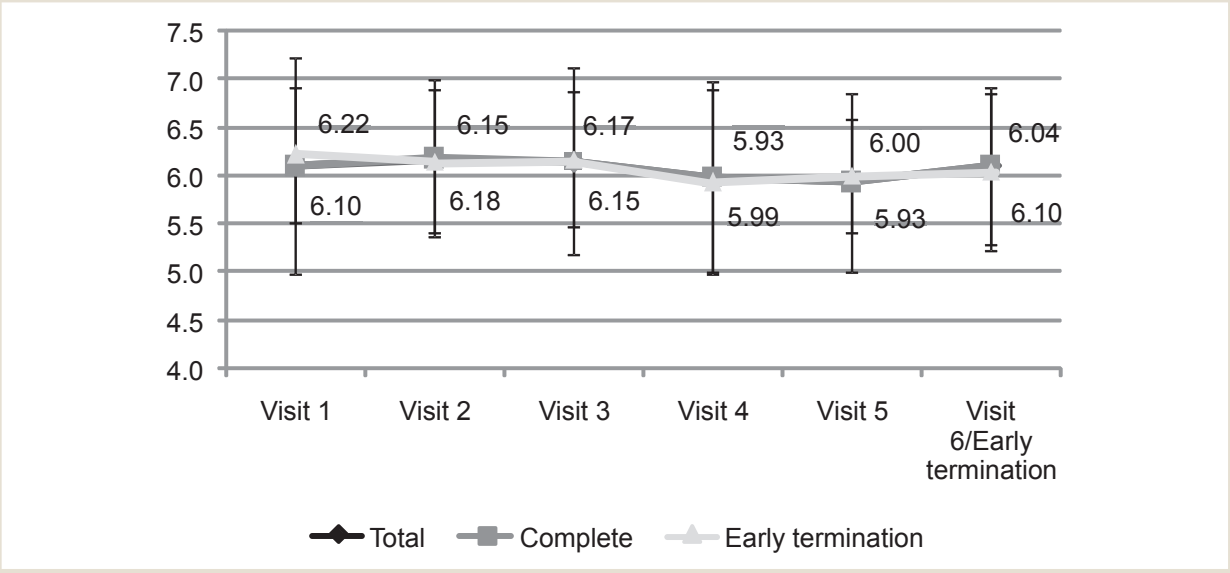


Table 6 Frequency of Adverse Events According to Affected Organ Class/System

Affected Organ	n	Patients With AE, %	All Patients, %
Hematologic Toxicity	48	54.5	27.1
Skin and Subcutaneous Tissue Disorders	22	25.0	12.4
Diseases of the Digestive System	18	20.5	10.2
Musculoskeletal and Connective Tissue Disorders	5	5.6	2.8
Diseases of the Respiratory System	9	10.2	5.1
General Symptoms and Signs	9	10.2	5.1
Diseases of the Circulatory System	7	8.0	4.0
Diseases of the Genitourinary System	5	5.7	2.8
No Data	2	2.3	1.1
Symptoms and Signs Involving the Nervous and Musculoskeletal Systems	2	2.3	1.1
Gastrointestinal Disorders	2	2.3	1.1
Diseases of the Eye and Adnexa	2	2.3	1.1
Symptoms and Signs Involving Cognition, Perception, Emotional State, and Behavior	1	1.1	0.6
Mental and Behavioral Disorders	1	1.1	0.6
Endocrine, Nutritional, and Metabolic Diseases	1	1.1	0.6
Diseases of the Nervous System	4	4.5	2.2

Abbreviation: AE = adverse event.

second-line therapy for CML with TKIs. It is well established that treatment adherence is one of the key factors to achieve good outcomes of therapy with TKIs. In the Adherence Assessment with Glivec: Indicators and Outcomes study conducted on 202 patients with CML treated with imatinib approximately one-third of the trial participants were nonadherent. Only 14.2% of patients were perfectly adherent with 100% of prescribed imatinib taken.[8] In the other study of 120 CML patients treated with imatinib, nilotinib and dasatinib patient-reported adherence was evaluated using the 8-item MMAS and the treating physicians were asked to give their subjective opinion on their patients' adherence. A total of 23% of the patients were fully adherent according to the MMAS, whereas physicians evaluated 94% of the patients as fully adherent.[26] In our study compliance was assessed by patients and their physicians with the use of the 4-item MMAS. The expected compliance in this study population could be medium to low, because the average duration of the previous treatment of those patients was long (4.5 years), which could negatively affect the adherence to physician's therapy recommendations. In the US study, persistency defined as a time taking therapy without any significant gaps of refills was near 100% at month 4 and declined from 94% at month 5, to 23% at month 14.[27] Most of the patients who participated in our study were scoring themselves as highly compliant at first visit (83.2% of total), and this percentage increased during follow-up visits, reaching a peak at visit 5 (93.4%). Patients who scored themselves as low compliance at the first visit represented 15.0% of the study group. Nevertheless, from visit 4 none of the patients self-scored as low complaint. Physicians' evaluations were very similar. They assessed their patients' compliance very favorably—at the start of the study 85.3% of the patients were categorized as highly compliant. This percentage increased during last 3 visits reaching a value >96.0% of all of the patients. Correlation between patients' and their physicians' assessment was found to be high and statistically significant in all cases. Another factor that could potentially adversely influence

Table 7 Serious Adverse Events During the Study

Patient Identification	Serious Adverse Event	Number of Events	Association With Drug	Early Termination
04-03	Pancytopenia	1	Yes	Yes
04-03	Plasmacytosis	1	No	—
08-05	Musculoskeletal and joints ache	2	Yes	Yes
08-05	Weakness	2	Yes	—
08-05	Head ache	2	Yes	—
12-02	Hepatitis B	1	No	No
19-07	Myocardial infarction	1	No	No
20-04	Hyperbilirubinemia	1	No	Yes
20-04	Cirrhosis	1	Yes	—
21-04	Anemia	1	Yes	Yes
26-03	Anemia	2	Yes	Yes
28-21	Myocardial infarction	1	Yes	No
28-22	Thrombocytopenia	1	Yes	No
28-25	Myocardial infarction/death	1	Yes	Yes
29-01	Erythema	1	Yes	Yes
30-01	Cerebrovascular accident (stroke)	1	No	No

the compliance in the study group was a more challenging dosing schedule of nilotinib compared with other TKIs (twice daily, taken with no food). In a review of the studies that measured compliance to different medications using electronic monitoring methods confirmed that the prescribed number of doses per day is inversely related to compliance.[28] The results of our study did not show a negative correlation between dosing schedule and compliance, however, it has to be acknowledged that there were only a few patients taking nilotinib once a day during the study (the total percentage of patients receiving nilotinib once daily never reached more than 10.7% of all of the patients). Thus, the statistical analysis was very difficult and has some limitations.

The patients themselves and treating physicians assessed compliance of a study group to nilotinib as higher compared with compliance to previous therapies. A potential rationale might be a poor outcome of preceding therapies and patients' willingness to improve their treatment results. Taking into consideration generally high adherence to nilotinib therapy, it comes as no surprise that only few statistically significant correlations between drug compliance and parameters measured using the EORTC QLQ-C30 were found. However, those (negative) correlations were found between compliance and symptoms such as dyspnea, appetite loss, and diarrhea. It seems that compliance in our study was affected most by adverse events or unexpected outcomes of the disease. These findings are in line with results by McHorney, who showed that good compliance depends mainly on adverse events experienced and their intensity as well as side effects of administered therapy.[29] There were some correlations found between demographic data and compliance. Generally men were less likely to follow physicians' recommendations regarding drug use. Patients' social status proved to have some correlations with adherence. Among patients living with a partner or alone the percentage of medium or even low compliance persons was higher compared with patients living with family and reached 23.9% and 23.1%, respectively ($P < .05$). However, since visit 3 the vast majority of patients in all 3 groups were classified as high compliance. An explanation of this trend could be that patients were informed they were participating in the study, that the compliance would be measured, and therefore they might have been more strict in their medication-taking than usual. Interestingly, neither level of education nor satisfaction with medical care played any significant role in determining medical adherence.

The interpretation of these trial results should acknowledge several limitations of the study. Because this was an observational, noninterventional study there was no control group or randomization. Further, the compliance was assessed by patients as well as their physicians using the same method (MMAS questionnaire) in a subjective way only. Compliance groups (low, medium, and high) were not comparable with respect to number of patients. The high compliance group consisted of approximately 80%-90% of patients recruited to this study, whereas the low compliance group consisted of only 2% of all patients. The proportion of patients receiving a daily single dose of nilotinib was very low, which makes the statistical analysis of adherence correlation with the drug administration schedule very difficult.

Conclusion

The results of this prospective observational study of a Polish population of 177 CML-CP patients treated with nilotinib as second- or third-line therapy deliver important data on QOL and adherence to therapy. The QOL among patients receiving nilotinib was very good and adherence to the treatment was high, despite a challenging dosing schedule. Additionally, high efficacy and good safety profile of the drug were confirmed in the real-life setting. These results support a favorable benefit-risk ratio for nilotinib in second-line treatment in CML-CP patients and deliver important data that should be considered among the other clinical parameters when choosing the optimal and patient-adjusted therapy.

Clinical Practice Points

- Nilotinib is an oral second-generation TKI administered twice daily approximately 12 hours apart. It must be taken on an

empty stomach and food must be avoided for at least 2 hours before, and for at least 1 hour after the dose is taken.

- Contradictory data are reported regarding the adherence to nilotinib therapy in patients with CML-CP.
- Limited data are available regarding the QOL of CML-CP patients treated with nilotinib.
- A multicenter, prospective observational study conducted in 23 Polish centers showed that the QOL among 177 patients receiving nilotinib administered as a second-line therapy was very good and adherence to the treatment was high despite the dosage pattern.
- Adherence to therapy and patient QOL and possible adherence to therapy should be taken into consideration among the other clinical parameters in the process of TKI treatment choice.
- Results of our study provide important data that could be useful in the TKI selection decision-making process.

Acknowledgments

The authors acknowledge investigators: Patrycja Bizgalska-Skrzypek, Bożena Katarzyna Budziszewska, Dorota Dawidowska, Izabela Dereń-Wagemann, Jarosław Dybko, Jacek Dybowicz, Julita Dziamska, Ludmiła Gawron, Magdalena Górska-Kosicka, Alina Grzywacz, Jadwiga Hołojda, Adam Hołub, Piotr Jerzmanowski, Agnieszka Gontarska, Marek Karasiewicz, Agnieszka Kłak-Skubis, Marek Kriegler, Władysława Kosmala-Niewiadomska, Katarzyna Kościów, Małgorzata Kowal, Janusz Lange, Wojciech Legieć, Agata Lehmann-Kopydłowska, Maria Lewandowska, Anna Masternak, Ewa Mendek-Czajkowska, Elżbieta Morawiec-Szymonik, Monika Mordak-Domagała, Andrzej Moskwa, Krzysztof Myśliwiec, Joanna Niesiobędzka-Krężel, Maria Nowakowska Domagała, Katarzyna Olszewska, Elżbieta Patkowska, Iwona Pietkun, Joanna Pogrzeba, Witold Prejzner, Ilona Seferyńska, Marek Seweryn, Aleksander B. Skotnicki, Anna Strabużyńska, Danuta Szadziewska-Kowalska, Maja Twardosz, Halina Urbańska-Ryś, Adam Walter-Croneck, Ewa Wasilewska, Ewa Wasińska, Ewa Wąsik-Szczepanek, Marzena Wątek, Ryszard Wichary, Małgorzata Wojciechowska, Anna Wosztyl, and Marcin Wójtowicz for participation in the study, support, and data collection.

Disclosure

Tomasz Sacha has received honoraria from Novartis, Pfizer, Bristol-Myers Squibb, and Angelini; Joanna Góra-Tybor has received honoraria from Novartis, Pfizer, Bristol-Myers Squibb, and Angelini; Ewa Wąsak-Szulkowska has received honoraria from Novartis, and is an employee of Novartis; Sławomira Kyrcz-Krzemień has received honoraria from Novartis, Pfizer, and Bristol-Myers Squibb; Ewa Mędraś has received honoraria from Novartis, Bristol-Myers Squibb, and Angelini; Rafał Becht has received honoraria from Novartis and Bristol-Myers Squibb; Grażyna Bober has received honoraria from Novartis and Bristol-Myers Squibb; Aneta Kotowska has received honoraria from Novartis, and is an employee of Novartis; Joanna Wącław has received honoraria from Novartis and Angelini; and Andrzej Hellmann has received honoraria from Novartis, Pfizer, Bristol-Myers Squibb, and Angelini.

References

1. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia, v.4* May 14, 2013, Available at: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
2. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001; 344:1031-7.
3. Druker BJ, Guilhot F, O'Brien SG, et al, IRIS Investigators. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 2006; 355: 2408-17.
4. Efficace F, Baccarani M, Breccia M, et al. Health-related quality of life in chronic myeloid leukemia patients receiving long-term therapy with imatinib compared with the general population. *Blood* 2011; 118:4554-60.
5. Philips KM, Pinilla-Ibarz J, Sotomayor E, et al. Quality of life outcomes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a controlled comparison. *Support Care Cancer* 2013; 21:1097-103.
6. Sabate E. *Adherence to Long-Term Therapies: Evidence for Action*. Geneva: World Health Organization; 2003.
7. Marin D, Bazeos A, Mahon FX, 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.
8. Noens L, van Lierde MA, De Bock R, 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.
9. Darkow T, Henk HJ, Thomas SK, et al. Treatment interruptions and nonadherence with imatinib and associated healthcare costs: a retrospective analysis among managed care patients with chronic myelogenous leukaemia. *Pharmacoeconomics* 2007; 25:481-96.
10. Trivedi D, Landsman-Blumberg P, Darkow T, et al. Adherence and persistence among chronic myeloid leukemia patients during second-line tyrosine kinase inhibitor treatment. *J Manag Care Spec Pharm* 2014; 20:1006-15.
11. Wu EQ, Johnson S, Beaulieu N, et al. Health care resource utilization and costs associated with non-adherence to imatinib treatment in chronic myeloid leukemia patients. *Curr Med Res Opin* 2010; 26:61-9.
12. Daley GQ, Van Ette RA, Baltimore D. Induction of chronic myelogenous leukemia in mice by the p210 *BCR-ABL* gene of the Philadelphia chromosome. *Science* 1990; 247:824-30.
13. Kantarjian HM, Giles FJ, Bhalla KN, et al. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. *Blood* 2011; 117:1141-5.
14. Larson RA, Hochhaus A, Hughes TP, et al. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. *Leukemia* 2012; 26:2197-203.
15. *TASIGNA (nilotinib) [summary of product characteristics]*. Basel, Switzerland: Novartis Pharma AG; 2014.
16. Guérin A, Chen L, Wu EQ, et al. 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; 28:1155-62.
17. Yood MU, Oliveria S, Cziraky M, et al. Adherence to treatment with second-line therapies, dasatinib and nilotinib, in patients with chronic myeloid leukemia. *Curr Med Res Opin* 2012; 28:213-9.
18. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia. *Blood* 2013; 122:872-84.
19. Sprangers MA, Cull A, Bjordal K, et al. The European Organization for Research and Treatment of Cancer. Approach to quality of life assessment: guidelines for developing questionnaire modules. EORTC Study Group on Quality of Life. *Qual Life Res* 1993; 2:287-95.
20. McLachlan SA, Devins GM, Goodwin PJ. Validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) as a measure of psychosocial function in breast cancer patients. *Eur J Cancer* 1998; 34:510-7.
21. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality of life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85:365-76.
22. Tomaszewski KA, Püsküllüoğlu M, Biesiada K, et al. Validation of the polish version of the EORTC QLQ-C30 and the QLQ-OG25 for the assessment of health-related quality of life in patients with esophagi-gastric cancer. *J Psychosoc Oncol* 2013; 31:191-203.
23. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986; 24:67-74.
24. de Almeida MH, Pagnano KB, Vigorito AC, et al. Adherence to tyrosine kinase inhibitor therapy for chronic myeloid leukemia: a Brazilian single-center cohort. *Acta Haematol* 2013; 130:16-22.
25. Efficace F, Baccarani M, Rosti G, 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.

26. Kekäle M, Talvensaari K, Koskenvesa P, et al. Chronic myeloid leukemia patients' adherence to peroral tyrosine kinase inhibitors compared with adherence as estimated by their physicians. *Patient Prefer Adherence* 2014; 8:1619-27.
27. Tsang JP, Rudychev I, Pescatore SL. ASCO 2006 June 2-6, 2006, Atlanta, GA; Part 1, Vol. 24, No. 18S, *J Clin Oncol* 2006; 24:330s. Abstract 6119.
28. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001; 23:1296-310.
29. McHorney CA. The Adherence Estimator: a brief proximal screener for propensity to adhere to medications for chronic disease. *Curr Med Res Opin* 2009; 25:215-38.