Original Article

Health-Related Quality of Life in Patients With Chronic Myeloid Leukemia Receiving First-Line Therapy With Nilotinib

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BACKGROUND: Although a wealth of efficacy and safety data is available for many tyrosine kinase inhibitors used in chronic myeloid leukemia (CML), there is a dearth of information on their impact on patients' health-related quality of life (HRQOL). The primary objective of this study was to evaluate HRQOL and fatigue outcomes in patients with CML receiving first-line therapy with nilotinib. **METHODS:** This was a multicenter, prospective study enrolling 130 patients with chronic-phase CML. HRQOL and fatigue were evaluated with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and its validated Fatigue module at the baseline and then at 3, 6, 12, 18, and 24 months. The primary prespecified HRQOL endpoints defined in the study protocol for longitudinal analysis were the Physical Functioning, Social Functioning, Role Functioning, and Fatigue scales. The remaining scales were investigated on an exploratory basis. **RESULTS:** The rate of baseline compliance with the HRQOL assessment was 95.4% (124 of 130), and the rate of overall compliance with HRQOL forms was 91%. Among the 4 prespecified primary HRQOL endpoints, statistically significant improvements over time were found for Physical Functioning ($P = .013$), Role Functioning ($P = .004$), and Fatigue ($P < .001$). Clinically meaningful improvements were found already 3 months after the treatment start. The baseline patient self-reported fatigue severity was an independent predictive factor for the achievement of a major molecular response with an odds ratio of 0.960 (95% confidence interval, 0.934-0.988; $P = .005$). **CONCLUSIONS:** For most patients, HRQOL improvements with nilotinib occur during the early phase of therapy and are maintained over time. Also, a more systematic HRQOL evaluation during the diagnostic workup of CML may help to predict clinical outcomes. ***Cancer*** **2018;000:000-000**. © *2018 American Cancer Society*.

KEYWORDS: chronic myeloid leukemia, fatigue, nilotinib, quality of life, tyrosine kinase inhibitors.

INTRODUCTION

The development of oral tyrosine kinase inhibitors (TKIs) to treat chronic myeloid leukemia (CML) is a great triumph of personalized medicine. The clinical outcomes of patients with CML have dramatically improved in comparison with previous interferon-based therapies,[1] and the life expectancy of these patients now approaches that of the general population.[2]

Since the introduction of the first oral TKI (ie, imatinib) approved as first-line therapy in 2003,[1] the treatment of CML has become more challenging with the development of second-generation TKIs such as nilotinib and dasatinib that

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can also be used as alternative first-line strategies.[3] The results of the phase 3 randomized controlled trials (RCTs) leading to the Food and Drug Administration approvals of first-line nilotinib[4] and dasatinib[5] have shown that both drugs provide faster and deeper molecular responses (MRs) than imatinib therapy. However, differences in overall survival among these 3 drugs have yet to be demonstrated.[3]

Therefore, first-line treatment selection is one of the major challenges of patient management in clinical practice. The availability of multiple TKIs now also offers the opportunity to change drugs, regardless of the type of initial therapy, not only in patients reporting a negative outcome during the course of therapy (eg, a loss of cytogenetic response) but also in those with a somewhat favorable outcome who have not reached an optimal outcome.[6] In such a complex scenario and because in most cases CML therapy is lifelong, information on the impact of these drugs on patients' wellbeing and symptom burden becomes critical for making more informed treatment decisions.

Although a wealth of efficacy and physician-reported safety data is available for approved first-line TKIs, there is a dearth of information regarding patient-reported health-related quality of life (HRQOL) outcomes.[7] Also, most of the available HRQOL studies in CML have been confined to patients receiving imatinib therapy,[8-10] and to the best of our knowledge, no prospective HRQOL data are available on patients with CML treated with first-line nilotinib therapy.

The primary objective of this study was to investigate HRQOL and fatigue outcomes in patients receiving first-line nilotinib therapy over a 2-year period. A secondary objective was to investigate the predictive value of pretreatment patient-reported HRQOL outcomes for achieving a clinical response.

MATERIALS AND METHODS

Study Design and Treatment

This was a Italian Group for Adult Hematologic Diseases (GIMEMA) single-arm study of nilotinib (300 mg twice daily) in adult patients with newly diagnosed chronic-phase CML. Patients were included from 32 GIMEMA centers from December 2011 to November 2012. The results of the primary endpoint and clinical efficacy data at 2 years have been reported previously.[11] Briefly, a dose increase to 400 mg twice daily was scheduled in case of a suboptimal response or failure according to 2009 European LeukemiaNet recommendations.[12] Pretreatment with hydroxyurea or anagrelide for a duration of up to 3 months and pretreatment with imatinib for up to 30 days were permitted. The MR was assessed by peripheral blood reverse transcription–polymerase chain reaction at selected GIMEMA LabNet laboratories able to express the results according to the International Scale.[13] Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0). The risk scores were calculated according to the Sokal,[14] Euro,[15] and European Treatment and Outcome Study formulations.[16] The HRQOL assessment over a 2-year period was a prespecified secondary endpoint of the research protocol, and we herein report the full analysis.

The study protocol was approved by the ethics committees of all participating centers and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. This study is registered at ClinicalTrials.gov (NCT01535391).

Procedures for HRQOL and Fatigue Assessment

HRQOL was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).[17] This is a self-reported questionnaire whose validity and test-retest reliability have been demonstrated in several studies.[18] The EORTC QLQ-C30 consists of 30 items and includes 5 functional scales (Physical, Role, Emotional, Social, and Cognitive), 3 symptoms (fatigue, nausea and vomiting, and pain), a global health status/quality-of-life scale, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The raw scores of the questionnaire are transformed into a linear scale ranging from 0 to 100, with a higher score representing either a higher level of functioning and health status/quality-of-life or a higher level of symptoms. In the study protocol, fatigue was assessed with the validated EORTC Quality of Life Questionnaire-Fatigue 13 (QLQ-FA13).[19] However, for the purpose of this analysis, outcomes are reported according to the most recent validation of this questionnaire, which resulted in the EORTC Quality of Life Questionnaire-Fatigue 12 (QLQ-FA12) and was based on the recommended EORTC scoring algorithm[20] (therefore, we herein refer to the EORTC QLQ-FA12). Because of the multidimensional nature of fatigue, this questionnaire consists of the following 5 domains: Physical, Cognitive, and Emotional Fatigue as well as Interference With Daily Living and Social Sequelae. In this questionnaire, a higher score (range, 0-100) represents a greater impairment in the corresponding domain.

The protocol stipulated that HRQOL and fatigue had to be assessed at the baseline (ie, before the treatment) and then at 3, 6, 12, 18, and 24 months. These time points were a priori selected on the basis of clinical relevance as associated with an assessment of clinical efficacy endpoints.

Because of the importance of the mode of HRQOL questionnaire administration to data quality,[21] standard operating procedures for administering questionnaires were included in the study protocol to ensure homogeneity in data collection among all participating centers.

Statistical Analysis

The primary prespecified HRQOL endpoints defined in the study protocol for longitudinal analysis were the Physical Functioning, Social Functioning, Role Functioning, and Fatigue scales from the EORTC QLQ-C30. The remaining scales were investigated on an exploratory basis. Fisher's exact test and the Wilcoxon-Mann-Whitney test were used as appropriate to assess differences between subgroups. We estimated mean HRQOL patterns over time with a linear mixed model with an unstructured covariance structure, and we reported means, standard deviations, and corresponding 95% confidence intervals for any HRQOL assessment. For each scale, we tested the null hypothesis of no global change from the baseline with an overall F test. We also considered the minimally important difference (MID) in HRQOL outcomes, which can be considered the smallest change in an outcome that a patient would identify as important and is not necessarily related to statistical significance.[22] Clinically meaningful improvements from the baseline were, therefore, evaluated for both the EORTC QLQ-C30[17] and the EORTC QLQ-FA12.[20] For the EORTC QLQ-C30, the MID for each scale was defined according to specific thresholds reported by Cocks et al[23] for this questionnaire. The clinical significance of scales of the EORTC QLQ-FA12 was based on previous work by Norman et al[24] because no specific guidelines are yet available to determine the MID for this questionnaire. On the basis of previous work,[25,26] we used MIDs to assess the time until a definitive HRQOL improvement as measured from the date of the baseline HRQOL to that of the first achievement of a clinically meaningful HRQOL improvement (from the baseline), with no further impairment of more than an MID.[27] We used the Cox proportional hazards model with the Fine-Gray method, and we considered failure, a suboptimal response, disease progression, and toxicity as possible competing events. Patients were censored at the date of either the last follow-up or last HRQOL questionnaire completion if they had experienced neither a definitive HRQOL improvement nor a competing event within 2 years of follow-up. For each scale, we calculated the proportions of patients achieving a definitive HRQOL improvement and the corresponding cumulative incidence curves for the time until a definitive HRQOL improvement. As specified in the protocol, the predictive value of baseline HRQOL scores for traditional clinical responses (including a major molecular response [MMR]) was also examined. Univariate and multivariate logistic regression analyses were used. When performing multivariate analyses, we included key baseline clinical and demographic variables as possible confounders: age at diagnosis, sex, hemoglobin level, Eastern Cooperative Oncology Group performance status, comorbidity, previous treatment, dose reduction/interruption (at least once), and Sokal risk. Two multivariate models were considered: one using each component of the Sokal risk (to more thoroughly examine the actual predictive value of HRQOL outcomes against key laboratory variables) and another using the computed Sokal risk group categories.

We performed sensitivity analyses to identify possible systematic missing data–generating mechanisms. We used logistic regression analysis to evaluate the possible impact on the missingness of baseline characteristics and HRQOL at any time point and of previously observed HRQOL at the next assessment. We also graphically inspected mean HRQOL patterns over time. Statistical significance was set at $\alpha = .05$ for all analyses, which were performed with SAS statistical software (version 9.4; SAS Institute, Cary, North Carolina) and R software (version 3.2.4).

RESULTS

One hundred thirty patients were enrolled in this study, and full results for clinical and efficacy data have been published elsewhere.[11] Briefly, at 24 months, 65% of the patients had an MMR, and among the nonhematologic and noncardiovascular adverse events, the following low-grade (ie, grade 1 or 2) adverse events were reported in more than 10% of the patients: fatigue (17%), bone and muscle and joint pain (22%), and skin rash (29%).

Baseline HRQOL Characteristics and Compliance Over Time

The baseline rate of compliance with the HRQOL assessment was 95.4% (124 of 130), and patients' characteristics are reported in Table 1. The overall rate of compliance with the HRQOL forms was 91%, and details on compliance over time are reported in Table 2.

No statistically significant difference existed between patients with (n = 124) and without a baseline evaluation (n = 6) with respect to key sociodemographic and clinical characteristics. Also, there were no statistically significant differences in baseline HRQOL characteristics by the Sokal risk at diagnosis (Supporting Table 1) or by previous therapy (Supporting Table 2), and this indicated that HRQOL outcomes over time were not affected by this variable.

Longitudinal Analysis of HRQOL Outcomes Over Time

Of the 4 prespecified primary HRQOL outcomes, only Social Functioning did not show a statistically significant change over time ($P = .512$). Statistically significant improvements over time were found for Physical Functioning ($P = .013$), Role Functioning ($P = .004$), and Fatigue ($P < .001$; Fig. 1). In these 3 scales, a clinically meaningful improvement (albeit small) was found already 3 months after the treatment start. Other significant improvements in EORTC QLQ-C30 scales were found for Global Health Status/HRQOL ($P < .001$), Emotional Functioning ($P = .004$), Nausea and Vomiting ($P = .003$), and Appetite Loss ($P = .002$). Also, statistically significant improvements in the Physical ($P < .001$) and Cognitive Fatigue scales ($P = .014$) of the EORTC QLQ-FA12 were found. HRQOL trajectories over time for select secondary scales are reported in Figure 2.

TABLE 1. Patient Characteristics (n = 124)

Characteristic	Value
At diagnosis	
Age, median (range), y	49.5 (18-81)
Sex: male, No. (%)	80 (64.5)
ECOG performance status ≥ 1, No. (%)	20 (16.1)
Hb level, median (range), g/dL	12.0 (7.6-16.3)
Platelet count, median (range), $\times 10^3$/L	396 (101-4093)
Spleen, median (range), cm	1.0 (0-26)
Blast cells in PB, median (range), %	1.0 (0-14.0)
Eosinophils in PB, median (range), %	2.0 (0-10.0)
Basophils in PB, median (range), %	2.4 (0-13.0)
Sokal score, No. (%)	
Low	53 (43)
Intermediate	45 (36)
High	26 (21)
Euro score, No. (%)	
Low	57 (46)
Intermediate	60 (48)
High	7 (6)
EUTOS score, No. (%)	
Low	114 (92)
High	10 (8)
Comorbidity, No. (%)	
No	50 (40)
Yes	74 (60)
Before nilotinib start	
Previous therapy, No. (%)	
No	50 (40)
Yes	74 (60)
If yes to previous therapy, No. (%)	
Hydroxyurea	67 (91)
Imatinib	7 (9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EUTOS, European Treatment and Outcome Study; Hb, hemoglobin; PB, peripheral blood.

Analysis of Time Until a Definitive Improvement in HRQOL Outcomes

Overall, 58% of the patients (72 of 124) achieved, at any time point during the study, a clinically meaningful improvement in the Global Health Status/HRQOL scale (EORTC QLQ-C30) that was maintained throughout the study period. The 3 other largest proportions of definitive improvements were found for Emotional Functioning, Fatigue, and Physical Functioning: 54% (67 of 124), 48% (59 of 124), and 36% (45 of 124), respectively. Already 6 months after the baseline assessment, 37% of the patients (46 of 124) reported definitive improvements in fatigue. Details are reported in Figure 3.

Sensitivity Analyses

A graphical inspection of the mean scores of HRQOL scales over time by the number of assessments did not suggest missing-not-at-random data. When we investigated a possible missing-at-random mechanism by logistic regression analysis, neither sociodemographic nor clinical pretreatment variables showed a statistically significant impact on missingness at any time point. These variables included age, sex, comorbidity, hemoglobin level, white blood cell count, blasts, Sokal risk score, Eastern Cooperative Oncology Group performance status, and the receipt of previous treatment for CML. Pretreatment HRQOL scores were also not significant in predicting missingness

TABLE 2. HRQOL Compliance Over Time

HRQOL Questionnaire	T0 (Baseline)	T1 (3 mo)	T2 (6 mo)	T3 (12 mo)	T4 (18 mo)	T5 (24 mo)
Expected, No.	130	126	120	115	112	104
Complete, No.	124	118	113	102	102	84
Compliance, %	95.4	93.7	94.2	88.7	91.1	80.8

Abbreviation: HRQOL, health-related quality of life.

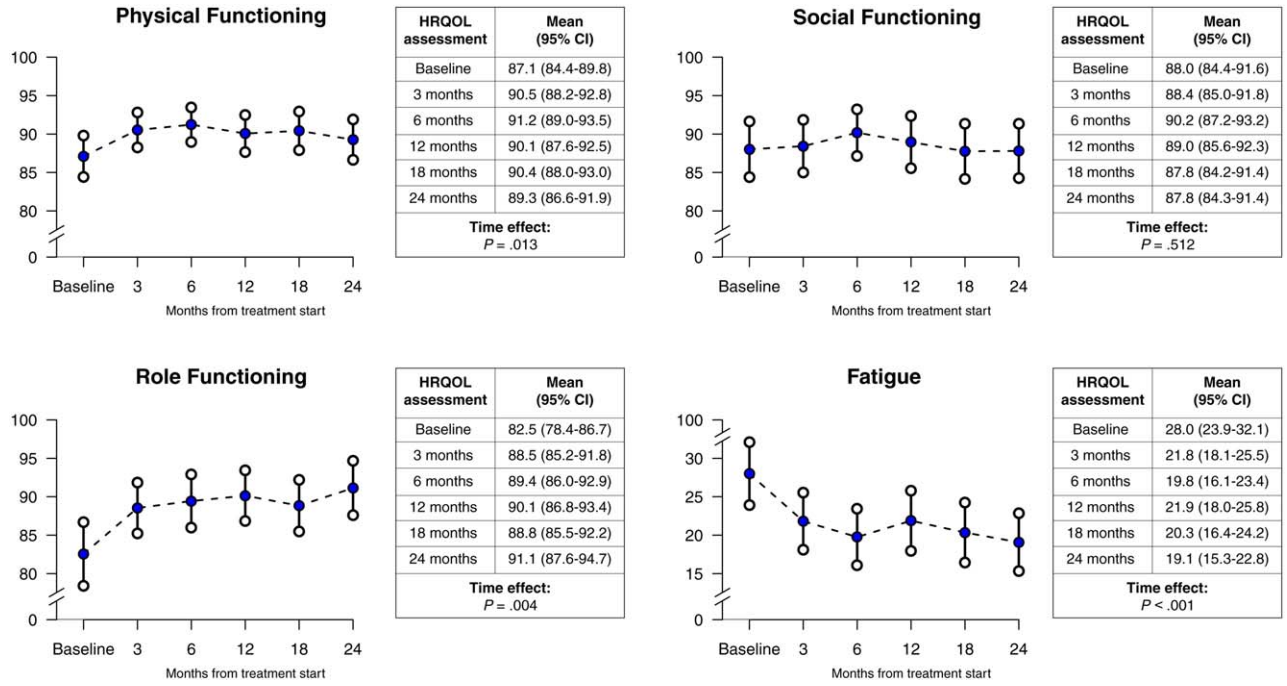

Figure 1. Mean patient-reported HRQOL and 95% confidence intervals over 2 years on prespecified primary scales (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30). Higher scores on the Physical Functioning, Role Functioning, and Social Functioning scales indicate better HRQOL outcomes. Higher scores on the Fatigue scale indicate a higher severity of fatigue. CI indicates confidence interval; HRQOL, health-related quality of life.

at any time point, and previous HRQOL scores were not statistically significant for missingness at a subsequent evaluation. These results allow us to be confident in the robustness of the final findings about HRQOL patterns over time.

Predictive Value of Baseline HRQOL Outcomes for the Achievement of an MR

The results of a univariate analysis investigating the predictive value of baseline HRQOL and fatigue outcomes for the achievement of an MR (ie, MMR, $MR^{4.0}$, and $MR^{4.5}$) showed that patients with greater physical fatigue severity (EORTC QLQ-FA12) at the baseline were less likely to achieve an MMR (odds ratio [OR], 0.975; 95% confidence interval, 0.956-0.995; $P = .016$). No other scales were statistically significant in the univariate analysis. No association was found between baseline fatigue and the achievement of $MR^{4.0}$ or $MR^{4.5}$. The proportions of dose reduction/interruption in patients with higher fatigue (ie, equal to or greater than the median value of 20 points) or lower fatigue (ie, less than 20 points) were 32.3% (21 of 65) and 22% (13 of 59), respectively ($P = .230$).

A multivariate analysis, controlling for age, sex, hemoglobin level, spleen size, platelet count, blast cells, performance status, comorbidity, previous treatment, and dose reduction/interruption, was also performed, and it confirmed the independent predictive value of a patient's self-reported fatigue severity with an OR of 0.960 (95% confidence interval, 0.934-0.988; $P = .005$) for the achievement of an MMR (Table 3). This OR of 0.960 indicates a 40% decrease in the odds to achieve an MMR at any time point with every 10-point increase (ie, worsening) in the baseline fatigue scale. A multivariate analysis was also performed with Sokal risk groups (in place of single components of the score), and fatigue still remained statistically significant in the final model (Supporting Table 3).

For descriptive purposes, the baseline HRQOL and fatigue profile of patients who eventually achieved an MMR at least once (n = 95) versus those who did not (n = 23) is reported in Supporting Figure 1.

DISCUSSION

This study shows that newly diagnosed patients with CML who are starting first-line therapy with nilotinib report a number of HRQOL improvements over time in comparison with their baseline health conditions.

Clinically meaningful improvements were found already at 3 months in 3 of the 4 a priori selected scales for

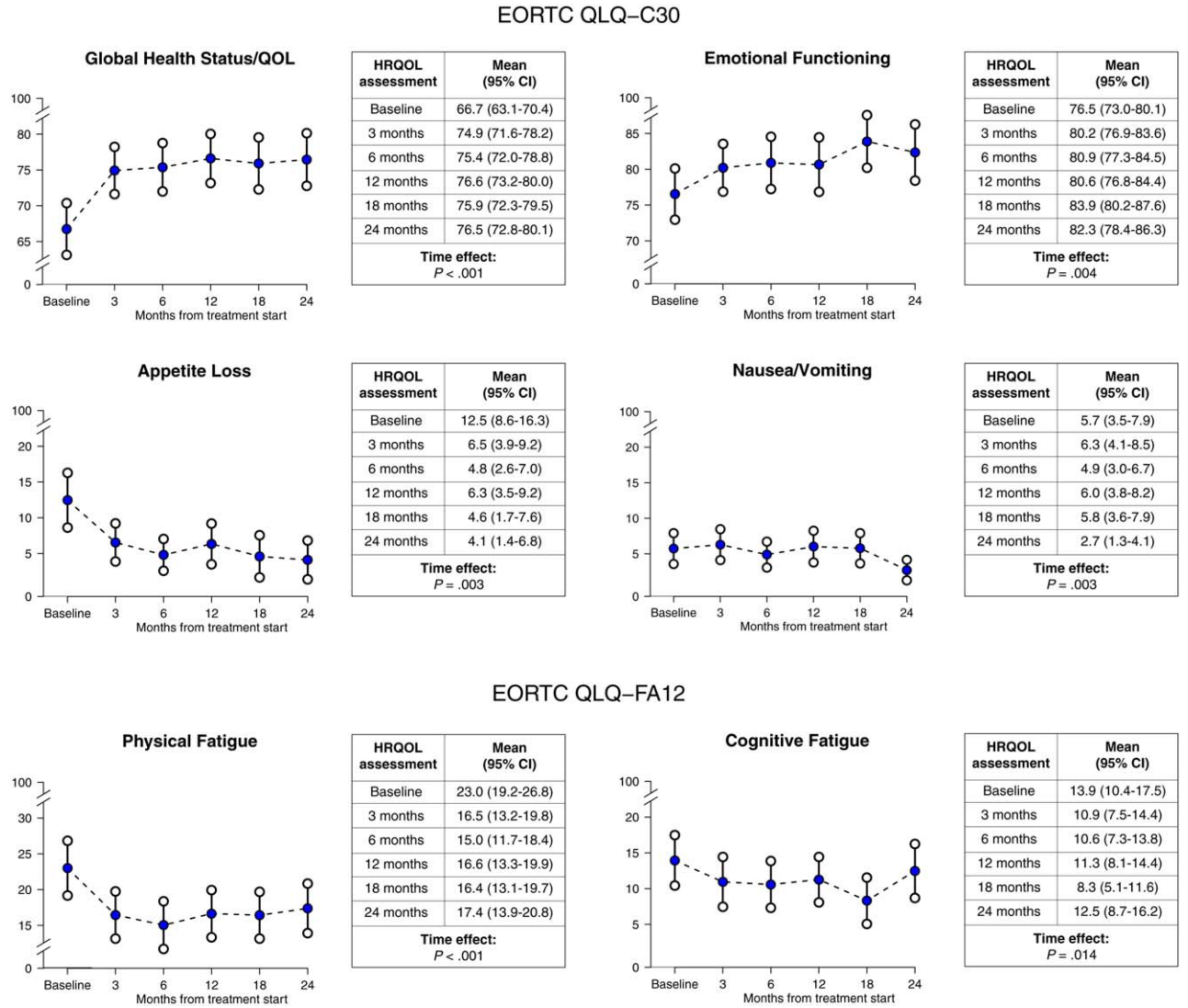

Figure 2. Mean patient-reported HRQOL and 95% confidence intervals over 2 years on selected secondary scales. Higher scores on the Global Health Status/QOL and Emotional Functioning scales indicate better HRQOL outcomes. Higher scores on all other scales indicate worse outcomes. CI indicates confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; HRQOL, health-related quality of life; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-FA12, Quality of Life Questionnaire Fatigue 12.

the primary analysis: Fatigue, Physical Functioning, and Role Functioning. Our study was designed to address not only general HRQOL aspects but also fatigue with a well-validated measure[19,20] that confirmed a statistically significant reduction of physical and cognitive fatigue severity over time. Previous work indicated that fatigue is a main concern for patients with CML receiving TKIs[28,29]; therefore, our findings provide further evidence that nilotinib therapy might contribute to improved key patient outcomes. Also, our additional analysis investigating definitive improvements over time revealed that some 60% of patients reported a clinically meaningful benefit on the global HRQOL scale that was maintained over the 2-year period of observation. This finding suggests that for most patients treated with nilotinib, HRQOL benefits are not transient and can be maintained over time. Very little prospective information exists on the impact of TKIs on long-term HRQOL outcomes; therefore, it is difficult to put our results into a larger perspective. However, in a recent study of patients with CML with 264 weeks or more of follow-up who were mainly treated with second- or third-line bosutinib therapy, Kantarjian et al[30] also demonstrated that patients' wellbeing can be preserved over the long term.

Two recent studies described HRQOL outcomes of patients with CML receiving nilotinib therapy as second-

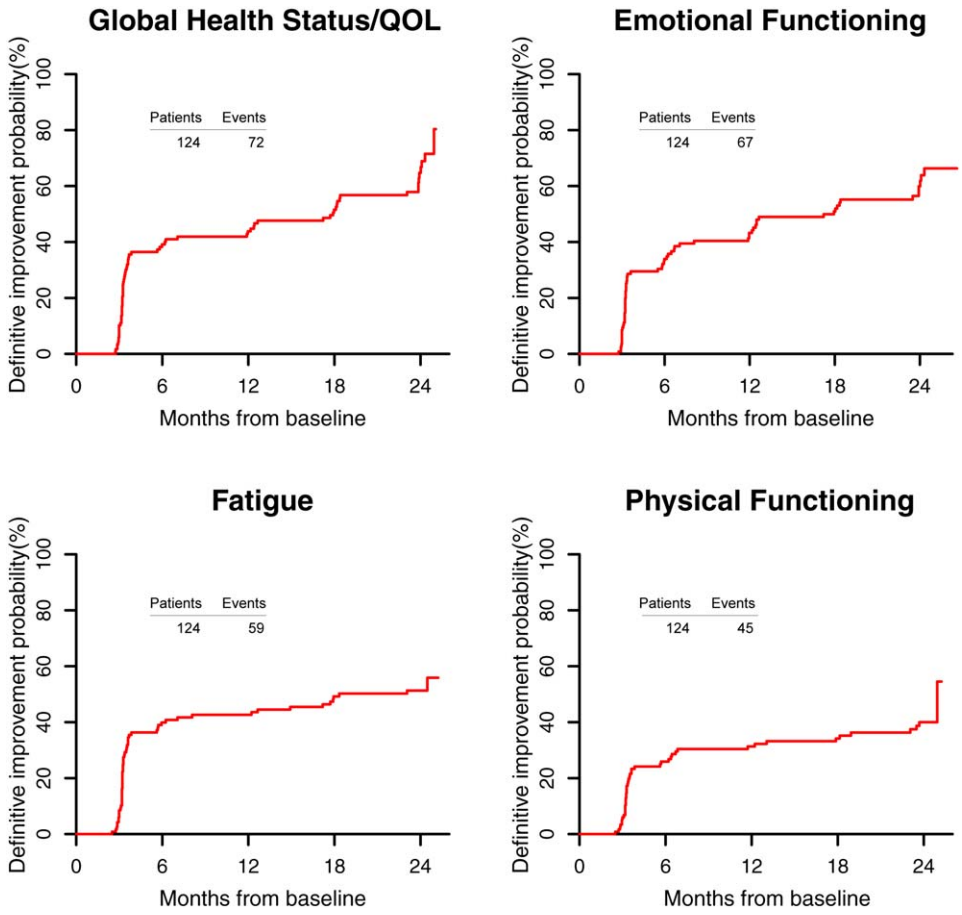

Figure 3. Time until definitive improvement on selected scales of health-related quality of life. When we calculated the cumulative probability of achieving a definitive improvement, we accounted for competing risks, which were defined as failure, a suboptimal response, disease progression, and toxicity.

TABLE 3. Multivariate Logistic Regression Analysis for the Achievement of a Major Molecular Response

Variable	OR (95% CI)	*P*
Age at diagnosis (y)[a]	0.982 (0.937-1.030)	.459
Sex: male	0.486 (0.129-1.832)	.286
Patient-reported fatigue[b]	0.960 (0.934-0.988)	.005
Hb level (g/dL)	0.992 (0.691-1.424)	.965
Spleen (cm)[a]	0.827 (0.730-0.938)	.003
Platelet count ($\times 10^3$/L)[a]	1.003 (1.000-1.007)	.057
Blast cells (%)[a]	1.046 (0.747-1.466)	.793
ECOG performance status $\geq$1	0.284 (0.058-1.379)	.118
Comorbidity	0.621 (0.140-2.766)	.532
Previous treatment	2.608 (0.644-10.561)	.179
Dose reduction/interruption	0.474 (0.143-1.572)	.222

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; OR, odds ratio.
[a] Component of the Sokal risk score.
[b] Patient-reported Physical Fatigue scale assessed with the Quality of Life Questionnaire-Fatigue 12 (QLQ-FA12) from the European Organisation for Research and Treatment of Cancer.

line therapy. Sacha et al[31] documented the effects of nilotinib used as second-line therapy for chronic-phase CML over a 1-year period in patients switching mainly from imatinib therapy because of intolerance and/or resistance, and HRQOL was evaluated with the same questionnaire used in our study. Although a direct comparison with our findings is not possible because of major differences in the study design and statistical analysis, we note that nilotinib therapy was also found to improve some HRQOL outcomes. However, the magnitude of these improvements was smaller than that found in our analysis, and this could be explained by the greater burden of previous TKI therapies and a substantially longer time since diagnosis (mean time, 4.5 years). Cortes et al[32] found that switching to nilotinib therapy is a valuable strategy for reducing the symptom burden and improving HRQOL in imatinib-treated patients who have experienced low-grade, nonhematologic adverse events. Although the median duration

time of previous imatinib therapy was 31 months, benefits from switching to nilotinib therapy were already found at the end of the first cycle of therapy.

Another finding of our study was that patients with a greater burden of pretreatment fatigue were less likely to achieve an MMR. This finding remained significant in the multivariate analysis when we controlled for key potential confounders. Our results might be corroborated by several studies of other solid and hematologic malignancies,[33] which have found that patient self-reported symptoms, including fatigue, provide independent prognostic information for survival outcomes beyond well-established disease-related factors.[34-36] In the CML arena, our findings are partly consistent with 3 studies published in an abstract form[37-39] that indicate that a patient's health status, as measured by validated HRQOL instruments, can provide unique clinically relevant information. Beaumont et al[37] found that baseline HRQOL was predictive for treatment discontinuation but not for an MR in patients receiving first-line imatinib or nilotinib. However, it is challenging to compare our findings with this study because their analysis did not distinguish by the type of TKI, and this hampers disentangling the possible effects of drugs on study outcomes. In addition, all their patients were enrolled in an RCT setting,[4] and they thus possibly represented a more select patient population than the one included in our study. Nicolini et al[38] analyzed the predictive value of HRQOL in a population of patients with CML for whom imatinib failed and who switched to either dasatinib or nilotinib. They found that failure-free survival was significantly longer for patients with higher HRQOL scores at the time of switching the TKI from imatinib therapy. Another recent study by Ionova et al[39] found that baseline HRQOL was predictive for the achievement of a complete cytogenetic response and MMR in patients with CML treated with dasatinib as first- or second-line therapy.

It is possible to speculate that the patients with higher baseline fatigue in our study were those with a greater disease burden and that this cannot be fully captured with traditional clinical examinations or physician-reported tools such as the performance status. Rather, well-validated patient-reported outcome measures might be more sensitive indicators of the overall disease burden. Further research is needed to elucidate underlying reasons for this relation and to investigate possible mediating factors. Anyway, current findings underscore the value of a more systematic HRQOL evaluation during the diagnostic workup.

A limitation of this study is that we cannot directly compare the HRQOL outcomes of our patients with those of patients receiving other first-line TKIs. Future comparative studies are needed to contrast HRQOL outcomes with various TKIs. Also, although we found that baseline fatigue predicted MMR, we could not demonstrate this association with a deeper MR ($MR^{4.0}$ and $MR^{4.5}$). This might be due to the short period of observation, and longer follow-up is needed to better ascertain this relation in future analyses.

This study also has notable strengths. Because it is a multicenter academic and non-RCT study, our findings are likely to be highly generalizable to the wider CML population most typically seen in a real-world setting. Also, we included a well-validated measure of fatigue,[19,20] which is a critical concern for patients with CML.

In conclusion, our results extend our knowledge of the efficacy and safety of frontline nilotinib therapy by providing the patient's perspective of the impact of this drug on his or her HRQOL and symptom burden. Our findings may help physicians to make more informed treatment decisions at the time of starting CML therapy with TKIs.

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CONFLICT OF INTEREST DISCLOSURES

Fabio Efficace reports consultancy work for Seattle Genetics, Teva, Amgen, and Incyte and research funding from Lundbeck, Teva, and Amgen. Fausto Castagnetti reports consultancy work for Novartis, Bristol-Myers Squibb, Incyte, and Pfizer and honoraria from Novartis, Bristol-Myers Squibb, Incyte, and Pfizer. Massimo Breccia reports honoraria from Novartis, Bristol-Myers Squibb, Pfizer, and Incyte. Emanuele Angelucci reports working on advisory boards for Novartis, Roche, Jazz Pharma, Bluebird Bio, and Celgene; receiving speaker fees from Novartis; working as the steering committee chair for Novartis; and working as the data monitoring committee chair for Celgene. Gabriele Gugliotta reports consultancy work for Novartis, Bristol-Myers Squibb, and Incyte and honoraria from Novartis, Bristol-Myers Squibb, and Incyte. Michele Baccarani reports consultancy work for Novartis, Bristol-Myers Squibb, Incyte, and Pfizer and honoraria from Novartis, Bristol-Myers Squibb, Incyte, and Pfizer. Gianantonio Rosti reports speaker fees from Novartis, Bristol-Myers Squibb, Pfizer, and Incyte and research funding from Novartis, Bristol-Myers Squibb, Pfizer, and Incyte.

AUTHOR CONTRIBUTIONS

Fabio Efficace: Conception and design, data analysis and interpretation, statistical analysis, manuscript writing, and final approval of the manuscript. **Fausto Castagnetti:** Data analysis and interpretation, manuscript writing, and final approval of the manuscript. **Bruno Martino:** Data analysis and interpretation and final approval of the manuscript. **Massimo Breccia:** Data analysis and interpretation, manuscript writing, and final approval of the manuscript. **Mariella D'Adda:** Data analysis and interpretation and final approval of the manuscript. **Emanuele Angelucci:** Data analysis and interpretation and final approval of the manuscript. **Fabio Stagno:** Data analysis and interpretation and final approval of the manuscript. **Francesco Cottone:** Data analysis and interpretation, statistical analysis, manuscript writing, and final approval of the manuscript. **Alessandra Malato:** Data analysis and interpretation and final approval of the manuscript. **Elena Trabacchi:** Data analysis and interpretation and final approval of the manuscript. **Silvana Franca Capalbo:** Data analysis and interpretation and final approval of the manuscript. **Marco Gobbi:** Data analysis and interpretation and final approval of the manuscript. **Giuseppe Visani:** Data analysis and interpretation and final approval of the manuscript. **Marzia Salvucci:** Data analysis and interpretation and final approval of the manuscript. **Isabella Capodanno:** Data analysis and interpretation and final approval of the manuscript. **Patrizia Tosi:** Data analysis and interpretation and final approval of the manuscript. **Mario Tiribelli:** Data analysis and interpretation and final approval of the manuscript. **Anna Rita Scortechini:** Data analysis and interpretation and final approval of the manuscript. **Luciano Levato:** Data analysis and interpretation and final approval of the manuscript. **Elena Maino:** Data analysis and interpretation and final approval of the manuscript. **Gianni Binotto:** Data analysis and interpretation and final approval of the manuscript. **Gabriele Gugliotta:** Data analysis and interpretation and final approval of the manuscript. **Marco Vignetti:** Data analysis and interpretation and final approval of the manuscript. **Michele Baccarani:** Data analysis and interpretation and final approval of the manuscript. **Gianantonio Rosti:** Conception and design, data analysis and interpretation, manuscript writing, and final approval of the manuscript.

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