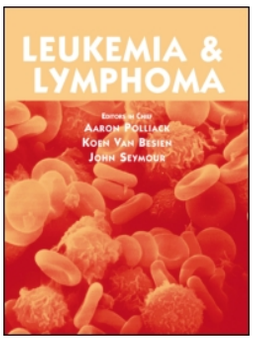

Leukemia & Lymphoma

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

Validation and reference values of the EORTC QLQ-CML24 questionnaire to assess health-related quality of life in patients with chronic myeloid leukemia

Fabio Efficace , Alessandra Iurlo , Andrea Patriarca , Fabio Stagno , Ping-Chong Bee , Geneviève Ector , Isabella Capodanno , Chiara Elena , Massimiliano Bonifacio , Nicole M. A. Blijlevens , Giovanni Caocci , Chonghua Wan , Elisabetta Abruzzese , Massimo Breccia , Francesco Cottone , Iris Okumura , Simone Oerlemans , Nicola Cascavilla , Francesco Albano , Vamsi Kota , Monika Sztankay , Maria Cristina Miggiano , Susanne Saussele , Nicola Di Renzo , Federica Sorà , Fausto Castagnetti , Michele Baccarani , Marco Vignetti & Gianantonio Rosti

To cite this article: Fabio Efficace , Alessandra Iurlo , Andrea Patriarca , Fabio Stagno , Ping-Chong Bee , Geneviève Ector , Isabella Capodanno , Chiara Elena , Massimiliano Bonifacio , Nicole M. A. Blijlevens , Giovanni Caocci , Chonghua Wan , Elisabetta Abruzzese , Massimo Breccia , Francesco Cottone , Iris Okumura , Simone Oerlemans , Nicola Cascavilla , Francesco Albano , Vamsi Kota , Monika Sztankay , Maria Cristina Miggiano , Susanne Saussele , Nicola Di Renzo , Federica Sorà , Fausto Castagnetti , Michele Baccarani , Marco Vignetti & Gianantonio Rosti (2020): Validation and reference values of the EORTC QLQ-CML24 questionnaire to assess health-related quality of life in patients with chronic myeloid leukemia, Leukemia & Lymphoma, DOI: 10.1080/10428194.2020.1838509

To link to this article: https://doi.org/10.1080/10428194.2020.1838509

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2020.1838509

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Validation and reference values of the EORTC QLQ-CML24 questionnaire to assess health-related quality of life in patients with chronic myeloid leukemia

Fabio Efficace[a], Alessandra Iurlo[b], Andrea Patriarca[c], Fabio Stagno[d], Ping-Chong Bee[e], Geneviève Ector[f], Isabella Capodanno[g], Chiara Elena[h], Massimiliano Bonifacio[i], Nicole M. A. Blijlevens[f], Giovanni Caocci[j], Chonghua Wan[k], Elisabetta Abruzzese[l], Massimo Breccia[m], Francesco Cottone[a], Iris Okumura[n], Simone Oerlemans[o], Nicola Cascavilla[p], Francesco Albano[q], Vamsi Kota[r], Monika Sztankay[s], Maria Cristina Miggiano[t], Susanne Saussele[u], Nicola Di Renzo[v], Federica Sorà[w], Fausto Castagnetti[x], Michele Baccarani[x], Marco Vignetti[a] and Gianantonio Rosti[x]

[a]Italian Group for Adult Hematologic Diseases (GIMEMA), Data Center and Health Outcomes Research Unit, Rome, Italy; [b]Hematology Division, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [c]Department of Translational Medicine, Division of Hematology, University of Eastern Piedmont, Novara, Italy; [d]Hematology Section with BMT Unit, AOU Policlinico – V. Emanuele, Catania, Italy; [e]Department of Medicine, University of Malaya Medical Centre, Kuala Lumpur, Malaysia; [f]Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands; [g]Hematology, AUSL-IRCCS, Reggio Emilia, Italy; [h]Division of Hematology, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; [i]Department of Medicine, Section of Hematology, University of Verona, Verona, Italy; [j]Dipartimento Scienze Mediche e Sanità Pubblica, Università di Cagliari, Ospedale Businco, Cagliari, Italy; [k]School of Humanities and Management, Research center for quality of life and applied psychology, Key Laboratory for Quality of Life and Psychological Assessment and Intervention, Guangdong Medical University, Dongguan, China; [l]Division of Hematology, Ospedale S. Eugenio, Tor Vergata University, ASL Roma 2, Roma, Italy; [m]Department of Cellular Biotechnologies and Hematology, "Sapienza" University of Rome, Rome, Italy; [n]Unidade de Hematologia, Hemoterapia e Oncologia (UHHO), Serviço de Transplante de Medula Óssea (STMO), Complexo Hospital de Clínicas da Universidade Federal do Paraná, Curitiba, Brazil; [o]Department of Research and Development, Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands; [p]Department of Hematology and Stem Cell Transplant Unit, Fondazione IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Italy; [q]Department of Emergency and Transplantation, Hematology Section, University of Bari Medical School, Bari, Italy; [r]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [s]Medical University of Innsbruck, University Hospital Innsbruck, Psychiatry II, Innsbruck, Austria; [t]Hematology Unit, San Bortolo Hospital, Vicenza, Italy; [u]III. Med. Klinik, Universitätsmedizin Mannheim, Theodor-Kutzer-Ufer 1-3, Mannheim, Germany; [v]Haematology and SCT Unit, Vito Fazzi Hospital, Lecce, Italy; [w]Istituto di Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; Università Cattolica del Sacro Cuore, Rome, Italy; [x]Department of Experimental, Diagnostic and Specialty Medicine (DIMES), Institute of Hematology "L. & A. Seràgnoli", "Sant'Orsola-Malpighi" University Hospital, University of Bologna, Bologna, Italy

ABSTRACT

Health-related quality of life (HRQOL) assessment is important to facilitate decisions in the current treatment landscape of chronic myeloid leukemia (CML). Therefore, the availability of a validated HRQOL questionnaire, specifically developed for CML patients treated with tyrosine kinase inhibitors (TKIs), may enhance quality of research in this area. We performed an international study including 782 CML patients to assess the validity of the EORTC QLQ-CML 24 questionnaire, and to generate HRQOL reference values to facilitate interpretation of results in future studies. Internal consistency, assessed with Cronbach's alpha coefficients, ranged from 0.66 to 0.83. In the confirmatory factor analysis, all standardized factor loadings exceeded the threshold of 0.40 (range 0.49–0.97), confirming the hypothesized scale structure. Reference values stratified by age and sex were also generated. Our findings support the use of the EORTC QLQ-CML 24, in conjunction with the EORTC QLQ-C30, as a valuable measure to assess HRQOL in CML patients.

ARTICLE HISTORY
Received 16 July 2020
Accepted 8 October 2020

KEYWORDS
Quality of life; tyrosine kinase inhibitors; symptoms; chronic myeloid leukemia; patient-reported outcomes

Introduction

Since the introduction of oral tyrosine kinase inhibitors (TKIs) for the treatment of chronic myeloid leukemia (CML), the number of people living with this disease has remarkably increased [1] and health-related quality of life (HRQOL) has become an important goal of therapy [2]. Indeed, life expectancy of CML patients now approaches that of their peers from the general population [3].

Imatinib was the first TKI approved for the treatment of CML in early 2000 [4] and subsequently, other

CONTACT Fabio Efficace f.efficace@gimema.it Italian Group for Adult Hematologic Diseases (GIMEMA), GIMEMA Data Center, Rome, Italy
Supplemental data for this article can be accessed here.

TKIs were also approved as frontline treatment by the US Food and Drug Administration (FDA) based on results from pivotal randomized controlled trials (RCTs) and these include: nilotinib [5], dasatinib [6], and bosutinib [7]. There are now four TKIs which can be used as alternative front-line therapies for newly diagnosed CML patients, with no major differences with regard to survival outcomes [8]. However, these drugs do have specific side effects profiles which require appropriate management in routine practice [9]. This scenario briefly illustrates why treatment decision-making in CML is particularly challenging, and underscores the importance of better understanding patient-reported HRQOL to more robustly inform patient care.

Also, as administration of TKI therapy is typically lifelong, even low grade side effects may impact on daily living and overall patient's wellbeing [10–12], with potential negative implications with regard to optimal adherence to therapy and long-term clinical outcomes [13–17].

Despite substantial knowledge is available on safety and clinical efficacy of CML therapies, little is known on patients' HRQOL outcomes, particularly for patients treated with second generation TKIs [13], thereby limiting our knowledge on how to further improve healthcare quality in this cancer population. Therefore, the EORTC Quality of Life Group (QLG) started in 2010 the international development of a multidimensional HRQOL measure (i.e. the EORTC QLQ-CML24) for CML patients [18] to be used in conjunction with the EORTC QLQ-C30 [19]. Examples of validated multidomain HRQOL measures that have been used in previous CML studies, include the Functional Assessment of Cancer Therapy (FACT)-BRM [20] or the FACT-Leu [21]. Both measures have been implemented in pivotal RCTs and have greatly helped in providing important data to better understand the impact of newer CML therapies on patients' HRQOL. This was the case, for example, for the IRIS study which compared imatinib versus interferon alfa plus low-dose cytarabine [22] and for the more recent BFORE trial, which compared bosutinib versus imatinib in chronic phase (CP) CML patients [23]. However, these questionnaires were not specifically developed for CML patients in treatment with modern TKI therapies. Another validated patient-reported outcome (PRO) measure used in CML research, is the MD Anderson Symptom Inventory (MDASI) CML [24]. As well illustrated in the ENRICH study, for example, this measure has contributed to provide valuable data to understand patient-reported symptom burden when switching TKI therapies [25]. However, rather than broader multidimensional HRQOL aspects, the MDASI-CML has been developed to assess symptom burden [24].

Therefore, the availability of a well-validated CML specific HRQOL measure in the current CML arena, may contribute to more thoroughly capture the burden of disease and therapy in this cancer population [26]. Indeed, the specific population in which validity data of a given PRO instrument was generated, is an important aspect to consider when evaluating if the PRO instrument is fit for purpose for the specific context of use [27,28].

We previously published the initial development of the EORTC QLQ-CML24 questionnaire, by also documenting item generation process [18], and we herein report the results of a large additional study to assess its validity. Given the importance of relying on reference values to enhance HRQOL outcome interpretation [29], we also aimed to provide age and sex-specific reference values for the EORTC QLQ-C30 and the QLQ-CML24 in CML patients.

Patients and methods

Study design and development process

Full results of the previous phases of the development of the EORTC QLQ-CML 24 questionnaire have been reported in a previous work [18], which included adult patients with a confirmed CML diagnosis. The first phase consisted in the identification of a core set of relevant issues for CML patients, through an iterative process involving both patients and healthcare providers. In the second phase, these issues were formatted as specific items of a questionnaire, according to the EORTC standards. This questionnaire was then tested for relevance and acceptability in the third phase. Overall, 637 CML patients participated from nine countries and a provisional questionnaire (i.e. the EORTC QLQ-CML24) including 24 items organized into four multi-item scales and two single items, was developed (see supplementary Table S1) [18].

The hypothesized multi-item scales are symptoms burden (SB) (13 items), impact on worry/mood (WA) (four items), impact on daily life (DL) (three items), satisfaction with care and information (SA) (two items) while the single items are: body image (BI) problems and satisfaction with social life (SS). A higher score in SB, WA, DL, and BI scales reflects a larger impairment in the corresponding domain, while a higher score on the SA and SS scales reflects a higher level of satisfaction. The EORTC QLQ-CML24 questionnaire was translated for each language according to the EORTC translation guidelines [30] and it is currently available

in 21 language versions including: Arabic (Iraq), Arabic (Qatar), Chinese Mandarin (Malaysia), Chinese Mandarin (Taiwan), Czech, Danish, Dutch, English, Finnish, French (Europe), German, Greek, Hebrew, Hungarian, Italian, Japanese, Korean, Malay (Malaysia), Portuguese (Brazil), Spanish (Mexico), and Spanish (Spain).

Population and enrollment criteria

In order to maximize broad coverage of disease and treatment-related characteristics, four groups of adult CML patients in treatment with TKIs were considered, who had not been enrolled in any of the previous phases of the initial development of the EORTC QLQ-CML 24 questionnaire [18]. These included, patients who were in first line therapy with first generation TKI (i.e. imatinib only) (group A, $N=$ 121) or with second generation TKIs (e.g. dasatinib or nilotinib) (group B, $N=$ 68). In these two patient groups, HRQOL was assessed twice: before ($t0$) and after ($t1$) the achievement of the first complete cytogenetic response (CCyR). The median time from treatment start to $t0$ was of 0.6 weeks, while the median time from CCyR to $t1$ was 1 week. A third group consisted of patients who were in 2nd or greater line of therapy with any TKI, due to being resistant or intolerant to first line therapy (group C, $N=$ 66). In this group, HRQOL was measured only at study entry, after start of current treatment (median time 27.2 weeks). The fourth group (group D, $N=$ 70) consisted of patients who were in treatment with any TKI for at least 3 years and in CCyR. In this group, the median time from current treatment start to HRQOL assessment was 46.4 weeks. This latter group was a priori selected for the test–retest analysis and completed the questionnaires twice, that is, at baseline and follow-up (3–7 days after baseline). This group was not expected to show any changes in health status between the two HRQOL assessments (e.g. loss of CCyR, change in ECOG performance status). Debriefing interviews regarding the time taken to complete the questionnaires, any assistance needed, and if they had additional comments were also performed in these patients. Patients were recruited from Austria, Italy, Netherlands, Brazil, China, Iraq, Malaysia, and the U.S.A. This study was registered at clinicaltrials.gov as NCT03075969 and overall included 325 patients.

In an effort to enrich validation data by increasing sample size and patients' heterogeneity, two additional cohorts of CML patients were also included post-hoc in the analysis. None of the patients from these additional cohorts had been enrolled in any of the previous phases of the development of the EORTC QLQ-CML 24 questionnaire. A cohort of 145 CP CML patients was recruited in the Netherlands, who were receiving imatinib ($N=64$) or second generation TKIs ($N=81$) in any line of treatment, whose HRQOL was measured only at study entry; and a cohort of 312 CP-CML patients was recruited from Germany and Italy, who were in first-line treatment with either imatinib ($N=215$) or second generation TKIs (i.e. dasatinib, $N=97$) [31]. HRQOL was measured only at study entry, after start of current treatment (median time 17 months). Participating centers provided approval by their ethical committee and all patients provided informed consent.

Statistical analysis

Patients' demographic and clinical characteristics were summarized by frequencies, means, standard deviations, and ranges, as appropriate. For each scale, characteristics of the corresponding score distribution were described by mean, standard deviation, median, minimum, and maximum scores, as well as skewness and kurtosis values. Cronbach's alpha [32] was used to estimate the internal consistency of each multi-item scale at $t0$. A Cronbach alpha coefficient $\geq$0.70 was considered acceptable [33]. Test–retest reliability was assessed by estimating the intraclass correlation coefficient (ICC) as a measure of agreement between the first and second assessment ($t0$ and $t1$) of patients in group D, using a two-way random effects model [34]. We considered ICC values between 0.5 and 0.75, 0.75 and 0.90, and greater than 0.90 as indicating respectively a 'moderate', 'good', and 'excellent' reliability [35].

To establish a fit for the hypothesized underlying scale structure of the EORTC QLQ-CML24, we performed a confirmatory factor analysis (CFA). We used the weighted least squares estimator with adjustment for means and variances procedure, which allows for the modeling of ordinal data, and model identification was ensured by fixing the factor loading of one item per factor to one and by fixing the error variance of the single-item factors to zero. The goodness-of-fit of the CFA model was evaluated by the comparative fit index (CFI), the Tucker-Lewis index (TLI), and the root mean squared error of approximation (RMSEA) [36]. CFI and TLI values above 0.95 or 0.90 indicate good or acceptable fit, respectively. RMSEA values below 0.05 or 0.08 indicate good or acceptable fit, respectively [37].

Table 1. Socio-demographic and clinical characteristics of CML patients ($N = 782$).

Variable	Value
Gender, *N* (%)	
Female	355 (45.4)
Male	427 (54.6)
Age, *N* (%)	
18–44 years	134 (17.1)
45–64 years	311 (39.8)
≥65 years	337 (43.1)
Highest level of education, *N* (%)	
Compulsory school	230 (31.4)
High school degree	328 (44.7)
University degree or higher	175 (23.9)
Missing	49 (.)
TKI treatment, *N* (%)	
Imatinib	456 (58.5)
Dasatinib	185 (23.8)
Nilotinib	113 (14.5)
Other TKI	25 (3.2)
Missing	3 (.)

TKI: tyrosine kinase inhibitors.

Convergent and divergent validity was assessed by examining the correlations between the scales of the EORTC QLQ-CML24 and the EORTC QLQ-C30 using Spearman's rank correlation coefficient. The discriminant validity of the EORTC QLQ-CML24 was assessed by performing known-group comparisons, comparing the means of the following patient subgroups: comorbidity (0 versus ≥1), ECOG performance status (0 versus ≥1), and treatment (imatinib versus 2nd generation TKIs). We used the Wilcoxon–Mann–Whitney test to evaluate differences between the patient subgroups.

Responsiveness to change of the EORTC QLQ-CML24 scales was determined using the following anchors: (1) obtainment of a CCyR and (2) clinically meaningful deterioration and improvement, respectively, in the EORTC QLQ-C30 global health status/quality of life (QL) scale. We assessed clinically meaningful deterioration and improvement of the QL scale according to thresholds criteria reported by Cocks et al. [38]. The Wilcoxon signed-rank test was used to examine differences between baseline and follow-up scores. Patients in group A and group B were used for the responsiveness to change analyses. Finally, to provide reference HRQOL scores, mean scores with standard deviations were calculated for each scale of the EORTC QLQ-C30 and EORTC QLQ-CML 24 and the analyses were stratified by sex (male, female) and age groups (18–44, 45–64, ≥65 years). These age group categories were based on consensus among authors and on balance of number of patients represented in each of the three groups. p values of $<.05$ were considered statistically significant. All analyses were performed with SAS version 9.4 (SAS Inc., Cary, NC) and with the R software version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Table 2. Reliability and scale structure of the EORTC QLQ-CML24.

Scale	No. of items	Cronbach's alpha	ICC[a]	Standardized factor loadings
SB	13	0.83	0.83	0.49–0.68
WA	4	0.69	0.76	0.59–0.73
DL	3	0.66	0.75	0.58–0.86
BI	1	NA	0.66	NA
SA	2	0.79	0.70	0.80–0.97
SS	1	NA	0.70	NA

ICC: intraclass correlation coefficient; SB: symptom burden; WA: impact on worry/mood; DL: impact on daily life; BI: body image problems; SA: satisfaction with care and information; SS: satisfaction with social life; NA: not available.
[a]ICC was measured in group D.

Results

Patient characteristics

Overall, 782 CML patients enrolled from 59 centers in nine countries were considered. Distribution of patients per country was the following: Austria ($N = 2$), Brazil ($N = 3$), China ($N = 7$), Iraq ($N = 14$), Italy ($N = 574$), Malaysia ($N = 23$), Netherlands ($N = 146$), Germany ($N = 8$), and the U.S.A. ($N = 5$). The majority of the patients were receiving imatinib at study inclusion ($N = 456$, 58.5%). Five patients were excluded from analyses of measurement properties and generation of reference values due to non-valid questionnaires. Further details are provided in Table 1.

Questionnaire characteristics

The characteristics of the EORTC QLQ-CML24 module were examined using the baseline scores (supplementary Table S2). With the exception of the SB scale and WA scale, we observed the entire range of possible scores (0–100). Overall, the percentage of missing values was low across all items of the EORTC QLQ-CML24, with the mean percentage of missing items at baseline being around 1%.

Reliability and scale structure of the QLQ-CML24

In the CFA, all standardized factor loadings exceeded the threshold of 0.40 (range 0.49–0.97), confirming the hypothesized scale structure of the EORTC QLQ-CML24 (Table 2). The CFI (0.96), the TLI (0.95), and the RMSEA (0.05) indicated good fit of the model. For the multi-item scales, Cronbach's alpha coefficients ranged from 0.66 for DL scale to 0.83 for the SB scale. The ICC in group D ranged between 0.66 and 0.83 (Table 2), showing moderate to good reliability for the CML-24 scales.

Table 3. Differences in the EORTC QLQ-CML24 scales by presence of comorbidities, ECOG performance status, and TKI treatment.

	Comorbidity					ECOG performance status					TKI treatment				
	No $N=274$		Yes (≥1) $N=354$			0 $N=447$		≥1 $N=182$			1st generation $N=453$		≥2nd generation $N=322$		
Scale	Mean	SD	Mean	SD	*p* value	Mean	SD	Mean	SD	*p* value	Mean	SD	Mean	SD	*p* value
SB	18.4	14.7	23.6	16.3	<.001	18.7	14.5	27.8	17.2	<.001	23.4	16.4	18.8	13.8	<.001
WA	20.8	18.2	24.5	19.6	.007	19.5	17.0	31.0	21.3	<.001	22.5	19.5	20.3	17.3	.225
DL	18.7	20.1	26.2	23.0	<.001	17.8	17.6	35.2	26.6	<.001	23.6	22.1	19.2	20.0	.002
BI	16.1	26.9	19.5	27.3	.028	13.9	23.0	28.1	33.3	<.001	19.2	27.0	18.2	27.6	.467
SA	80.9	21.8	80.4	22.5	.720	80.5	22.8	80.8	20.6	.521	80.0	22.8	78.9	25.3	.886
SS	71.1	26.2	64.0	27.5	<.001	68.3	27.1	64.1	26.9	.020	65.3	27.7	69.9	28.3	.012

SD: standard deviation; SB: symptom burden; WA: impact on worry/mood; DL: impact on daily life; BI: body image problems; SA: satisfaction with care and information; SS: satisfaction with social life.
For $N=145$, Dutch patients data about comorbidity, ECOG performance status, and Sokal risk score were not available.

Convergent and divergent validity of the scales

Size and direction of the 90 possible correlations between the EORTC QLQ-C30 and QLQ-CML24 scales were in accordance with the conceptual assumptions (see supplementary Table S3), indicating convergent and divergent validity. The SB scale, WA scale, DL scale, and BI scale correlated positively with the EORTC QLQ-C30 symptoms scales and negatively with the EORTC QLQ-C30 functional scales. The SS scale correlated positively with the EORTC QLQ-C30 functional scales and negatively with the EORTC QLQ-C30 symptom scales. The SA scale did not correlate significantly with the majority of the EORTC QLQ-C30 scales, except for a positive correlation with the global health status/QL scale.

Discriminant validity

The mean scores of the QLQ-CML24 scales for each group comparisons (comorbidity, ECOG performance status, and type of TKI treatment) are reported in Table 3. Comparing CML patients with no comorbidities against those with one or more comorbidities, we found that patients with no comorbidities reported statistically significant better scores for SB ($p<.001$), WA ($p=.007$), DL ($p<.001$), BI ($p=.028$), and SS ($p<.001$). Correspondingly, patients with a better ECOG performance status (ECOG = 0) reported statistically significant better scores for SB ($p<.001$), WA ($p<.001$), DL ($p<.001$), BI ($p<.001$), and SS ($p=.020$). Finally, patients who were treated with imatinib (i.e. first generation TKI) reported statistically significant worse scores compared to patients who were treated with 2nd or 3rd generation TKIs for the following CML24 scales: SB ($p<.001$), DL ($p=.002$), and SS ($p=.012$). After having adjusted for age, which was unbalanced between the two groups, the results were in line with unadjusted comparisons (data not shown).

Responsiveness to change

This analysis yielded no statistically significant differences in any of the QLQ-CML24 scales from baseline to follow-up in patients who obtained a CCyR. However, patients who reported a clinically meaningful deterioration in the EORTC QLQ-C30 global health status/QL scale, reported changes in mean scores in the expected direction and with a statistically significant deterioration in the SB scale ($p=.005$) and the DL scale ($p=.023$) (Figure 1). Correspondingly, patients who reported a clinically meaningful improvement in the EORTC QLQ-C30 global health status/QL scale, reported a statistically significant improvement in the SB scale ($p=.005$) and the DL scale ($p=.033$) (Figure 2).

Reference HRQOL values by age and sex

Overall, men reported better EORTC QLQ-C30 scores than women across all domains. Differences between younger and older group categories (i.e. 18–44 versus ≥65 years) exceeding 10 points were observed in men for PF, RF, QL, FA, DY, SL, and AP, and in women for PF, RF, SF, PA, DY, SL, and CO. For most domains of the QLQ-C30, scores deteriorated with increasing age. Full results are reported in Table 4.

Men showed better scores than women across all domains of the QLQ-CML24. The two largest differences between older and younger patients (i.e. 18–44 versus ≥65 years) in men and women were found for DL (9.4 points) and SS (9.6 points) and for BI (9.3 points) and SS (10.5 points), respectively. The majority of domains of the QLQ-CML24 deteriorated with increasing age. Details are reported in Table 5.

Discussion

We present the results of an international validation study of the EORTC QLQ-CML24 questionnaire, which

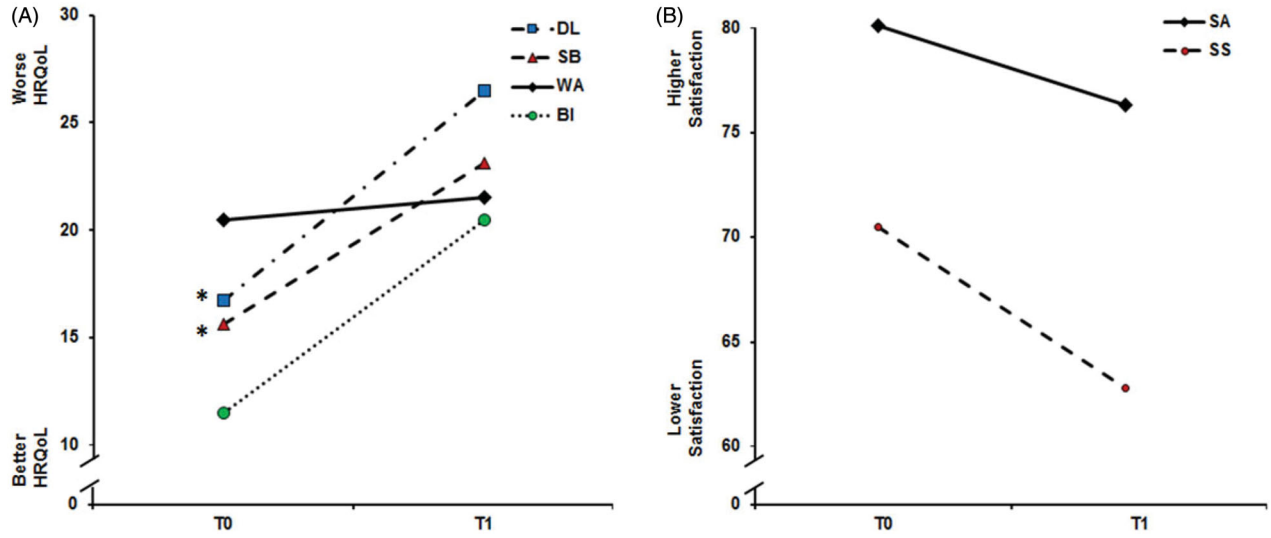

Figure 1. Responsiveness to change of EORTC QLQ-CML24 scales by clinically meaningful deterioration in the EORTC QLQ-C30 global health status/quality of life scale. SB: symptom burden; WA: impact on worry/mood; DL: impact on daily life; BI: body image problems; SA: satisfaction with care and information; SS: satisfaction with social life; HRQOL: health related quality of life. *$p<.05$. Twenty-six out of 120 patients reached a clinically meaningful deterioration in the EORTC QLQ-C30 global health status/quality of life scale.

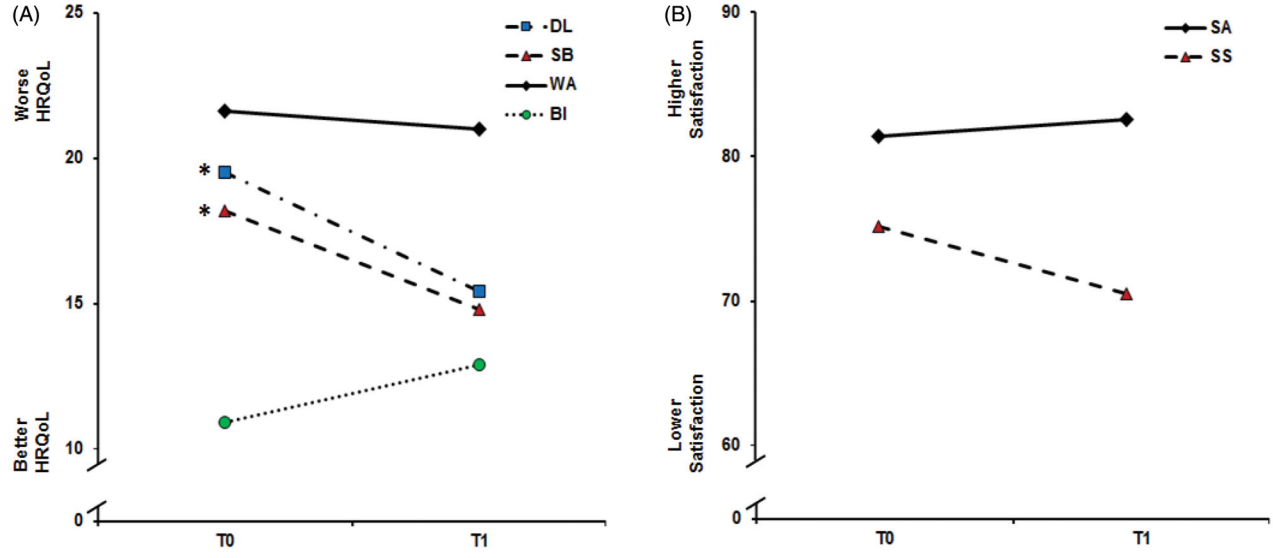

Figure 2. Responsiveness to change of EORTC QLQ-CML24 scales by clinically meaningful improvement in the EORTC QLQ-C30 global health status/quality of life scale. SB: symptom burden; WA: impact on worry/mood; DL: impact on daily life; BI: body image problems; SA: satisfaction with care and information; SS: satisfaction with social life; HRQOL: health related quality of life. *$p<.05$. Forty-four out of 120 patients reached a clinically meaningful improvement in the EORTC QLQ-C30 global health status/quality of life scale.

is meant to be used in conjunction with the EORTC QLQ-C30, to assess HRQOL in patients with CML.

Considering also previous initial validation steps [18], the development of this questionnaire was based on more than 1400 unique patients, mainly from Europe, enrolled across 73 centers. Current findings build on previous phases, which were mainly focused on items generation and questionnaire scale structure definition [18], and corroborate the robustness of its psychometric properties.

Factor analysis confirmed the hypothesized structure and fit indices were high. Overall, its scales' reliability, validity, and sensitivity to change were good and there were also very few missing values, indicating high acceptance from the patients' perspective. Readability and use of plain-language in PRO

Table 4. EORTC QLQ-C30 reference values by age and sex.

	Men				Women			
Scales	All $N = 425$ *M* (SD)	18–44 years $N = 91$ *M* (SD)	45–64 years $N = 154$ *M* (SD)	≥65 years $N = 180$ *M* (SD)	All $N = 352$ *M* (SD)	18–44 years $N = 40$ *M* (SD)	45–64 years $N = 156$ *M* (SD)	≥65 years $N = 156$ *M* (SD)
(A) Functional scales and global QoL								
Physical functioning (PF)	83.6 (19.9)	93.9 (9.8)	87.8 (16.1)	74.8 (22.8)	79.1 (20.0)	89.3 (14.1)	82.5 (17.9)	73.1 (21.5)
Role functioning (RF)	83.3 (25.5)	92.7 (13.2)	83.6 (24.0)	78.3 (29.8)	77.7 (26.5)	86.3 (19.9)	79.5 (25.1)	73.6 (28.8)
Emotional functioning (EF)	84.6 (20.9)	87.6 (17.5)	85.0 (20.8)	82.7 (22.4)	79.5 (22.5)	84.2 (20.2)	80.4 (23.5)	77.5 (22.1)
Cognitive functioning (CF)	83.8 (18.8)	84.3 (17.1)	84.8 (18.7)	82.7 (19.7)	79.5 (21.1)	83.1 (17.0)	79.2 (22.1)	78.9 (21.1)
Social functioning (SF)	88.3 (19.2)	93.4 (10.8)	88.0 (19.3)	86 (21.8)	83.7 (22.7)	92.1 (13.6)	83.4 (21.4)	81.7 (25.4)
Global QoL (QoL)	72.1 (20.3)	78.6 (17.1)	73.4 (19.0)	67.7 (21.8)	67.9 (21.0)	74.2 (16.8)	68.8 (21.1)	65.3 (21.6)
(B) Symptom scales								
Fatigue (FA)	28.0 (24.4)	22.0 (18.5)	26.0 (23.5)	32.9 (26.9)	35.2 (24.4)	31.7 (24.3)	33.5 (22.4)	37.9 (26.3)
Nausea/vomiting (NV)	6.2 (13.0)	6.2 (11.3)	4.4 (10.1)	7.7 (15.7)	9.4 (18.5)	9.2 (13.6)	7.1 (13.3)	11.8 (23.3)
Pain (PA)	16.0 (21.9)	10.6 (17.0)	16.6 (22.6)	18.3 (23.1)	19.7 (25.1)	9.6 (13.0)	16.4 (23.9)	25.6 (27.2)
Dyspnea (DY)	17.0 (24.6)	11.7 (19.5)	14.2 (21.2)	22.2 (28.5)	22.3 (26.5)	14.2 (19.8)	18.4 (24.0	28.3 (29.1)
Sleep disturbances (SL)	19.2 (27.7)	12.8 (23.7)	17.1 (24.8)	24.2 (31.0)	25.7 (29.0)	15.8 (23.9)	23.9 (27.8)	30.1 (30.7)
Appetite loss (AP)	10.2 (22.9)	5.5 (16.7)	6.3 (18.6)	16 (27.5)	12.3 (24.5)	7.5 (19.2)	8.8 (20.1)	17.1 (28.7)
Constipation (CO)	9.9 (19.3)	5.9 (13.7)	7.8 (18.2)	13.6 (22.0)	14.3 (23.7)	7.5 (16.0)	12.1 (24.4)	18.3 (24.3)
Diarrhea (DI)	12.0 (22.4)	8.4 (17.6)	12.6 (22.9)	13.2 (24.1)	13.0 (22.3)	13.3 (22.4)	12.4 (21.3)	13.4 (23.3)
Financial problems (FI)	9.8 (22.6)	15.4 (28.2)	10.7 (23.5)	6.3 (17.5)	10.2 (21.4)	8.3 (18.1)	10.1 (22.3)	10.8 (21.5)

M: mean; SD: standard deviation; QoL: quality of life.
A higher score in functional scales and global QoL reflects better outcomes, while a higher score on symptom scales reflect higher symptom severity.

Table 5. EORTC QLQ-CML24 reference values by age and sex.

	Men				Women			
Scales	All $N = 425$ *M* (SD)	18–44 years $N = 91$ *M* (SD)	45–64 years $N = 154$ *M* (SD)	≥65 years $N = 180$ *M* (SD)	All $N = 352$ *M* (SD)	18–44 years $N = 40$ *M* (SD)	45–64 years $N = 156$ *M* (SD)	≥65 years $N = 156$ *M* (SD)
Symptom burden (SB)	19.6 (15.0)	15.0 (12.8)	19.0 (15.8)	22.6 (14.8)	23.8 (15.8)	18.0 (11.1)	23.3 (15.0)	25.9 (17.3)
Impact on worry/mood (WA)	19.8 (17.5)	18.8 (15.2)	18.9 (17.4)	21.0 (18.6)	23.7 (19.8)	22.3 (17.1)	22.9 (19.3)	25.0 (21.0)
Impact on daily life (DL)	20.3 (20.7)	15.5 (16.6)	17.9 (19.1)	24.9 (22.9)	23.5 (22.1)	23.1 (17.7)	22.2 (21.0)	24.9 (24.1)
Body image problems (BI)	16.3 (25.4)	12.7 (24.4)	13.7 (23.1)	20.3 (27.3)	21.8 (29.1)	15.8 (22.6)	20.1 (29.1)	25.1 (30.2)
Satisfaction with care and information (SA)	80.8 (22.6)	79.2 (22.4)	85.2 (19.1)	77.9 (24.8)	77.9 (25.3)	79.6 (22.5)	79.9 (25.7)	75.4 (25.4)
Satisfaction with social life (SS)	69.4 (27.1)	73.5 (24.3)	73.4 (25.2)	63.9 (29.0)	64.6 (29.0)	72.5 (26.0)	65.1 (29.2)	62.0 (29.3)

M: mean; SD: standard deviation.
A higher score in SB, WA, DL, and BI scales reflects a larger impairment in the corresponding domain, while a higher score on the SA and SS scales reflects a higher level of satisfaction.

questionnaires in oncology is important to enhance their value and impact on real-ward practice [39] and, in this regard, we observe that our validation sample mainly consisted of lower educated patients (i.e. more than 70% had up to a high-school degree).

While a large body of knowledge is available on safety and clinical efficacy of current CML therapies, little is known on patients' HRQOL [13], and this may partly be related to the lack of available disease-specific PRO measures.

The EORTC QLQ-C30, either used alone or in conjunction with the EORTC QLQ-CML24, have been used in a number of studies [15,31,40,41] and the establishment of CML specific reference values stemming from our analysis, will help interpretation of findings in future research using these questionnaires. Interpretation of HRQOL results is often challenging and the availability of age and sex-specific benchmark data are important to better contextualize findings from clinical studies. We observed that male patients reported better outcomes than female patients across all scales of both EORTC questionnaires and this finding is in line with previous evidence using other PRO measures, which indicated better HRQOL profiles in male CML patients compared to women [22,42]. These data are in keeping with a recent large HRQOL study on the general population, which indicated that men tended to report better outcomes compared to women, in various health domains of the EORTC QLQ-C30 questionnaire [29].

With regard to CML disease specific aspects, we found large differences in *satisfaction with social life* favoring younger (18–44 years) versus older patients (≥65 years), and this finding was consistent both in men and women. Conversely, differences in age groups with regard to *impact on daily life* were only evident in men with negligible differences among age group categories in women, and this finding begs for more research in future studies.

Implementation of the EORTC QLQ-CML24 questionnaire is envisaged both in clinical research and routine practice settings. In the former case, for example, it can provide unique PRO information to better balance clinical efficacy and (physician-reported) toxicity data. However, it should be observed that selection of the most appropriate PRO measure in clinical research, always depends on the specific research question and other aspects related to the logistic of the study. For example, as in some studies including CML patients, investigators may only be interested in examining symptom burden, rather than more general aspects regarding the impact of the disease and therapy on patients' life, the use of multidomain HRQOL questionnaires might not be the preferred option.

In the latter case (i.e. routine practice settings), the systematic use of the QLQ-CML24 might improve a timely recognition of key symptoms or other health concerns, which might otherwise get unrecognized by physicians [43] with several negative implications for disease management. Considering the chronic nature of current oral TKI therapies, which are typically administered on a daily basis, prompt recognition, and appropriate management of even low-grade side effects, becomes critical to facilitate optimal medication-taking behavior and in turn maximize response to therapy [16,17]. There is convincing evidence on the clinical value of using PRO measures in clinical practice of patients with solid tumors, for example, improving patient–clinician communication or symptom management [44], therefore, laying the groundwork for future implementation of PRO measures in CML routine care. Recent initiatives, well illustrate the importance of using PRO data in real-life in order to improve patient-centered care for CML patients [45].

Our study has limitations. Although we expected to find an HRQOL improvement at the obtainment of CCyR, this was not the case. One possible reason is that current HRQOL improvements with modern targeted therapies, already occur in the early phase of treatment (i.e. even before reaching a CCyR) [46], therefore, making it difficult to demonstrate further HRQOL improvements after a clinical response. However, analysis of clinically meaningful deteriorations and improvements over time in global health status, revealed changes in QLQ-CML24 scales in the expected directions, therefore supporting its sensitivity. Also, despite we included several countries, the majority of patients were from Italy and the Netherlands and, therefore, a larger representation of patients from other countries in future works is needed to strengthen its use in international studies.

This analysis also has key strengths. First, patients were enrolled across more than 50 centers, therefore, lending further credit to generalizability of findings to the larger CML population seen in daily practice. Also, the large sample size allowed to generate disease specific reference values, that will help to better contextualize HRQOL results of future CML studies an interpretation of scores in individual patients.

In conclusion, as HRQOL has become a critical issue in the current CML arena, disease specific PRO measures, such as the EORTC QLQ-CML24, could contribute to generate unique data to improve healthcare delivery in CML patients.

Acknowledgements

The authors thank Kathrin Sommer from the GIMEMA Data Center, Rome, Italy. The authors acknowledge the essential contribution of all patients who participated in this study.

Disclosure statement

AI: Speaker honoraria: Novartis, Pfizer, and Incyte, outside the submitted work. CE: advisory board Novartis e Pfizer, outside the submitted work. EA: consultancy for BMS, Incyte, Novartis, Pfizer, outside the submitted work. FCa: Consultancy: Novartis, Incyte, Pfizer, BMS; Honoraria: Novartis, Incyte, Pfizer, BMS, outside the submitted work. FE: Consultancy: BMS, Amgen, Orsenix, Takeda and research grant (to his Institution) from Amgen, outside the submitted work. FE, also declares a grant by the EORTC Quality of Life Group (to his Institution) for the conduct of this study. FSt: Honoraria: BMS, Incyte, Novartis, Pfizer, outside the submitted work. GR: speaker honoraria: Novartis, Pfizer, Incyte. Research grant (to his institution): Novartis, Pfizer, Incyte, outside the submitted work. MBa: Honararia: Novartis, Incyte, Takeda, Fusion Pharma; consultancy: Novartis, Incyte, Takeda, Fusion Pharma, outside the submitted work. MBo: Novartis (research support and honoraria), Pfizer (honoraria), Incyte (honoraria), Amgen (honoraria), outside the submitted work. MBr: Honoraria by Novartis, Pfizer, Incyte, Celgene, outside the submitted work. MV: personal fees from Jazz Healthcare Italy SRL, Amgen, Millennium Pharmaceuticals Inc., Celgene, Janssen, Novartis and Incyte, outside the submitted work. SS: Honoraria: BMS, Incyte, Novartis, Pfizer; Research support: BMS, Incyte, Novartis, outside the submitted work. FA: Honoraria by Incyte, Novartis, outside the submitted work; VK: honorarium for advisory board for Novartis and Pfizer, outside the submitted work.

Funding

This study was partly supported by a research grant from the EORTC Quality of Life Group, grant number 004/2015.

ORCID

Andrea Patriarca http://orcid.org/0000-0003-4415-2906
Fabio Stagno http://orcid.org/0000-0002-7947-158X
Geneviève Ector http://orcid.org/0000-0002-1558-944X
Nicole M. A. Blijlevens http://orcid.org/0000-0002-1801-2072
Massimo Breccia http://orcid.org/0000-0003-1163-6162
Francesco Albano http://orcid.org/0000-0001-7926-6052
Federica Sorà http://orcid.org/0000-0002-9607-5298

References

[1] Bjorkholm M, Ohm L, Eloranta S, et al. Success story of targeted therapy in chronic myeloid leukemia: a population-based study of patients diagnosed in Sweden from 1973 to 2008. J Clin Oncol. 2011;29(18):2514–2520.
[2] Hochhaus A, Breccia M, Saglio G, et al. Expert opinion—management of chronic myeloid leukemia after resistance to second-generation tyrosine kinase inhibitors. Leukemia. 2020;34(6):1495–1502.
[3] Bower H, Bjorkholm M, Dickman PW, et al. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. J Clin Oncol. 2016;34(24):2851–2857.
[4] Hochhaus A, Larson RA, Guilhot F, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med. 2017;376(10):917–927.
[5] Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010;362(24):2251–2259.
[6] Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010;362(24):2260–2270.
[7] Cortes JE, Kim DW, Kantarjian HM, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. J Clin Oncol. 2012;30(28):3486–3492.
[8] Rosti G, Castagnetti F, Gugliotta G, et al. Tyrosine kinase inhibitors in chronic myeloid leukaemia: which, when, for whom? Nat Rev Clin Oncol. 2017;14(3):141–154.
[9] Radich JP, Deininger M, Abboud CN, et al. Chronic myeloid leukemia, version 1.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16(9):1108–1135.
[10] Efficace F, Baccarani M, Breccia M, et al. Chronic fatigue is the most important factor limiting health-related quality of life of chronic myeloid leukemia patients treated with imatinib. Leukemia. 2013;27(7):1511–1519.
[11] Pinilla-Ibarz J, Cortes J, Mauro MJ. Intolerance to tyrosine kinase inhibitors in chronic myeloid leukemia: definitions and clinical implications. Cancer. 2011;117(4):688–697.
[12] Guerin A, Chen L, Ionescu-Ittu R, et al. Impact of low-grade adverse events on health-related quality of life in adult patients receiving imatinib or nilotinib for newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase. Curr Med Res Opin. 2014;30(11):2317–2328.
[13] Efficace F, Cannella L. The value of quality of life assessment in chronic myeloid leukemia patients receiving tyrosine kinase inhibitors. Hematology Am Soc Hematol Educ Program. 2016;2016(1):170–179.
[14] Noens L, Hensen M, Kucmin-Bemelmans I, et al. Measurement of adherence to BCR-ABL inhibitor therapy in chronic myeloid leukemia: current situation and future challenges. Haematologica. 2014;99(3):437–447.
[15] Unnikrishnan R, Veeraiah S, Mani S, et al. Comprehensive evaluation of adherence to therapy, its associations, and its implications in patients with chronic myeloid leukemia receiving imatinib. Clin Lymphoma Myeloma Leuk. 2016;16(6):366–371e3.
[16] 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(22):5401–5411.
[17] 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(14):2381–2388.
[18] Efficace F, Baccarani M, Breccia M, et al. International development of an EORTC questionnaire for assessing health-related quality of life in chronic myeloid leukemia patients: the EORTC QLQ-CML24. Qual Life Res. 2014;23(3):825–836.
[19] 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(5):365–376.
[20] Bacik J, Mazumdar M, Murphy BA, et al. The Functional Assessment of Cancer Therapy-BRM (FACT-BRM): a new tool for the assessment of quality of life in patients treated with biologic response modifiers. Qual Life Res. 2004;13(1):137–154.
[21] Cella D, Jensen SE, Webster K, et al. Measuring health-related quality of life in leukemia: the functional assessment of cancer therapy-leukemia (FACT-Leu) questionnaire. Value Health. 2012;15(8):1051–1058.
[22] Hahn EA, Glendenning GA, Sorensen MV, et al. Quality of life in patients with newly diagnosed chronic phase chronic myeloid leukemia on imatinib versus interferon alfa plus low-dose cytarabine: results from the IRIS Study. J Clin Oncol. 2003;21(11):2138–2146.
[23] Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Patient-reported outcomes in the phase 3 BFORE trial of bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia. J Cancer Res Clin Oncol. 2019;145(6):1589–1599.
[24] Williams LA, Gonzalez AG, Ault P, et al. Measuring the symptom burden associated with the treatment of chronic myeloid leukemia. Blood. 2013;122(5):641–647.

[25] Cortes JE, Lipton JH, Miller CB, et al. Evaluating the impact of a switch to nilotinib on imatinib-related chronic low-grade adverse events in patients with CML-CP: the ENRICH study. Clin Lymphoma Myeloma Leuk. 2016;16(5):286–296.
[26] Efficace F, Cocks K, Breccia M, et al. Time for a new era in the evaluation of targeted therapies for patients with chronic myeloid leukemia: inclusion of quality of life and other patient-reported outcomes. Crit Rev Oncol Hematol. 2012;81(2):123–135.
[27] US Food and Drug Administration. Patient-focused drug development: collecting comprehensive and representative input. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders; 2020; [cited 2020 Sep 15]. Available from: https://www.fda.gov/media/139088/download
[28] US Food and Drug Administration. Principles for selecting, developing, modifying, and adapting patient-reported outcome instruments for use in medical device evaluation. Draft Guidance for Industry and Food and Drug Administration Staff, and other Stakeholders; 2020; [cited 2020 Sep 15]. Available from: https://www.fda.gov/media/141565/download
[29] Nolte S, Liegl G, Petersen MA, et al. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. Eur J Cancer. 2019;107:153–163.
[30] Dewolf L, Koller M, Velikova G, et al. EORTC quality of life group translation procedure. 3rd ed. EORTC Quality of Life Group Publication, Brussels; 2009. (ISBN 978-2-930064-38-3).
[31] Efficace F, Stagno F, Iurlo A, et al. Health-related quality of life of newly diagnosed chronic myeloid leukemia patients treated with first-line dasatinib versus imatinib therapy. Leukemia. 2020;34(2):488–498.
[32] Cronbach LJ, Warrington WG. Time-limit tests: estimating their reliability and degree of speeding. Psychometrika. 1951;16(2):167–188.
[33] Nunnally JC. Psychometric theory. 3rd ed. New York: McGraw-Hill; 1994.
[34] Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull. 1979;86(2):420–428.
[35] Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med. 2016;15(2):155–163.
[36] Hu L-t, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct Eq Model. 1999;6(1):1–55.
[37] Schermelleh-Engel K, Moosbrugger H, Müller H. Evaluating the fit of structural equation models: tests of significance and descriptive goodness-of-fit measures. Methods Psychol Res. 2003;8(2):23–74.
[38] Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Eur J Cancer. 2012;48(11):1713–1721.
[39] Papadakos JK, Charow RC, Papadakos CJ, et al. Evaluating cancer patient-reported outcome measures: readability and implications for clinical use. Cancer. 2019;125(8):1350–1356.
[40] Sacha T, Gora-Tybor J, Wasak-Szulkowska E, et al. 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. Clin Lymphoma Myeloma Leuk. 2017;17(5):283–295.
[41] Tan BK, Chua SS, Chen LC, et al. Efficacy of a medication management service in improving adherence to tyrosine kinase inhibitors and clinical outcomes of patients with chronic myeloid leukaemia: a randomised controlled trial. Support Care Cancer. 2020;28(7):3249–3249.
[42] 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(17):4554–4560.
[43] Efficace F, Rosti G, Aaronson N, et al. Patient- versus physician-reporting of symptoms and health status in chronic myeloid leukemia. Haematologica. 2014;99(4):788–793.
[44] Basch E, Barbera L, Kerrigan CL, et al. Implementation of patient-reported outcomes in routine medical care. Am Soc Clin Oncol Educ Book. 2018;38:122–134.
[45] Ector GI, Westerweel PE, Hermens RP, et al. The development of a web-based, patient-centered intervention for patients with chronic myeloid leukemia (CMyLife): design thinking development approach. J Med Internet Res. 2020;22(5):e15895.
[46] Efficace F, Castagnetti F, Martino B, et al. Health-related quality of life in patients with chronic myeloid leukemia receiving first-line therapy with nilotinib. Cancer. 2018;124(10):2228–2237.