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Variables associated with patient-reported symptoms in persons with chronic phase chronic myeloid leukemia receiving tyrosine kinase inhibitor therapy

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Abstract

Purpose: The aim of this study was to evaluate the variables associated with patient-reported symptoms and the impact of symptoms on health-related quality-of-life (HRQoL) in patients with chronic myeloid leukemia (CML) receiving tyrosine kinase inhibitors (TKIs).

Methods: Anonymous Chinese-language questionnaires were distributed to adults with chronic-phase CML (CML-CP) receiving TKIs therapy >3 months regarding symptoms' incidence, severity, and HRQoL. The multivariate cumulative logistic regression model was built to identify variables associated with the symptoms. General Linear Model was used to model the relationship between symptoms and HRQoL using stepwise-forward algorithm.

Results: A total of 1142 respondents were included in this study. The top 10 common TKI-related symptoms were fatigue, periorbital and lower limb edema, chest distress and shortness of breath, memory deterioration, skin color change, alopecia, muscle cramp, weight gain and musculoskeletal pain, and itchy skin. One hundred forty-one (50%) females ≤50 years reported menstrual disorders. Female, married, therapy duration 1 to 3 years, and foreign generic TKIs were associated with increased symptoms' frequency and severity. In contrast, receiving nilotinib or dasatinib, and achieving a complete cytogenetic response but not complete molecular response were associated with fewer and milder symptoms. Chest distress and shortness of breath and loss of appetite were associated with both lower physical component summary (PCS) and mental component summary (MCS) scores; fatigue, musculoskeletal pain, dizziness and abdominal pain, were associated with lower PCS score; anxiety-depression, was associated with lower MCS score in multivariate analyses.

Conclusions: Demographic and social variables, type of TKI-therapy, therapy duration, and depth of response were associated with patient-reported symptoms in persons with chronic phase CML. Certain symptoms have adverse impact on HRQoL.

Abbreviations: HRQoL = health-related quality-of-life, CML = chronic myeloid leukaemia, CP = chronic phase, TKI = tyrosine kinase inhibitor, PCS = lower physical component summary, MCS = mental component summary, CCyR = complete cytogenetic response, CMR = complete molecular response, SF-36 = medical Outcomes Study 36-Item Short-Form Health Survey, OR = odd ratio.

Keywords: chronic myeloid leukemia, chronic phase, tyrosine kinase inhibitor, patient-reported symptom, health-related quality-of-life

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1. Introduction

Many persons with chronic phase chronic myeloid leukemia (CML-CP) treated with tyrosine kinase inhibitors (TKIs) have a normal life-span.[1–4] However, most persons experience ≥1 therapy-related adverse events during their therapy which are important because they decrease therapy adherence and satisfaction resulting in poor outcomes.[5,6] The adverse events might be related to many factors, including polymorphism in genes and downstream that affect TKI movement and metabolism.[7–9] Studies of these issues in other cancers report physicians often underestimate prevalence and severity of patients' symptom.[10–12] The GIMEMA and EORTC Quality of Life Group reported persons with CML value some issues related to symptoms much higher than their physicians.[13] We also found persons with CML-CP are more concerned with TKI-related adverse events than their physicians.[14] For physicians treating persons with CML-CP identifying and relieving patients' symptom burden is important.

Physician-based reports of frequency and severity of TKI-related symptoms vary considerably.[4,15–23] Data on patient-reported symptoms were mostly concerned with the occurrence of TKI-related symptoms.[13,24–26] We performed a cross-sectional study where we directly queried persons with CML-CP regarding symptoms' incidence and severity they were experiencing on the current TKI, focused on analyzing the variables associated with symptoms and the impact of symptoms on their health-related quality-of-life (HRQoL).

2. Methods

2.1. Study population and methods

An anonymous Chinese-language questionnaire (See Supplemental Content 1, http://links.lww.com/MD/D399 and 2, http://links.lww.com/MD/D400 which demonstrated the Questionnaire of English-language version) was designed by Qian Jiang with a reading comprehension level of grade 10. New Sunshine Charity Foundation, a Chinese CML patient advocacy organization, helped the authors distribute and collect the questionnaires. The survey was available as a link on the New Sunshine Charity Foundation website with a paragraph outlining objectives and inclusion criteria of the study. Printed copies of the survey were also distributed at patient advocacy meetings, education conferences in the large- and middle-size cities and at the outpatient clinic at Peking University People's Hospital. Chinese (mostly Han) ≥18 years with CML-CP receiving TKI-therapy >3 months were eligible. The study protocol was approved by the Ethics Committee of Peking University People's Hospital.

The survey was conducted from September 2015 to September 2016. The multiple-choice questionnaire consisted of 3 dimensions (See Supplemental Content 1, http://links.lww.com/MD/D399 and 2, http://links.lww.com/MD/D400 which demonstrated the Questionnaire). The first included 22 questions assessing demographics (age, sex, household registration [urban or rural], and education level), CML-related data (date of diagnosis, disease phase), TKI-therapy, specific TKI, interval from diagnosis to starting TKI, therapy-duration, response (complete cytogenetic response [CCyR; Y/N], and/or complete molecular response [CMR; Y/N], *BCR-ABL1*-negative, Y/N), annual out-of-pocket expense for TKIs, satisfaction with therapy, impact of TKI-therapy on daily life and work and 16 common issues related to TKI-therapies such as cost and reimbursement. The second dimension including 37 common TKI-therapy-related symptoms specified that patients should report their current symptoms while completing the questionnaire, that is, the symptoms related to the current TKI used. Each symptom was ranked none, mild, moderate, and severe. Because there were no questionnaires of general leukemia and CML-specific patient-reported symptoms in Chinese version, we designed a questionnaire including 37 common symptoms reported by Chinese CML patients receiving TKI-therapy, which included all important symptoms in the MDASI-CML and the EORTC QLQ-C24. The third dimension was HRQoL measured by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). The SF-36 is a well-established generic HRQoL measure with a questionnaire consisting of 36 items yielding 8 scales: physical functioning, role limitation due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The 8 subscales are grouped to form 2 summary measures: the physical component summary (PCS) and the mental component summary (MCS). Higher scores represent better health outcomes. We focused on the TKI-therapy-related symptoms and their impact on HRQoL.

2.2. Statistical analyses

Descriptive analysis results are presented as median (range) or number (percent) as appropriate. Pearson χ^2 (for categorical variables) and Mann-Whitney *U*/Kruskal-Wallis tests (for continuous variables) were used to measure between-group differences. Univariate analyses were done to determine variable significantly associated with subjects' symptoms. Variables associated at a level of $P < .20$ were included in the multivariate cumulative logistic regression model built to identify variables associated with the symptoms. General Linear Model was used to model the relationship between symptoms and HRQoL using stepwise-forward algorithm. Factors with an effect significant at $P < .05$ were interpreted as independently predicting outcomes. Analyses were conducted with SAS Version 9.2 software (SAS Institute, Inc, Cary, NC).

3. Results

3.1. Respondent variables

A total of 1708 questionnaires were collected including 442 (26%) from internet respondents and 1266 (78%) from hard copy respondents at patient advocacy meetings, education conferences, and the out-patient clinic at Peking University People's Hospital. Respondents were from 31 provinces and municipalities across China. Questionnaires from 566 (33%) respondents <18 years (N=25), not in the chronic phase (N=75), with TKI-therapy duration <3 months (N=81), never received a TKI (N=9) and had not completed the second dimension of the questionnaire (N=376) were excluded. Data from 1142 valid questionnaires including 308 (27%) from internet respondents and 834 (73%) from hard copy respondents are included in this report.

Subject-, disease-, and therapy-related variables of respondents are presented in Table 1. Seven hundred twenty-four (63%) respondents were male. Median age was 42 years (range 18–88 years). Eight hundred fifty-nine (75%) respondents were receiving imatinib when they completed the questionnaire, 183 nilotinib (16%), and 100 dasatinib (9%). Seven-hundred sixty-one of these

Table 1

Respondent variables (N = 1142).

Variables	N (%)
Male	724 (63%)
Age, y, median (range)	42 (18–88)
18–< 30	253 (22%)
30–< 40	278 (24%)
40–< 50	265 (23%)
50–< 60	213 (19%)
≥60	133 (12%)
Household registration	
Urban	813 (71%)
Rural	329 (29%)
Marital state	
Unmarried	188 (17%)
Married	885 (78%)
Divorced	49 (4%)
Widowed	20 (2%)
Education level	
<Bachelor degree	554 (49%)
≥Bachelor degree	588 (51%)
Co-morbidity (ies)	
None	840 (74%)
Cardiovascular	176 (15%)
Other	126 (11%)
Current TKI used	
Imatinib	859 (75%)
Nilotinib	183 (16%)
Dasatinib	100 (9%)
Current TKI used	
Branded	761 (66%)
Chinese generic	225 (20%)
Foreign generic	156 (14%)
Therapy duration, (median; range; mo)	27 (3-183)
3–< 12	263 (23%)
12–< 36	388 (34%)
36–< 60	222 (19%)
60–< 84	100 (9%)
≥84	169 (15%)
Response	
CMR	472 (41%)
CCyR but no CMR	405 (36%)
No CCyR	265 (23%)

CCyR = complete cytogenetic response, CMR = complete molecular response, TKI = tyrosine kinase-inhibitor.

drugs were branded (66%), 225 Chinese generics (20%), and 156 foreign generics (14%). Eight hundred two (70%) respondents were in first-line therapy, and 340 (30%) were in second-/third-line therapy. Median TKI-therapy duration was 27 months (range 3–183 months). Four hundred seventy-two (41%) respondents reported they achieved a CMR; 405 (36%) CCyR but no CMR; and 265 (23%) no CCyR.

3.2. Patient-reported symptoms

A total of 1114 (97%) respondents reported ≥1 symptom(s). The top 10 common TKI-related symptoms were fatigue (77%), periorbital and lower limb edema (72%), chest distress and shortness of breath (61%), memory deterioration (54%), skin color change (44%), alopecia (44%), muscle cramp (42%), weight gain (42%), musculoskeletal pain (42%), and itchy skin (38%). Ninety-seven (23%) female respondents reported breast pain and/or swelling. Seventy-three (10%) male respondents reported gynecomastia. In female respondents ≤50 years, 17 (6%) reported amenorrhea, 48 (17%) hypermenorrhea, and 76 (27%) hypomenorrhea. Incidence and severity of patient-reported symptoms by TKI used are presented in Figure 1A–C.

3.3. Factors associated with the number of symptoms

Median number of patient-reported symptoms was 10 (range 0–34). Twenty-eight respondents (3%) reported no symptom, 283 reported 1 to 5 symptoms (25%), 278 reported 6 to 10 symptoms (24%), and 553 reported ≥11 symptoms (48%). In multivariate analyses, female sex (odds ratio [OR] = 2.7, 95% confidence interval [CI] [2.0–3.3]; $P < .001$), married persons (OR = 1.9, 95% CI [1.3–2.8]; $P = .002$), divorced persons (OR = 2.5, 95% CI [1.2–5.0]; $P = .010$), therapy duration 1 to 3 years (OR = 1.5, 95% CI [1.1–2.1]; $P = .013$), and foreign generic TKIs (OR = 2.1, 95% CI [1.4–3.0]; $P < .001$) were significantly associated with increased symptoms frequency. In contrast, receiving nilotinib (OR = 0.5, 95% CI [0.4–0.7]; $P < .001$) or dasatinib (OR = 0.5, 95% CI [0.3–0.7]; $P < .001$) compared with imatinib and achieving a CCyR but not a CMR (OR = 0.6, 95% CI [0.5–0.8]; $P < .001$) were significantly associated with decreased symptom frequency.

3.4. Variables associated with the incidence and severity of each symptom

In multivariate analyses of each symptom, female sex (OR = 1.5–2.7; $P = < .001–.007$), urban registration (OR = 1.4–1.6; $P = .004–.023$), having ≥1 co morbidity (OR = 1.4–2.3; $P = < .001–.049$), foreign generic TKIs (OR = 1.5–4.0; $P = < .001–.027$), therapy duration 1 to 3 years (OR = 1.5–2.5; $P = < .001–.048$), and being married (OR = 1.5–2.7; $P = < .001–.021$) or divorced (OR = 2.3–6.5; $P = .007–.005$) were significantly correlated with more frequent and more severe symptoms. In contrast, receiving nilotinib (OR = 0.1–0.7; $P = < .001–.046$) compared with imatinib, achieving a CCyR but no CMR (OR = 0.5–0.8; $P = < .001–.052$) were significantly correlated with less frequent and milder symptoms. Increasing age (reference <30 years) had discordant associations with incidence and severity of certain symptoms such as more common and more severe periorbital and lower limb edema, insomnia, skin bleeding, hair color change, conjunctiva hemorrhage, and or amenorrhea in females ≤50 years (OR = 1.5–3.8; $P < .001–.058$). However, older subjects had less frequent and milder alopecia, weight gain, anxiety-depression, nausea, vomit, diarrhea, decreased sexual desire and breast pain, and/or swelling in females (OR = 0.4–0.7; $P = < .001–.051$). Education level ≥bachelor (OR = 1.4, 95% CI [1.1–1.8]; $P = .004$) was associated with more frequent and more severe skin color change but less frequent and milder weight gain (OR = 0.8, 95% CI [0.6–1.0]; $P = .031$). Variables associated with each symptom in multivariate analyses are displayed in Tables 2 and 3 and see Table, Supplemental Digital Content 3 -Table 1A, http://links.lww.com/MD/D401 and Supplemental Digital Content 4, Table 1B, http://links.lww.com/MD/D402 which illustrates the multivariate analyses in numeric value. No variables were significantly associated with gynecomastia or hypermenorrhea in female ≤50 years. We also compared branded imatinib and dasatinib with Chinese and foreign generics, respectively; the results supported our current conclusion (data not shown).

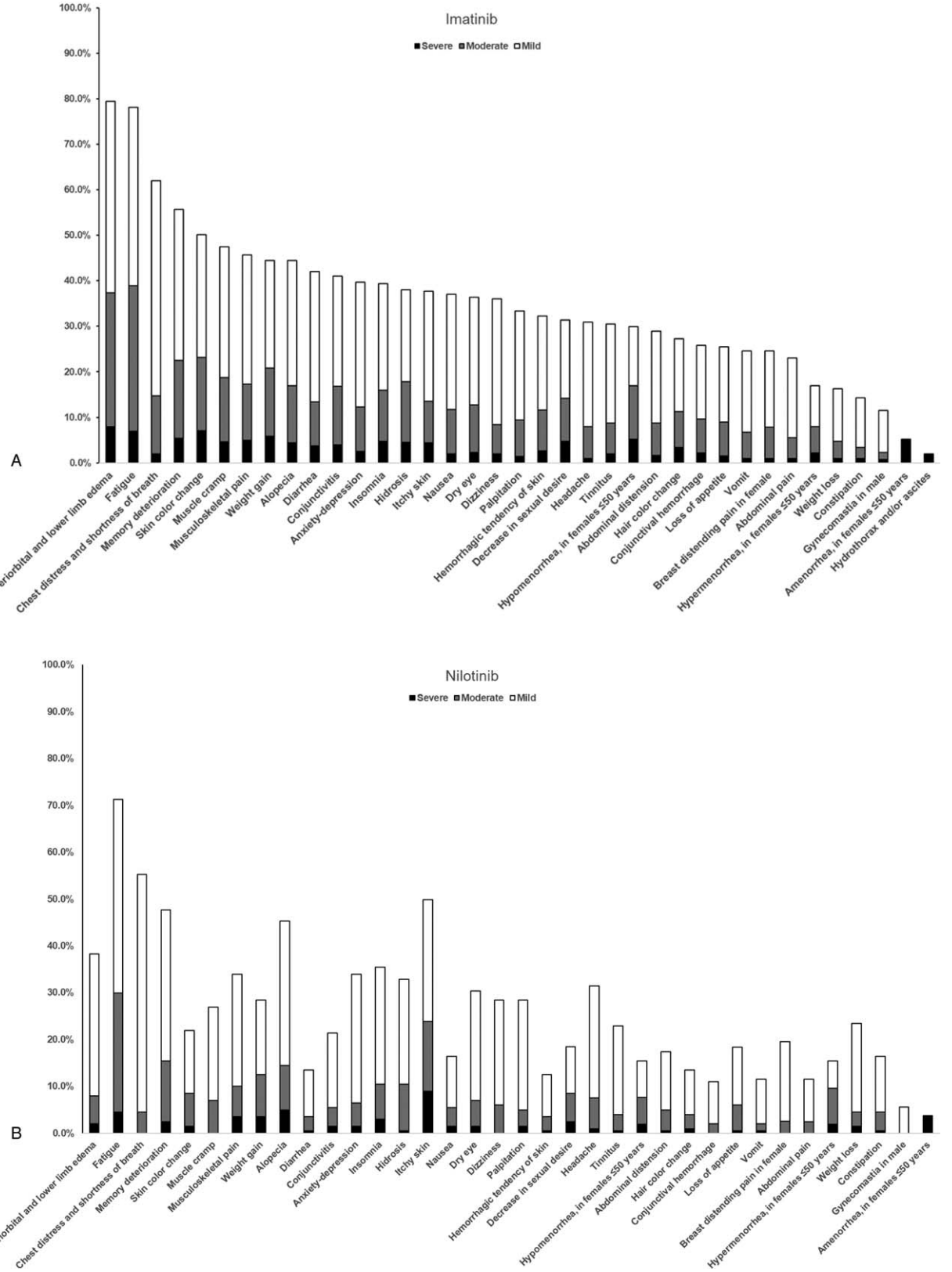

Figure 1. (A) Prevalence and severity of patient-reported symptoms in persons with chronic myeloid leukemia in chronic phase receiving imatinib. (B) Prevalence and severity of patient-reported symptoms in persons with chronic myeloid leukemia in chronic phase receiving nilotinib. (C) Prevalence and severity of patient-reported symptoms in persons with chronic myeloid leukemia in chronic phase receiving dasatinib.

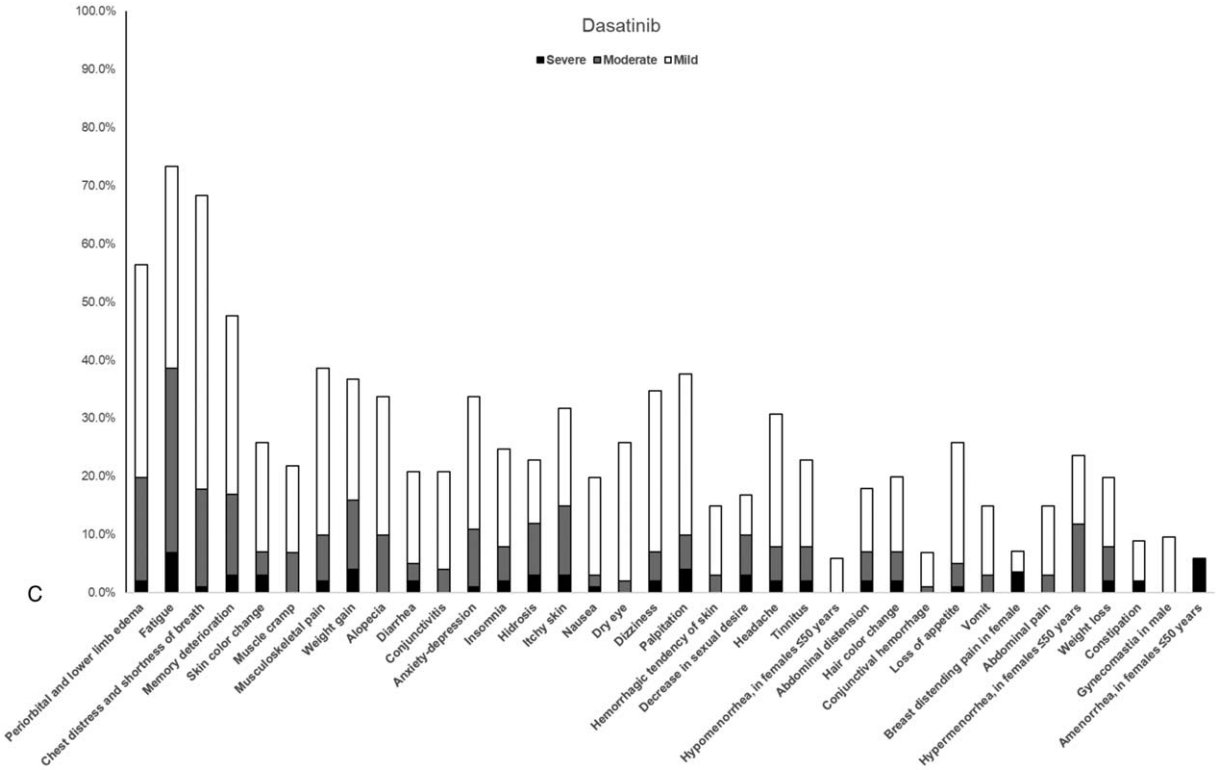

Figure 1. (Continued).

3.5. Symptoms associated with the patients' HRQoL

The mean scores of PCS and MCS were 47.1 (±8.5) and 50.2 (±10.4). After adjusting for age, chest distress and shortness of breath (−2.4, $P < .001$ and −2.1, $P = < .001$) and loss of appetite (−1.6, $P = .005$ and −2.8, $P < .001$) were significantly associated with both lower PCS and MCS scores in multivariate analyses. In addition, fatigue (−2.6, $P < .001$), musculoskeletal pain (−1.7, $P = .001$), dizziness (−1.7, $P = .002$), and abdominal pain (−1.7, $P = .007$) were significantly associated with lower PCS score; anxiety-depression (−7.2, $P < .001$), lower MCS score (Table 4).

4. Discussion

We interrogated prevalence and severity of patient-reported symptoms in patients with CML-CP receiving TKI-therapy. A total of 97% of the respondents reported ≥1 symptom(s) they were experiencing. The top 10 common TKI-related symptoms in our study were fatigue, periorbital or/and lower limb edema, chest distress or/and shortness of breath, memory deterioration, skin color change, alopecia, muscle cramp, weight gain, and musculoskeletal pain. Several demographic, social, and clinical variables were significantly associated with patient-reported symptoms. Female sex, foreign generic TKIs, and therapy duration 1 to 3 years were significantly associated with more frequent and more severe symptoms. Second-generation TKIs and achieving a CCyR but not a CMR correlated with less frequent and milder symptoms.

Patient-reported symptoms in our study were more common than those reported in several clinical trials.[15,18–20,22,23,27] It may due to symptoms reported by patients not assessed by physicians. We suspected some symptoms were not caused by the TKI-therapy but they were the current status of patients' health conditions that came directly from patients, without interpretation by physicians. Efficace et al[13] reported that patients with CML on imatinib therapy concerned more about their symptoms than physicians. Zulbaran-Rojas et al[21] reported that nearly 90% patients on TKI-therapy experienced persistent mild symptoms by 24 months in a prospective study, which was consistent with our findings.

We found that 50% of female respondents ≤50 years reported menstrual disorder including amenorrhea, hypermenorrhea, or hypomenorrhea; hypomenorrhea was significantly associated with foreign generic TKIs; and amenorrhea was associated with age 40-50 years. These data indicate about half of females of reproductive age with CML-CP receiving TKI-therapy have menstrual disorders which were rarely reported in other studies. ABL, KIT, and platelet-derived growth factor receptor are expressed in mammalian ovaries and are important in growth and development of oocytes and follicles.[28] Inhibition of these kinases by TKIs may cause the menstrual abnormalities and accelerate occurrence of amenorrhea in the females.[29] In addition, the possible effects of TKIs on the menstrual bleeding (especially menorrhagia) in our study were not only the endocrinological side-effects, but also the impact of TKI on the platelet function. Because CML is diagnosed at an earlier age in Asians compared with European.[30–35] TKI-related menstrual disorders may be a greater issue in Asian female subjects than elsewhere. Also, nearly 30% of respondents reported decreased sexual desire which may lower quality of life in persons otherwise sexually active. Awareness of these potential TKI-related adverse

Table 2

Demographic and social variables associated with patient-reported symptoms in multivariateanalyses.

Symptom	Female	Increasing age (ref. 18–<30 y)	Urban (ref. rural)	Marital state (ref. unmarried)		≥Bachelor (ref.<bachelor)	Co-morbidity (ref. no)
				Married	Divorced		
Fatigue	>>			>			>
Periorbital and lower limb edema	>>	>a, >>bcd		>			>
Chest distress and shortness of breath	>>			>			
Memory deterioration	>>			>>	>		>
Skin color change	>>					>	
Alopecia	>>	<d					>
Muscle cramp	>>			>>	>		
Weight gain	>>	<c, <<d				<	
Musculoskeletal pain	>>			>>	>		
Pruritis			<	>			>
Anxiety-depression	>>	<bcd					>
Insomnia	>>	>ac					>
Conjunctivitis	>>			>>	>		>>
Diarrhea	>	<d		>			>
Hidrosis							
Pleural effusion and/or ascites							
Dry eye	>>		<	>			>>
Dizziness	>>		>	>			
Palpitation	>>						>
Nausea	>>	<ab, <<cd					
Headache	>>		>	>			
Hypomenorrhea (females ≤50 y)							
Decrease in sexual desire		<cd, <<ab		>			
Tinnitus	>>			>			
Skin hemorrhage	>>	>ab, >>c					
Abdominal distension	>>						
Hair color change	>>	>c, >>ab					
Loss of appetite	>						
Breast pain/swelling (females)		<ad		>			
Hyper-menorrhea (females ≤50 y)							
Conjunctival hemorrhage		>>bcd					>
Emesis	>>	<bc, <<d					
Abdominal pain	>						>
Weight loss							>
Constipation	>>		>				
Amenorrhea (females ≤50 y)		>b					

">" more common and severer symptom, $P < .05$; ">>" more common and more severe symptoms, $P < .001$

"<" fewer and milder symptom, $P < .05$; "<<" fewer and milder symptoms; $P < .001$

a = 30–<40 years, b = 40–<50 years, c = 50–<60 years, d = ≥60 years.

events should help hematologists counsel patients before starting TKI-therapy.

Respondents with higher education level reported more common and more severe skin color during TKI therapy which may negatively impact their social life and daily work. This is consistent with our previous findings that higher education level was associated with more concern on TKI-therapy related issues.[14]

We found respondents receiving Chinese generic TKIs had a similar prevalence and severity of symptoms to those receiving branded TKIs except for some symptoms such as musculoskeletal pain, anxiety-depression, and loss of appetite. However, subjects receiving foreign generic TKIs reported more frequent and more severe symptoms compared with branded TKIs. This may be the result of poor adherence and worse management. Our previous study showed use of generic TKIs was associated with less frequent molecular monitoring.[36]

Respondents who achieved a CMR reported more frequent and more severe symptoms than those achieving only a CCyR. One interpretation of these data is once a patient achieves a CMR their attention shifts from therapy-response issues to quality of life issues. There are several implications of these data. A controversial one is CCyR and not CMR should be the target of TKI-therapy. This is based not only on more frequent reports of similar survival in persons achieving a CCyR and CMR.[3] Another implication is that this increased symptom burden in persons with CMR may motivate physicians and patients to attempt stopping TKI-therapy.[31,37,38]

The most common patient-reported symptoms and variables correlate in our study are similar to previous reports such as fatigue was the most common symptom [21,39], female sex was associated with more frequent and more severe symptoms, and longer therapy duration and 2nd generation TKIs were associated with less frequent and milder symptoms.[15,24,40,41]

Efficace et al[24] assessed HRQoL in CML-CP patients having received imatinib for at least 3 years by SF-36 questionnaire and found fatigue was an independent factor associated with both physical and mental HRQoL and musculoskeletal pain and

Table 3

Tyrosine kinase inhibitor therapy–related variables associated with patient-reported symptoms in multivariate analyses.

Symptom	Therapy duration (ref. 3–<12 mo)	TKI (ref. imatinib)		TKI (ref. branded drugs)		Response to TKI-therapy (ref. CMR)	
		Nilotinib	Dasatinib	Chinese generics	Foreign generics	CCyR but no CMR	No CCyR
Fatigue					>		>
Periorbital and lower limb edema		<	<				
Chest distress and shortness of breath		<				<	
Memory deterioration	>b				>>	<	
Skin color change	>ad	<	<		>>		
Alopecia					>	<	
Muscle cramp	>ad	<	<				
Weight gain	>ac	<			>		
Musculoskeletal pain				>	>	<	
Itchy skin		>>				<	
Anxiety-depression				>	>>	<	
Insomnia			<		>	<	
Conjunctivitis		<	<		>>	<	
Diarrhea	>a	<	<		>	<	
Hidrosis			<		>	<	
Hydrothorax and/or ascites			>>				
Dry eye	>a				>	<	
Dizziness					>	<	
Palpitation		<					>
Nausea	>a	<	<		>		
Headache					>	<	
Hypo-menorrhea (Females ≤50 y)					>>		
Decreased sexual desire		<	<		>	<	
Tinnitus					>	<	
Skin hemorrhage	>ab, >>d	<	<		>		
Abdominal distension		<			>	<	
Hair color change	>a, >>d	<				<	<
Loss of appetite	>a			>	>	<	
Breast pain/swelling (in females)			<			<	
Hyper-menorrhea (in females ≤50 y)							
Conjunctival hemorrhage	>cd	<	<			<	
Vomit	>a	<	<		>	<	
Abdominal pain		<			>	<	
Weight loss						<	
Constipation	<d				>>	<	
Amenorrhea (in females ≤50 y)							

">" more common and severer symptom, $P < .05$; ">>" more common and severer symptom, $P < .001$

"<" fewer and milder symptom, $p < .05$; "<<" fewer and milder symptom, $p < .001$

a = 12–<36 months, b = 36–<60 months, c = 60–<84 months, CCyR = complete cytogenetic response, CMR = complete molecular response, d = ≥84 months, TKI = tyrosine kinase-inhibitor.

muscular cramps were the 2 symptoms mostly correlated with fatigue. Uyanik et al[42] reported CML-CP patients taking imatinib or second-generation TKIs with high anxiety or depression scores had significantly lower cognitive, emotional, social functioning, and global QoL scores assessed by European organization for Research and Treatment in Cancer Quality of Life Questionnaire-C30 (EORTCQLQ-C30). Unnikrishnan et al[43] assessed symptom burden and QoL score in 221 CML-CP patients who were on imatinib for at least 6 months by M.D. Anderson Symptom Inventory specific for CML patients

Table 4

Multivariate analyses of physical and mental component summary.

	Physical component summary		Mental component summary	
	Estimate (SE)	*P*	Estimate (SE)	*P*
Fatigue	−2.6 (0.6)	<.001		
Chest distress and shortness of breath	−2.4 (0.5)	<.001	−2.1 (0.6)	<.001
Musculoskeletal pain	−1.7 (0.5)	.001		
Anxiety-depression			−7.2 (0.6)	<.001
Dizziness	−1.7 (0.6)	.002		
Loss of appetite	−1.6 (0.6)	.006	−2.8 (0.7)	<.001
Abdominal pain	−1.7 (0.6)	.007		

and Cancer Institute Quality of Life II questionnaire. They reported that HRQoL scores were negatively correlated with general and CML-specific symptoms.[43] In our study, we analyzed the relationship between all symptoms the respondents reported and HRQoL assessed by SF-36 questionnaire and found that chest distress and shortness of breath and loss of appetite were significantly-associated with both lower PCS and MCS scores in multivariate analyses. In addition, fatigue, musculoskeletal pain, dizziness, and abdominal pain were significantly associated with lower PCS score, anxiety-depression, and lower MCS score. These findings confirmed that certain symptoms had adverse impact on HRQoL in CML patients on TKI-therapy. Not mentioned in the current Chinese guidelines yet, treatment-free remission was a treatment goal worth pursuing, as symptom burden had been a nonnegligible issue, especially in patients achieving CMR. Stopping TKI could alleviate symptom burden, and perhaps improve patients' HRQoL in the future.

Our study has several limitations. It is impossible to know whether patient-reported symptoms associated with TKI therapy are caused by the TKI, other drugs, or other conditions, physical or psychological, or both. This can only be known with certainty in a randomized double-blind placebo controlled trial. Although the respondents were asked to report the symptoms they were experiencing, those they experienced when they received previous TKI-therapy cannot be excluded. Symptom severity was scored by respondents on a 4-point ordinal scale. Consequently, scoring was subjective and reproducibility untested. However, respondents' perceptions of severity are a valid variable regardless of whether they are quantifiable on an objective scale. Because the survey was available on website, some respondents were self-selected. Typically, these patients are computer competent and pro-active in seeking information and resources. However, we found no substantial difference in results when these subjects were excluded in sensitivity analyses or when we compared responses in subjects completing the questionnaire in hard copy or online. It was also impossible to confirm respondents' age, residence, diagnosis, and therapy or response state of subjects responding online. Because printed questionnaires were distributed at education meetings in large- and middle-size cities and provinces and at Peking University People's Hospital, there could be a selection bias toward respondents with an urban household registration. Response to TKI therapy was queried from respondents but not verified in the medical record. Finally, the associations and correlations we report should not be construed to imply cause-and-effect.

Our data indicate demographic and social variables, type of TKI-therapy, therapy duration, and depth of response are significantly associated with patient-reported symptoms in persons with CML-CP. Certain symptoms have adverse impact on HRQoL. This may help hematologists improve HRQoL of their patients and possibly TKI therapy outcomes.

Author contributions

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References

[1] Bower H, Bjã¶Rkholm 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;34:2851–7.
[2] Hochhaus A, Larson RA, Guilhot F, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med 2017;376:917–27.
[3] Hehlmann R, Lauseker M, Saussele S, et al. Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants. Leukemia 2017;31:2398–406.
[4] Gambacorti-Passerini C, Antolini L, Mahon FX, et al. Multicenter independent assessment of outcomes in chronic myeloid leukemia patients treated with imatinib. J Natl Cancer Inst Apr 6 2011;103:553–61.
[5] Jiang Q, Wang H, Yu L, et al. Higher out-of-pocket expenses for tyrosine kinase-inhibitor therapy is associated with worse health-related quality-of-life in persons with chronic myeloid leukemia. J Cancer Res Clin Oncol 2017;143:1–2.
[6] Bouwman L, Eeltink CM, Visser O, et al. Prevalence and associated factors of medication non-adherence in hematological-oncological patients in their home situation. BMC Cancer 2017;17:739.
[7] Dwivedi P, Muench DE, Wagner M, et al. Time resolved quantitative phospho-tyrosine analysis reveals Bruton's Tyrosine kinase mediated signaling downstream of the mutated granulocyte-colony stimulating factor receptors. Leukemia 2019;33:75–87.
[8] Dwivedi P, Muench DE, Wagner M, et al. Phospho serine and threonine analysis of normal and mutated granulocyte colony stimulating factor receptors. Scientific Data 2019;6:21.
[9] Giannoudis A, Wang L, Jorgensen AL, et al. The hOCT1 SNPs M420del and M408 V alter imatinib uptake and M420del modifies clinical outcome in imatinib-treated chronic myeloid leukemia. Blood 2013;121:628–37.
[10] Mesa RA, Miller CB, Thyne M, et al. Differences in treatment goals and perception of symptom burden between patients with myeloproliferative neoplasms (MPNs) and hematologists/oncologists in the United States: findings from the MPN Landmark survey. Cancer 2017;123:449–58.
[11] Wilson KA, Dowling AJ, Abdolell M, et al. Perception of quality of life by patients, partners and treating physicians. Qual Life Res 2000;9:1041–52.
[12] Steensma DP, Komrokji RS, Stone RM, et al. Disparity in perceptions of disease characteristics, treatment effectiveness, and factors influencing treatment adherence between physicians and patients with myelodysplastic syndromes. Cancer 2014;120:1670–6.
[13] Efficace F, Breccia M, Saussele S, et al. Which health-related quality of life aspects are important to patients with chronic myeloid leukemia receiving targeted therapies and to health care professionals?. GIMEMA and EORTC Quality of Life Group. Ann Hematol 2012;91:1371–81.
[14] Qian J, Lu Y, Gale RP. Patients' and hematologists' concerns regarding tyrosine kinase-inhibitor therapy in chronic myeloid leukemia. J Cancer Res Clin Oncol 2018;144:735–41.
[15] Kalmanti L, Saussele S, Lauseker M, et al. Safety and efficacy of imatinib in CML over a period of 10 years: data from the randomized CML-study IV. Leukemia 2015;29:1123–32.
[16] Guérin 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;30:2317–28.
[17] Larson RA, Druker BJ, Guilhot F, et al. Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: a subanalysis of the IRIS study. Blood 2008;111:4022–8.
[18] Kantarjian HM, Hochhaus A, Saglio G, et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase. Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. Lancet Oncol 2011;12:826–7.
[19] 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;30:3486–92.

[20] Brummendorf TH, Cortes JE, de Souza CA, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia: results from the 24-month follow-up of the BELA trial. Br J Haematol 2015;168:69–81.
[21] Zulbaran-Rojas A, Lin HK, Shi Q, et al. A prospective analysis of symptom burden for patients with chronic myeloid leukemia in chronic phase treated with frontline second- and third-generation tyrosine kinase inhibitors. Cancer Med 2018;7:5457–69.
[22] Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of dasision: the dasatinib versus imatinib study in treatment-naive chronic myeloid leukemia patients trial. J Clin Oncol 2016;34:2333–40.
[23] Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia 2016;30:1044–54.
[24] 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;27:1511–9.
[25] 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 Apr 2014;23:825–36.
[26] Williams LA, Garcia Gonzalez AG, Ault P, et al. Measuring the symptom burden associated with the treatment of chronic myeloid leukemia. Blood 2013;122:641–7.
[27] Kim DW, Saussele S, Williams LA, et al. Outcomes of switching to dasatinib after imatinib-related low-grade adverse events in patients with chronic myeloid leukemia in chronic phase: the DASPERSE study. Ann Hematol 2018;97:1357–67.
[28] Schmandt RE, Broaddus R, Lu KH, et al. Expression of c-ABL, c-KIT, and platelet-derived growth factor receptor-beta in ovarian serous carcinoma and normal ovarian surface epithelium. Cancer 2003;98:758–64.
[29] Christopoulos C, Dimakopoulou V, Rotas E. Primary ovarian insufficiency associated with imatinib therapy. N Engl J Med 2008;358:1079–80.
[30] Jiang Q, Wang HB, Yu L, et al. Variables associated with patient-reported outcomes in persons with chronic myeloid leukemia receiving tyrosine kinase-inhibitor therapy. J Cancer Res Clin Oncol 2017;143: 1013–22.
[31] Jiang Q, Liu ZC, Zhang SX, et al. Young age and high cost are associated with future preference for stopping tyrosine kinase inhibitor therapy in Chinese with chronic myeloid leukemia. J Cancer Res Clin Oncol 2016;142:1539–47.
[32] Hoffmann VS, Baccarani M, Hasford J, et al. The EUTOS population-based registry: incidence and clinical characteristics of 2904 CML patients in 20 European Countries. Leukemia 2015;29:1336–43.
[33] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
[34] Au WY, Caguioa PB, Chuah C, et al. Chronic myeloid leukemia in Asia. Int J Hematol 2009;89:14–23.
[35] Kim DW, Banavali SD, Bunworasate U, et al. Chronic myeloid leukemia in the Asia-Pacific region: current practice, challenges and opportunities in the targeted therapy era. Leuk Res 2010;34:1459–71.
[36] Jiang Q, Gale RP. Molecular monitoring of tyrosine kinase inhibitor therapy of chronic myeloid leukemia in China. J Cancer Res Clin Oncol 2016;142:1549–55.
[37] Hughes TP, Ross DM. Moving treatment-free remission into mainstream clinical practice in CML. Blood 2016;128:17.
[38] Saussele S, Richter J, Hochhaus A, et al. The concept of treatment-free remission in chronic myeloid leukemia. Leukemia 2016;30: 1638–47.
[39] 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.
[40] 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;124:2228–37.
[41] Aziz Z, Iqbal J, Aaqib M, et al. Assessment of quality of life with imatinib mesylate as first-line treatment in chronic phase-chronic myeloid leukemia. Leuk Lymphoma 2011;52:1017–23.
[42] Uyanik MS, Pamuk GE, Maden M, et al. The impact of new generic formulations of imatinib mesylate on general quality of life in chronic phase chronic myeloid leukaemia patients. Eur J Cancer Care (Engl) 2017;26:
[43] Unnikrishnan R, Veeraiah S, Ganesan P. Symptom burden and quality of life issues among patients of chronic myeloid leukemia on long-term imatinib therapy. Indian J Med Paediatr Oncol 2017;38:165–8.