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Fatigue in chronic myeloid leukemia patients on tyrosine kinase inhibitor therapy: predictors and the relationship with physical activity

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ABSTRACT

Fatigue is a common side effect of tyrosine kinase inhibitor (TKI) therapy in patients with chronic myeloid leukemia (CML). However, the prevalence of TKI-induced fatigue remains uncertain and little is known about predictors of fatigue and its relationship with physical activity. In this study, 220 CML patients receiving TKI therapy and 110 gender- and age-matched controls completed an online questionnaire to assess fatigue severity and fatigue predictors (Part 1). In addition, physical activity levels were objectively assessed for 7 consecutive days in 138 severely fatigued and non-fatigued CML patients using an activity monitor (Part 2). We demonstrated that the prevalence of severe fatigue was 55.5% in CML patients and 10.9% in controls ($P < 0.001$). We identified five predictors of fatigue in our CML population: age (odds ratio [OR] 0.96, 95% confidence interval [95% CI]: 0.93-0.99), female gender (OR 1.76, 95% CI: 0.92-3.34), Charlson Comorbidity Index (OR 1.91, 95% CI: 1.16-3.13), the use of comedication known to cause fatigue (OR 3.43, 95% CI: 1.58-7.44), and physical inactivity (OR of moderately active, vigorously active and very vigorously active compared to inactive 0.43 (95% CI: 0.12-1.52), 0.22 (95% CI: 0.06-0.74), and 0.08 (95% CI: 0.02-0.26), respectively). Objective monitoring of activity patterns confirmed that fatigued CML patients performed less physical activity of both light ($P = 0.017$) and moderate to vigorous intensity ($P = 0.009$). In fact, compared to the non-fatigued patients, fatigued CML patients performed 1 hour less of physical activity per day and took 2,000 fewer steps per day. Our findings facilitate the identification of patients at risk of severe fatigue and highlight the importance of setting reduction of fatigue as a treatment goal in CML care. This study was registered at The Netherlands Trial Registry, NTR7308 (Part 1) and NTR7309 (Part 2).

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Introduction

Survival of patients with chronic myeloid leukemia (CML) has improved significantly since the introduction of tyrosine kinase inhibitors (TKI) in 2001. This has translated into a life expectancy that is almost the same as that of the general population.¹ Nevertheless, health-related quality of life (QoL) of CML patients is inferior to that of the general population, which is mainly the result of TKI-induced fatigue.² CML patients require (potentially) lifelong treatment, which results in a persistent trigger for fatigue. Therefore, it is of the utmost importance to focus on prevention and management of fatigue in the care of CML patients. This is further supported by

the finding that adverse events lead to lower TKI treatment adherence³ and therefore to poorer disease control.⁴ Although TKI-induced fatigue is one of the most frequently reported adverse effects,^{5,6} its actual prevalence is unknown because of the heterogeneity in measurement techniques used across studies and it has not been compared to that in the general population. Furthermore, clinicians are unable to identify patients at risk of fatigue since predictors have never been assessed in this specific population of patients. Although a variety of predictors of fatigue, such as gender, age and socioeconomic status have been described in literature,^{7,9} it is unknown whether these predictors, even when obtained in cancer populations, can be extrapolated to this unique group of CML patients on TKI therapy. Aside from these unmodifiable predictors of fatigue, physical activity has been identified as a modifiable predictor of fatigue in several patient populations.¹⁰ The aim of this multicenter observational study was threefold. First, to assess the prevalence of fatigue in CML patients on TKI therapy compared to that in the general population. Second, to identify predictors of fatigue in CML patients. Third, to objectively assess physical activity levels and compare these between fatigued and non-fatigued patients. In this way, we will facilitate the identification of patients at risk of fatigue and provide insight into the association between fatigue and physical activity in the CML population.

Methods

CML patients aged ≥ 18 years who were receiving TKI therapy were invited to complete an online questionnaire to assess the prevalence and predictors of TKI-induced fatigue (Part 1). Control subjects were selected from a database consisting of over 20,000 subjects without CML who participated in previous research at the Department of Physiology at Radboud University Medical Center (Nijmegen, the Netherlands). Controls were matched for gender and age (± 3 years) in a 1:2 ratio to the CML patients. A subgroup of CML patients was asked to wear an activity monitor in order to measure physical activity levels objectively (Part 2). Patients were recruited through the outpatient clinics at the Radboud University Medical Center and Amsterdam University Medical Center (Amsterdam, the Netherlands), and via CMylife, a Dutch online platform for CML patients.¹¹ Informed consent was obtained from all participants. This study was approved by the Medical Review Ethics Committee region Arnhem-Nijmegen and registered at The Netherlands Trial Registry with numbers NTR7308 (Part 1) and NTR7309 (Part 2).

Part 1: questionnaire

Fatigue severity was measured by the Checklist Individual Strength subscale "subjective experience of fatigue" (CIS-fatigue), which is a validated fatigue questionnaire assessing fatigue over the preceding 2 weeks.¹² A score of 35 or above was considered as severe fatigue. The following general characteristics were collected: age, gender, body mass index, education level, and marital status. Time since CML diagnosis, TKI type and dose, duration of TKI treatment, and disease control (major molecular response, defined as $\leq 0.1\%$ BCR-ABL transcripts on the International Scale) were collected to assess CML-related medical history. The Charlson Comorbidity Index (CCI)¹³ was used to quantify participants' medical comorbidities. Both over-the-counter and prescribed medication known to cause fatigue (e.g., benzodiazepines, opioids, β -blockers, and metformin) were assessed. Lastly, potential lifestyle predictors were collected, including smoking, daily fluid and caf-

feine intake, alcohol consumption (beer and wine), and physical activity. Physical activity (defined as Metabolic Equivalent of Task [MET] min/week) was classified into four categories: inactive (< 500 MET min/week), moderately active (500-1,499 MET min/week), vigorously active (1,500-2,999 MET min/week), and very vigorously active ($> 3,000$ MET min/week).

Part 2: activity monitor

Physical activity was measured with the activPAL3 micro (PAL Technologies Ltd., Glasgow, UK)¹⁴ in a subgroup of 143 CML patients. The sample size calculation was based on data from previous research published on differences in objectively assessed activity levels between fatigued and non-fatigued elderly subjects¹⁵ using a power of 80%, with a two-tailed α level of 0.05, an estimated effect size of 0.50 and a drop-out rate of 10%. Participants wore the activity monitor 24 hours per day for 7 consecutive days and were asked to maintain normal daily activities. In addition, employment status and total work time were reported. BCR-ABL transcript levels, hemoglobin concentration, white blood cell count and platelet count were extracted from the patients' electronic records.

Statistical analysis

Continuous data are reported as means \pm standard deviation or median (interquartile range [IQR]) and categorical variables as counts and percentages. Logistic regression was performed to identify predictors of severe fatigue. Predictor variables with P values < 0.10 in univariable analysis were selected for multivariable logistic regression analysis. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated to estimate the effect size. The optimal model was selected based on the discriminative ability, assessed by the area under the receiving operating characteristic curve, and calibration slope. Differences in activity patterns were tested using Student t tests for independent samples when data were normally distributed, and Wilcoxon rank sum tests when data were skewed. To correct for potential confounding factors, multivariable linear regression was used. All data were analyzed using SPSS (version 22.0, IBM, Armonk, NY, USA). Statistical significance was set at a P value < 0.05 .

Detailed information on the questionnaire and activity monitor is provided in the *Online Supplementary Methods S1*.

Results

A total of 357 participants were enrolled in the study, consisting of 247 CML patients and 110 controls. Figure 1 shows a schematic flowchart of participants in the two parts of the study. Two-hundred twenty CML patients (58% females, mean age 56 ± 13 years) and 110 gender- and age-matched controls completed the online questionnaire between May 2018 and May 2019 (Part 1). Of these 220 patients, 216 (98.2%) had no missing data and were included in the multivariable regression analysis. The activity monitor was worn by 143 CML patients, but five patients were excluded from analysis because of an invalid number of days registered by the activity monitor (Part 2).

Part 1: prevalence and predictors of severe fatigue

The prevalence of severe fatigue was 55.5% in the CML patients and 10.9% in the matched controls ($P < 0.001$). Reported QoL was significantly poorer in CML patients than in controls (mean QoL scores 6.9 ± 1.5 and 8.1 ± 1.0 , respectively; $P < 0.001$), and also in severely fatigued CML patients when compared to patients without severe fatigue

(mean QoL 6.1 ± 1.3 and 7.8 ± 1.1 , respectively; $P < 0.001$). Table 1 shows the univariable and multivariable logistic regression analyses of the predictors of severe fatigue in CML patients. The final multivariable model included: age (OR 0.96, 95% CI: 0.93-0.99; $P = 0.004$), female gender (OR 1.76, 95% CI: 0.92-3.34; $P = 0.09$), CCI (OR 1.91, 95% CI: 1.16-3.13; $P = 0.011$), the use of comedication known to cause fatigue (OR 3.43, 95% CI: 1.58-7.44; $P = 0.002$), and physical activity at different intensities compared to physical inactivity, including moderately active (OR 0.43, 95% CI: 0.12-1.52; $P = 0.19$), vigorously active (OR 0.22, 95% CI:

0.06-0.74; $P = 0.014$), and very vigorously $P < 0.001$). The area under the curve of the final model was 0.79 (95% CI: 0.73-0.85) and the calibration slope was 1.01. The predicted severe fatigue and associated observed fatigue are displayed in Figure 2, showing a positive predictive value of 73%, a negative predictive value of 68%, a sensitivity of 76%, and a specificity of 65%. Our model can be described by the following equation: $\log\text{-odds} = 1.98 - 0.04 * \text{age} + 0.56 * \text{gender (male=0, female=1)} + 0.65 * \text{CCI} + 1.23 * \text{use of comedication known to cause fatigue (no=0, yes=1)} - \text{physical activity level (inactivity=0, moderately}$

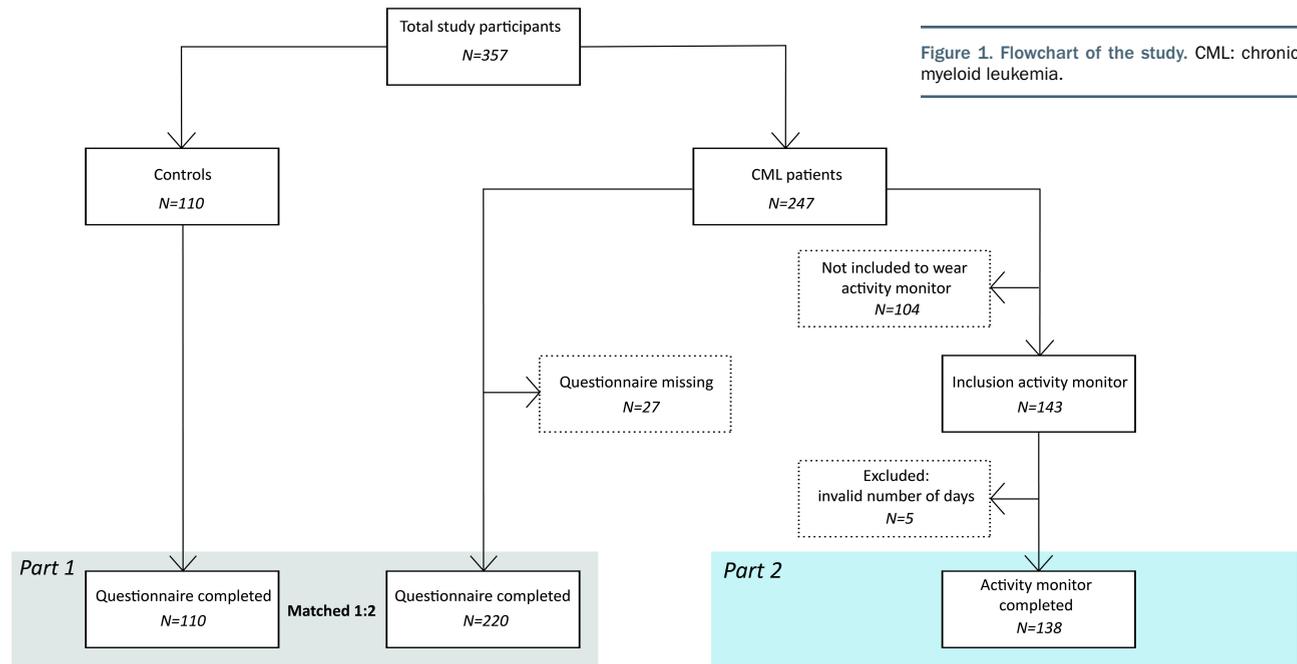


Figure 1. Flowchart of the study. CML: chronic myeloid leukemia.

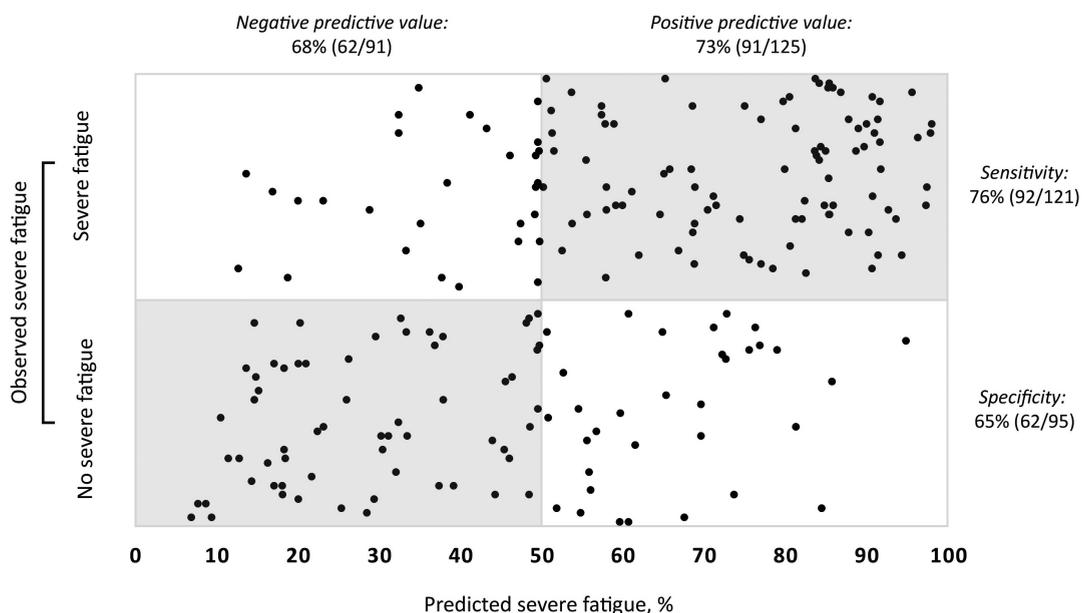


Figure 2. Predicted and observed severe fatigue. The predicted severe fatigue of the multivariable model is plotted against the observed severe fatigue. Each dot represents an individual.

active=0.85, vigorously active=1.53, very vigorously active=2.58).

Part 2: activity patterns in fatigued and non-fatigued patients

Table 2 shows the characteristics, including hematologic values, of the 138 CML patients who wore the activity monitor and were included in the final analysis. In line with the first part of the study, there was a higher propor-

tion of female patients in the severely fatigued group than in the non-fatigued group (61% vs. 44%, respectively; $P=0.039$). The employment status did not differ significantly across the groups (53% vs. 66% employed in the fatigued and non-fatigued groups, respectively; $P=0.20$). However, total work time was significantly shorter in both severely fatigued male and female patients than in non-fatigued patients (males: 29 ± 12 h/week vs. 38 ± 12 h/week, respectively; $P=0.048$; females: 15 ± 8 h/week vs.

Table 1. Univariable and multivariable logistic regression analysis of general characteristics, medical history, and lifestyle factors as potential predictors of severe fatigue in patients with chronic myeloid leukemia.

	Controls (N=110)	CML total (N=220)	Univariable analysis				Multivariable analysis	
			CML + severe fatigue (N=122)	CML + severe fatigue (N=98)	OR (95% CI)	P-value	OR (95% CI)	P-value
General characteristics								
Age, years	56 ± 13	56 ± 13	55 ± 13	58 ± 12	0.98 (0.96-1.00)	0.07	0.96 (0.93-0.99)	0.004
Gender, % female	58	58	66	48	2.14 (1.24-3.70)	0.006	1.76 (0.92-3.34)	0.09
BMI, kg/m ²	25.2 ± 3.9	26.2 ± 4.3	26.5 ± 4.6	25.8 ± 4.0	1.04 (0.98-1.11)	0.24		
Education level, %								
Low	10	14	11	17	REF			
Mediate	36	42	49	34	2.38 (1.03-5.50)	0.043		
High	55	44	40	49	1.34 (0.59-3.05)	0.49		
Marital status, % married	81	83	81	85	0.78 (0.38-1.59)	0.49		
Medical history								
Time since diagnosis, months	NA	64 (27-131)	61 (27-116)	66 (25-140)	1.00 (0.99-1.00)	0.46		
TKI type, %	NA							
Imatinib		38	34	44	REF			
Dasatinib		27	32	21	1.90 (0.96-3.76)	0.07		
Nilotinib		21	19	24	1.05 (0.51-2.15)	0.90		
Bosutinib		9	10	7	1.80 (0.65-5.01)	0.26		
Ponatinib		5	6	4	1.83 (0.50-6.74)	0.36		
TKI dose (mg/day)	NA							
Imatinib		400 (400-400)	400 (400-400)	400 (400-400)	1.00 (1.00-1.00)	0.77		
Dasatinib		100 (700-100)	100 (50-100)	100 (85-100)	0.98 (0.95-1.00)	0.13		
Nilotinib		600 (400-600)	600 (400-600)	600 (400-600)	1.00 (1.00-1.00)	0.45		
Bosutinib		400 (300-500)	400 (300-500)	400 (300-400)	1.00 (0.99-1.01)	0.58		
Ponatinib		30 (15-45)	30 (15-45)	30 (19-42)	0.99 (0.89-1.09)	0.77		
Treatment duration of current TKI, months	NA	36 (12 – 69)	24 (6-60)	36 (12-72)	1.00 (1.00-1.01)	0.48		
BCR-ABL ^{IS} transcript level, % MMR	NA	80	75	86	0.47 (0.21 – 1.0)	0.05		
CCI	0 (0-0)	2 (2-3)	2 (2-3)	2 (2-2)	1.67 (1.10-2.53)	0.017	1.91 (1.16-3.13)	0.011
Comedication known to cause fatigue*, %	7	27	36	16	2.89 (1.51-5.54)	0.001	3.43 (1.58-7.44)	0.002
Lifestyle								
Smoking status, % smoker	8	5	7	2	3.40 (0.71-16.4)	0.13		
Fluid intake, mL/day	1806 ± 1760	1642 ± 545	1601 ± 557	1694 ± 528	1.00 (1.00-1.00)	0.21		
Caffeine intake, mg/day	336 ± 197	326 ± 175	312 ± 175	344 ± 173	1.00 (1.00-1.00)	0.17		
Alcohol consumption >1U/day, %	17	13	11	17	0.61 (0.28-1.34)	0.22		
Physical activity#, %								
Inactive	6	16	22	4	REF			
Moderately active	19	25	32	16	0.39 (0.12 – 1.29)	0.12	0.43 (0.12 – 1.52)	0.19
Vigorously active	28	30	28	33	0.16 (0.05 – 0.52)	0.002	0.22 (0.06 – 0.74)	0.014
Very vigorously active	47	30	17	47	0.07 (0.02 – 0.22)	<0.001	0.08 (0.02 – 0.26)	<0.001
Not performing sports, %	33	46	49	42	1.35 (0.79 – 2.30)	0.28		

Data are presented as mean ± standard deviation, percentages or median (interquartile range). *Benzodiazepines, opioids, beta-blockers, and metformin. #Physical activity was classified into four categories: inactive (<500 metabolic equivalent of task [MET] min/week), moderately active (500-1,499 MET min/week), vigorously active (1,500-2,999 MET min/week), and very vigorously active (>3,000 MET min/week). CML: chronic myeloid leukemia; OR: odds ratio; 95% CI: 95% confidence interval; BMI: body mass index; REF: reference group; TKI: tyrosine kinase inhibitor; IS: International scale; MMR: major molecular response; CCI: Charlson Comorbidity Index; NA: not applicable.

28 ± 10 h/week, respectively; $P=0.001$).

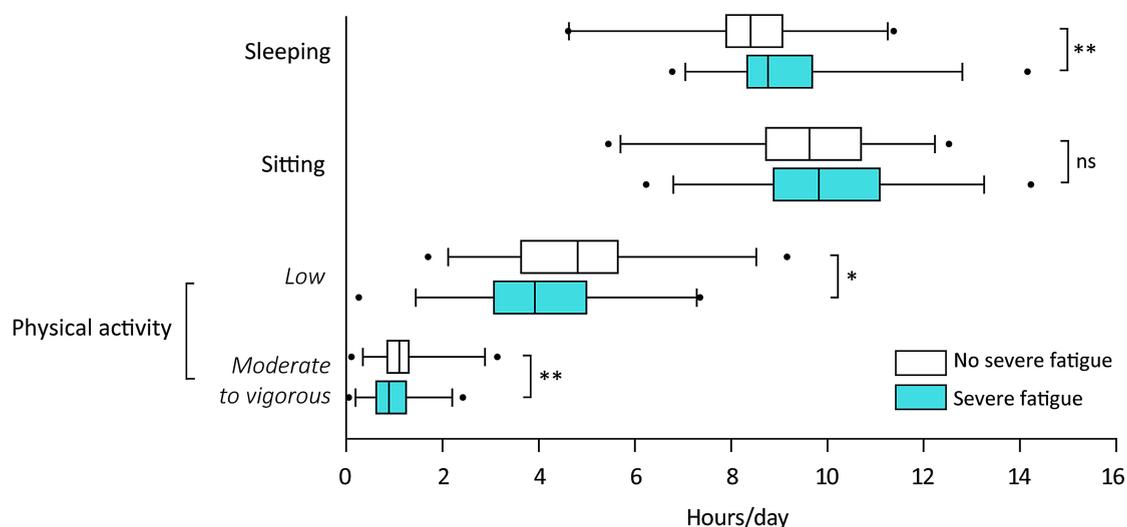
Figure 3 shows the daily activity patterns of fatigued and non-fatigued patients categorized into sleeping, sitting, light intensity physical activity, and moderate to vigorous physical activity. Severely fatigued CML patients slept significantly longer than patients without fatigue (8.8 h/day [IQR 8.3-9.7] vs. 8.4 h/day [IQR 7.9-9.1]; $P=0.006$). Sitting time was not significantly different between the groups ($P=0.43$). Severely fatigued CML patients were significantly less

active when compared to non-fatigued patients as shown by both lower physical activity of light intensity (3.9 h/day [IQR 3.1-5.0] vs. 4.8 h/day [IQR 3.6-5.6]; $P=0.017$) and moderate to vigorous physical activity (0.9 h/day [IQR 0.6-1.2] vs. 1.1 h/day [IQR 0.8-1.3]; $P=0.009$). In line, step counts were significantly lower in CML patients with severe fatigue (7,464 ± 3,486 steps/day) than in patients without fatigue (9,393 ± 4,200 steps/day; $P=0.004$). After adjustment for gender and age, sleeping time remained longer and

Table 2. Characteristics of chronic myeloid leukemia patients with and without severe fatigue in part 2 of the study.

	CML + fatigue (N=67)	CML - fatigue (N=71)	P-value
Age, years	55 ± 13	55 ± 16	0.88
Gender, % female	61	44	0.039
BMI, kg/m ²	26.8 ± 4.7	26.0 ± 4.9	0.37
Time since diagnosis, months	67 (30-162)	89 (39-153)	0.46
TKI type, %			0.12
Imatinib	37	23	
Dasatinib	27	28	
Nilotinib	16	32	
Bosutinib	15	10	
Ponatinib	5	7	
TKI dose, (mg/day)			
Imatinib	400 (350-400)	400 (400-400)	0.17
Dasatinib	100 (50-100)	95 (70-100)	0.99
Nilotinib	600 (300-600)	600 (600-600)	0.16
Bosutinib	350 (275-500)	400 (400-400)	0.88
Ponatinib	30 (15-30)	30 (15-37.50)	0.79
Treatment duration of current TKI, months	35 (12-61)	36 (16-79)	0.55
BCR-ABL ^{IS} transcript level, % MMR	87.3	94.0	0.18
Hemoglobin, mmol/L			
Male	8.5 ± 0.7	8.7 ± 0.9	0.24
Female	7.7 ± 0.9	8.0 ± 0.8	0.11
WBC count (x 10 ⁹ /L)	6.3 ± 1.6	6.1 ± 1.7	0.49
Platelet count (x 10 ⁹ /L)	220 ± 61	221 ± 68	0.93

CML: chronic myeloid leukemia; BMI: body mass index; TKI: tyrosine kinase inhibitor; IS: international scale; MMR: major molecular response; WBC: white blood cell.



physical activity remained lower in fatigued patients (mean difference 0.55 h/day, 0.67 h/day, 0.22 h/day, and 1,938 steps/day for sleeping time, light intensity physical activity, moderate to vigorous intensity physical activity, and step counts, respectively; all $P < 0.05$).

Physical activity patterns were also analyzed for week and weekend days separately. Although there was no difference between the fatigued and non-fatigued group in sitting time during week days (9.7 h/day [IQR 8.9-11.3] and 10.0 h/day [IQR 8.8-11.0], respectively; $P = 0.73$), we found a trend towards longer sitting time during weekend days in fatigued patients compared to non-fatigued ones (9.6 h/day [IQR 8.6-10.9] and 9.2 h/day [IQR 8.1-10.5], respectively; $P = 0.06$). Severely fatigued patients slept longer and performed less physical activity (of light as well as moderate to vigorous intensity) on both week and weekend days (all $P < 0.05$).

Discussion

This is the first study to assess the prevalence and predictors of severe fatigue in CML patients receiving TKI treatment and to provide insight into the relationship between severe fatigue and physical activity in this population. The prevalence of fatigue in our CML population was 55%. Using multivariable logistic regression, we built a model with good discriminative ability and found five significant predictors of severe fatigue in our population: younger age, female gender, higher CCI, the use of comedication known to cause fatigue, and physical inactivity. Using physical activity monitors, we objectively confirmed that severely fatigued CML patients are less physically active during the day, with regard to both light and moderate to vigorous intensity activity, on both week and weekend days. These findings suggest that: (i) there is a subset of CML patients particularly prone to TKI-induced fatigue, and (ii) severely fatigued patients have reduced levels of physical activity.

Over half of the CML patients in the present study experienced severe fatigue, which was significantly greater than that in matched controls and compared to TKI-induced fatigue rates reported in literature. In patients receiving imatinib, the prevalence of fatigue varied across large clinical trials from 34.5% (IRIS¹⁶) to 15.5% (CML IV¹⁷), 10% (DASISION¹⁸), 22% (ENESTnd¹⁹), 47% (BFORE²⁰), and 20% (EPIC²¹). However, these trials were not designed to assess fatigue, which may explain the wide range of prevalence rates. We did not find a difference in fatigue prevalence between patients taking different TKI, which is in agreement with the findings of these large trials.¹⁸⁻²⁰ Interestingly, severe fatigue was neither independently associated with treatment-related factors, such as TKI therapy dose and duration, nor with disease control. Although fatigue is a common sign of severe anemia, hemoglobin levels did not differ between fatigued and non-fatigued patients. Low hemoglobin levels were also not identified as an independent predictor of fatigue in patients with other hematologic malignancies.²²

We found that fatigue was more often present in younger and female patients. In line with this, Efficace *et al.* found that the largest differences in health-related QoL between CML patients and the general population was among younger subjects.² Contradictory findings are reported in the literature regarding the association between age and fatigue in other populations. For example, chronic fatigue

was more often present in younger breast cancer survivors,⁷ while older age has been identified as a risk factor for fatigue in both hematologic²³ and non-hematologic^{24,25} cancer patients. Several studies showed an association between fatigue and gender in line with our results, with a more prominent risk for female cancer patients.^{26,27} Interestingly, compared to the general population, female CML patients are more negatively affected than male CML patients in both mental and physical health.² Sex-related differences in disease perception and anxiety may contribute to the higher prevalence of fatigue in women,²⁸ although this aspect was beyond the scope of this study. Furthermore, we showed that patients with comorbidity were more often fatigued, as were patients taking comedication known to cause fatigue. This suggests the need to check patients' medication records critically, and to stop or reduce the dose of any comedication known to cause fatigue if possible (e.g., benzodiazepines as sleep medication), especially in those CML patients who are prone to fatigue.

Both subjective and objective assessments of physical activity showed that fatigued patients were more often inactive than were non-fatigued patients. More precisely, we found that compared to the non-fatigued patients, fatigued CML patients slept approximately 0.5 h/day longer, performed 1 h less of physical activity per day and took 2,000 fewer steps per day. Although it may seem self-evident that severely fatigued patients are less physically active as a result of fatigue, physical inactivity itself may contribute to the persistence of fatigue.⁹ Additionally, there is a significant body of evidence to support the beneficial effects of exercise interventions to reduce fatigue levels in various (post)-cancer patient populations.²⁹ Interestingly, our study showed that the vast majority of the CML patients, both fatigued and non-fatigued, already met the recommended American College of Sports Medicine/American Heart Association guidelines for physical activity (i.e., 150-300 min of moderate-intensity or 75-150 min of vigorous intensity physical activity per week, or an equivalent combination). However, higher activity levels were associated with lower levels of fatigue in our CML population. Furthermore, the extra amount of physical activity that non-fatigued patients performed when compared to fatigued patients (~6.3 h of light intensity and 1.4 h of moderate to vigorous intensity physical activity per week) may yield additional health benefits.³⁰ Consequently, it is of clinical relevance to focus on preventing and treating TKI-induced fatigue in clinical practice. This is further supported by our findings that fatigued CML patients have impaired QoL and work fewer hours when compared to non-fatigued patients.

There are several limitations to this study. First, due to the cross-sectional design of the study we cannot distinguish between cause and effect. Although we found that a reduced level of physical activity is associated with the presence of fatigue, and thus is a predictor of fatigue, we cannot state that reduced physical activity is a risk factor for fatigue. However, regardless of whether or not there is a causal relationship between fatigue and reduced levels of physical activity, our results highlight the importance of combating fatigue and of examining whether exercise interventions are useful to counteract fatigue. Secondly, because of the inclusion of a heterogeneous study population, we observed a considerable variation in physical activity levels. However, the representative sam-

ple in this population-based study allows translation of the findings to clinical practice. Lastly, we used a Likert scale for the assessment of QoL in order to reduce the length of our questionnaire to assess predictors of fatigue (Part 1) even though validated QoL questionnaires have been developed in the CML population. However, a simple Likert scale has been shown to measure QoL adequately in cancer patients.³¹ A major strength of our study is the objective assessment of physical activity, which ruled out response bias. Another strength is the relatively large sample size and the small amount of missing data (<3% in both parts of the study).

In conclusion, we demonstrated that the majority of the CML patients receiving TKI therapy experienced severe fatigue and that severely fatigued patients have impaired QoL. Independent predictors of severe fatigue include: younger age, female gender, higher CCI, the use of comedication known to cause fatigue, and physical inactivity. Objective assessment of physical activity showed that, compared to patients without fatigue, severely fatigued CML patients sleep more and are less active during the day

on both week and weekend days. These findings emphasize the importance of recognizing the reduction of fatigue as a treatment goal in CML care and the need for future studies to identify physical activity as a possible target to achieve this goal.

Disclosures

No conflicts of interest to disclose.

Contributions

LJ performed the research, analyzed data and wrote the manuscript with support from all authors. NB performed research and supervised the study. MD performed research and analyzed data. EB analyzed data. MN and JJ performed research. ST and MH supervised the study.

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