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LETTER TO THE EDITOR

Satisfaction with information on nilotinib treatment in chronic myeloid leukemia patients

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Introduction

Chronic myeloid leukemia (CML) is a chronic myeloproliferative disease, consistently associated with the presence of the Philadelphia chromosome coding for the BCR-ABL oncoprotein. The standard treatment for chronic phase CML (CP-CML) patients is daily orally taken tyrosine kinase inhibitors (TKIs) [1]. The use of TKIs in CML has highly improved prognosis of CML patients, who now have a similar life expectancy to the general population [2]. As patients take their oral medication at home and the drugs need to be taken indefinitely, adherence to the treatment is not guaranteed and the probability of achieving deep molecular response decreases [3]. In addition, side effects like fatigue, edema, skin toxicity and cardiovascular complications may cause significant morbidity and reduce the quality of life [4,5].

Adequate provision of information is an important determinant of both medication adherence in CML [6–13] and successful management of side effects [13,14]. However, patients' information needs might not always be met [15–17]. A recent study from our group among cancer patients using different TKI showed that, generally, satisfaction with information on oral anticancer treatment was good, however, a considerable number of patients still felt insufficiently informed about the effects and side effects of treatment and possible interference of treatment with various aspects of daily life [15]. Amongst other factors, more patients treated for a hematological malignancy felt insufficiently informed about their medication than patients treated for a solid tumor [15]. It is therefore interesting to obtain more insight into the (lack of) satisfaction with information about medication in this particular group of patients.

Considering the clinical importance of TKI adherence for attaining optimal disease control [3], it is of great interest that these drugs are used as prescribed. Specifically, for nilotinib, which is the only TKI that needs to be taken in a complicated, twice daily, fasted schedule, complicates its use and may increase nonadherence [10,13,18]. Providing adequate information may contribute to the optimal use of nilotinib treatment. The present study aimed to get insight into the experiences of CML patients with information on their treatment with nilotinib and variables relating to dissatisfaction with the information provided, as well as the relationship between information dissatisfaction and self-reported nonadherence to nilotinib.

Material and methods

Study design

The present study data were obtained when performing the RAND study (Response and Adherence to Nilotinib in Daily practice), a multicenter observational study conducted between August 2013 and April 2017 in six Dutch hospitals [19]. Patients with CP-CML on treatment with nilotinib were eligible for participation and completed a self-administered composite questionnaire (among other measures). Ethical approval was received by the Medical Ethics review board of Amsterdam University Medical Centres (location VUmc, Amsterdam) (2013.035), as well as the ethical boards of each participating hospital. Written informed consent was obtained from all patients.

Primary outcome and independent variables

The primary outcome of the present study was the patient satisfaction with information on nilotinib treatment, measured by means of the Dutch version of the validated Satisfaction with Information about Medicines Scale (SIMS) [20]. Patients were asked to rate 17 aspects of medicine use on the extent to which they feel that they have been given adequate information. Ratings *about right* and *none needed*

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indicate 'satisfaction' with information and ratings *too much, too little,* and *none received* indicate 'dissatisfaction'. A total SIMS score was calculated by summing the 'satisfaction' ratings of each item (score ranges from 0 to 17), with a higher score indicating a higher degree of overall satisfaction with information. Two subscales were calculated and identified patient satisfaction with information on *action and usage* (items 1–9, score ranges from 0 to 9) and *potential problems* of medication (items 10–17, score ranges from 0 to 8). The SIMS scale scores showed good internal reliability with Cronbach's alpha coefficients of 0.86 for the total score, and 0.84 and 0.85 for the subscales scores, respectively.

Independent variables used in the analysis were age, gender, living status (alone vs. not alone), educational level (≥higher general secondary education vs. lower education), work status (having paid work vs. not having paid work), study center, duration of treatment (≥6 months vs. <6 months), line of treatment (second- or third-line vs. first-line), patient-reported fatigue (severe vs. no/mild), physical and mental health composite scores derived from the SF-12 [21,22], cognitive and emotional dimension scores (consequences, timeline, personal control, treatment control, concern, identity, coherence and emotional response) derived from the Brief Illness Perception Questionnaire (IPQ) [23], and attitude towards nilotinib (accepting, ambivalent, indifferent and skeptical) derived from the Beliefs about Medicines Questionnaire-Specific [24,25].

Secondary outcome

The secondary outcome of this study was self-reported adherence to nilotinib treatment, measured by means of the validated Medication Adherence Report Scale (MARS) [26–28]. Four items assess intentional non-adherence (i.e., 'I decide to omit a dose') and one item assesses non-intentional non-adherence ('I forget to take my medication'). Items are scored using a 5-point scale (1 = always to 5 = never). Scores for each item can be summed to give a total score ranging from five to 25 with higher scores indicating higher levels of adherence.

Statistical analysis

Descriptive statistics were used to describe patient and treatment characteristics. Medians, means and standard deviations (SD) were used for continuous variables, and frequencies (percentages) for categorical variables. Logistic regression analyses were used to identify factors of dissatisfaction with information on nilotinib treatment. Age was associated with information dissatisfaction in the three SIMS scales ($p < .2$) and was used as a covariate in all regression analyses. Threshold values were used to distinguish dissatisfaction from satisfaction (<14 of 17 items, <8 of 9 items, and <6 of 8 items for, respectively, *overall satisfaction rating*, subscale *action and usage*, and subscale *potential problems)* and were based on previous research assessing patient satisfaction with information on several oral anticancer agents [15]. In exploratory analyses, other threshold values for dissatisfaction were used and showed comparable results (data not shown). The relationship between information dissatisfaction and self-reported nonadherence to nilotinib was assessed by means of chi-square test. A two-tailed significance level of .05 was used for all analyses. All statistical analyses were done using SPSS for Windows, version 22 (IBM Corp, Armonk, NY, USA).

Results

Study sample

A total of 68 patients were included. Seven patients had stopped treatment before completing the questionnaire due to progression ($n = 2$), side effects ($n = 4$), and death ($n = 1$). Six patients did not return the questionnaire and one patient had returned the questionnaire, but accidentally did not complete the SIMS questionnaire. A total of 54 patients (mean age 58.0 ± 14.3, 48% female) were included in the analysis. The median and mean duration of nilotinib treatment were 20 and 30 ± 20 months, respectively (from 5 to 99 months). Patient and treatment characteristics are shown in Table 1. No differences in the patient characteristics were found between the hospitals (data not shown).

Satisfaction with information on nilotinib treatment

Table 2 shows the extent patients felt they had been given adequate information on nilotinib per individual SIMS item. One-third of the patients (33%) were satisfied with all 17 SIMS items. Regarding the subscales, 59% and 39% were completely satisfied with all items on, respectively, *action and usage* and *potential problems*. When a threshold value is used to define satisfaction with information, 61%, 76% and 61% of the patients were satisfied, respectively. Satisfied patients found the provided information predominantly

Table 1. Patient and treatment characteristics ($N = 54$).

Patient characteristics		
Age, years		
Mean ± SD	58.0 ± 14.3	
>55 years, *n* (%)	30 (55.6%)	
Female gender, *n* (%)	26 (48.1%)	
Living alone, *n* (%)	5 (9.6%)	
Higher educated, *n* (%)	14 (26.9%)	
Employed, *n* (%)	27 (51.9%)	
Treatment characteristics		
Duration of nilotinib treatment		
Mean ± SD (months)	30.4 ± 20.4	
>6 months, *n* (%)	39 (72.2)	
Line of treatment		
First	29 (53.7%)	
Second	17 (31.5%)	
Third	8 (14.8%)	
Occurrence of side effects, *n* (%)	Mild[a]	Severe[a]
Headache	19 (35.8%)	1 (1.9%)
Nausea	11 (20.4%)	1 (1.9%)
Rash	19 (35.2%)	4 (7.4%)
Itching	28 (51.9%)	4 (7.4%)
Myalgia	25 (48.1%)	3 (5.8%)
Fatigue	28 (54.9%)	10 (19.6%)

SD: standard deviation.
[a]Side effects scored as 'a little bit' and 'rather' were considered 'mild', side effects scored as 'a lot' and 'very much' were considered 'severe'.

Table 2. CML patient satisfaction with information on nilotinib treatment (Satisfaction with Information about Medicines Scale [SIMS])($N = 54$).

	Satisfied, %			Dissatisfied, %			
	About right	None needed	Total	Too much	Too little	None received	Total
What your medicine is called	87.0	5.6	92.6	0.0	1.9	5.6	7.4
What your medicine is for	96.3	3.7	100.0	0.0	0.0	0.0	0.0
What it does	90.7	3.7	94.4	0.0	3.7	1.9	5.6
How it works	83.3	3.7	87.0	0.0	7.4	5.6	13.0
How long it will take to act	79.6	3.7	83.3	0.0	7.4	9.3	16.7
How you can tell if it is working	74.1	5.6	79.6	0.0	9.3	11.1	20.4
How long you will need to be on your medicine	79.2	5.7	84.9	0.0	7.5	7.5	15.1
How to use your medicine	94.4	3.7	98.1	1.9	0.0	0.0	1.9
How to get a further supply	92.6	3.7	96.3	0.0	3.7	0.0	3.7
Whether the medicine has any unwanted effects (side effects)	85.2	3.7	88.9	0.0	9.3	1.9	11.1
What are the risks of you getting side effects	66.0	5.7	71.7	0.0	15.1	13.2	28.3
What you should do if you experience unwanted side effects	64.8	1.9	66.7	0.0	14.8	18.5	33.3
Whether you can drink alcohol whilst taking this medicine	68.5	14.8	83.3	0.0	3.7	13.0	16.7
Whether the medicine interferes with other medicines	79.2	9.4	88.7	0.0	3.8	7.5	11.3
Whether the medicine will make you feel drowsy	53.7	5.6	59.3	0.0	9.3	31.5	40.7
Whether the medicine will affect your sex life	37.0	11.1	48.1	0.0	13.0	38.9	51.9
What you should do if you forget to take a dose	74.1	7.4	81.5	0.0	7.4	11.1	18.5

about right instead of none needed. Dissatisfied patients were particularly dissatisfied with information on potential problems: the risks of side effects (28%) and its management (33%) and the possibility of drowsiness (41%) and an affected sex life (52%). Regarding the information on action and usage, the percentage of dissatisfied patients was $\leq$20% for each of the individual 8 items. Only one patient indicated that too much information was provided.

Factors of dissatisfaction with information on nilotinib treatment

Table 3 shows the characteristics associated with patient dissatisfaction with information on nilotinib use: the occurrence of severe fatigue (9.7, 95% CI 1.7–55.8), lower physical health (OR 4.2, 95% CI 1.0–17.1), negative perception of the consequences of CML (IPQ item consequences, OR 5.9, 95% CI 1.3–27.9), higher perception of CML-related symptoms (IPQ item identity, OR 4.8, 95% CI 1.3–17.5), worse emotional response to CML (IPQ item emotional response, OR 6.6, 95% CI 1.6–27.1), and an ambivalent attitude (high necessity, high concerns) towards nilotinib compared to an accepting attitude (high necessity, low concerns) (OR 9.2, 95% CI 2.0–42.0). Patients from hospital 3 were more often satisfied compared to patients from the other hospitals (OR 0.1, 95% CI 0.0–0.7).

Information dissatisfaction and self-reported nonadherence to nilotinib

Occasional nonadherence to nilotinib was reported by 26% of the patients. Median and mean MARS scores of the nonadherent patients were 24 and 23.4 ± 0.8, respectively. Nine patients (17%) reported unintentional nonadherence (forget taking medication), one patient (2%) intentional nonadherence (stop taking medication), and four patients (7%) both intentional and unintentional nonadherence. No statistically significant associations were found between information dissatisfaction and self-reported nonadherence to nilotinib (Table 4).

Discussion

This study assessed CML patient satisfaction with information on nilotinib treatment in daily practice. Patients were generally satisfied with the information they had received, although improvements could be made regarding information on the potential problems of nilotinib. In particular, information on the risks of side effects and their management, the possibility of drowsiness, and interference of treatment with sex life need more attention. Factors influencing dissatisfaction were the occurrence of severe fatigue, poor physical health, a negative perception of CML, and an ambivalent attitude towards nilotinib. Dissatisfaction with information appeared not related to self-reported nonadherence to nilotinib.

CML patients were generally satisfied with the information on nilotinib treatment they had received. This result is in line with the results from previous research on patient satisfaction with information on oral anticancer treatments (predominantly capecitabine) [15–17]. Satisfaction in the present study even seems slightly higher, especially with regard to the information about the action and effectiveness of nilotinib treatment. Over 80% of the patients in the present study were satisfied with this part of information provision. Indeed, regular monitoring of treatment effectiveness is of vital importance in the TKI era of CML, as meeting response depth correlates with outcome [1,29,30]. A BCR-ABL transcript level of $\leq$0.1% on the International Scale should be achieved [1] and patients seem actively involved in achieving and maintaining this response milestone. Therefore, patients may be highly satisfied with the information on the action and effectiveness of nilotinib treatment.

Many patients felt that information on the risks of side effects and its management was inadequate, which is consistent with earlier studies in patients with cancer [15,17,31–33]. Although the side effects of nilotinib are generally mild, they do adversely impact the patients' quality of life and interfere with daily activities [5,34,35]. Both the occurrence of side effects and poor quality of life have been shown important factors affecting TKI adherence [6,10,13,36]. In addition, the occurrence of cardiovascular side effects of

Table 3. Factors associated with patient dissatisfaction with information on nilotinib treatment.

		Overall dissatisfaction with information (SIMS score <14/17)		Dissatisfaction with information on Action and Usage (SIMS score <8/9)		Dissatisfaction with information on Potential problems (SIMS score <6/8)	
	n/N	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Female gender	26/54	1.7 (0.5–5.4)	.360	1.9 (0.5–7.1)	.323	1.7 (0.6–5.3)	.346
Living alone	5/52	–		–		–	
Higher education	14/52	2.8 (0.7–11.9)	.169	3.0 (0.6–15.6)	.185	3.8 (0.9–16.1)	.071
Employed	25/52	0.5 (0.8–2.5)	.364	1.0 (0.1–7.0)	.958	1.1 (0.2–6.0)	.903
Study center[a]							
1	19/54	1.5 (0.5–5.1)	.514	1.4 (0.4–5.5)	.609	1.0 (0.3–3.2)	.961
2	10/54	1.1 (0.3–4.9)	.870	0.8 (0.1–4.4)	.770	1.1 (0.3–4.6)	.895
3	11/54	0.1 (0.0–0.7)	**.023**	0.4 (0.1–2.4)	.291	0.3 (0.1–1.6)	.168
4	2/54	1.3 (0.1–21.6)	.874	2.8 (0.2–49.0)	.476	1.3 (0.1–23.0)	.838
5	1/54	–		–		–	
6	11/54	2.2 (0.7–12.9)	.132	1.5 (0.3–7.3)	.595	2.7 (0.7–11.2)	.160
Duration of treatment >6 months	39/54	2.9 (0.7–12.6)	.152	2.2 (0.4–11.6	.373	1.8 (0.5–7.1)	.375
Second- or third-line nilotinib treatment	25/54	2.6 (0.8–8.4)	.110	1.3 (0.4–4.8)	.674	1.3 (0.4–4.2)	.607
Occurrence of severe fatigue	10/51	14.3 (2.2–94.6)	**.006**	20.2 (2.4–167.9)	**.005**	9.7 (1.7–55.8)	**.011**
Quality of life (SF-12)[b]							
Physical health	13/53	4.2 (1.0–17.1)	**.048**	1.7 (0.4–7.1)	.492	3.7 (1.0–14.5)	.057
Mental health	11/53	0.2 (0.0–1.4)	.104	0.2 (0.0–2.1)	.196	0.5 (0.1–2.2)	.350
Illness perception (IPQ)[b]							
Consequences	10/54	3.7 (0.8–16.4)	.088	0.8 (0.2–4.8)	.847	5.9 (1.3–27.9)	**.024**
Timeline	0/51	–	–	–		–	
Personal control	15/53	0.4 (0.1–1.6)	.209	1.1 (0.2–4.3)	.941	0.4 (0.1–1.7)	.234
Treatment control	14/54	0.5 (0.1–1.9)	.286	0.7 (0.2–3.4)	.694	0.3 (0.1–1.3)	.109
Identity	16/54	5.6 (1.4–21.9)	**.014**	1.2 (0.3–4.9)	.788	4.8 (1.3–17.5)	**.018**
Concerns	11/53	0.9 (0.2–3.9)	.919	0.8 (0.1–4.4)	.773	1.5 (0.4–5.9)	.577
Coherence	14/54	0.8 (0.2–3.3)	.766	2.5 (0.5–12.0)	.268	0.7 (0.2–2.8)	.616
Emotional response	16/54	5.08 (1.2–21.1)	**.025**	1.49 (0.35–6.48)	.591	6.6 (1.6–27.1)	**.009**
Beliefs about nilotinib (BMQ-S)							
Accepting	35/53	Ref.		Ref.		Ref.	
Ambivalent	15/53	6.6 (1.5–29.9)	**.014**	3.3 (0.7–15.0)	.127	9.2 (2.0–42.0)	**.004**
Indifferent	3/53	3.7 (0.2–87.6)	.424	5.7 (0.3–120.3)	.267	3.5 (0.2–70.7)	.417
Skeptical	0/53	–		–		–	

Significant relations are shown in bold ($p < .05$). OR: odds ratio; 95% CI: 95% confidence interval; SIMS: Satisfaction with Information about Medicine Scale; SF-12: SF-12 Health Survey; Brief-IPQ: Brief Illness Perception Questionnaire; BMQ-S: Beliefs about Medicines Questionnaire Specific.
[a]Dichotomized into study center versus the other five centers (reference).
[b]Dichotomized into the most adverse quartile versus the other three quartiles (reference).

Table 4. Dissatisfaction with information on nilotinib treatment and self-reported nonadherence to nilotinib.

	Adherent (MARS = 25) ($n = 30$)	Nonadherent (MARS < 25) ($n = 14$)	*p*-value
Overall satisfaction rating			
Satisfied with information (SIMS ≥14/17)	43.4%	17.0%	.727
Dissatisfied with information (SIMS <14/17)	30.2%	9.4%	
Information on Action and Usage			
Satisfied with information (SIMS ≥8/9)	52.8%	22.6%	.299
Dissatisfied with information (SIMS <8/9)	20.8%	3.8%	
Information on Potential problems			
Satisfied with information (SIMS ≥6/8)	41.5%	18.9%	.324
Dissatisfied with information (SIMS <6/8)	32.1%	7.5%	

MARS: Medication Adherence Report Scale; SIMS: Satisfaction with Information about Medicines Scale.

nilotinib can be hazardous and may limit long-term use in some patients [37]. Therefore, information on the management of side effects should be improved in CML care [14,35]. Healthcare providers (HCP) should inquire after (perceived) side effects of treatment and discuss the risk of side effects and options to mitigate its impact [14,35,38]. Furthermore, in the present study, the experience of severe fatigue as well as poor physical health was associated with information dissatisfaction. Apparently, these patients have higher information needs than patients in good physical health and experiencing only mild fatigue. HCP should inquire after (the severity of) fatigue and how this affects the patients' daily lives.

Information was deemed insufficient on the possible occurrence of drowsiness. This is in line with the results of previous research [15,17] and could be justified by the fact that drowsiness is a side effect of nilotinib not described in the Summary of Product Characteristics [39]. However, a recent observational study performed in the United States found a high number of CML patients experiencing TKI induced drowsiness [5]. It is also an overdose symptom of nilotinib and may, for example, compromise patients' ability to drive safely. It is important to inform patients on this subject. This also accounts for the insufficient information on the impact of nilotinib on a patients' sex life. Sexual problems are not a direct side effect of nilotinib, however, side effects such as fatigue or headache may influence sexual function. In addition, it should be taken into account that TKI use is accompanied with an increased risk of fetal

complications after TKI exposure [40]. It is not unlikely that patient dissatisfaction is related to sexual problems or patients' desire for pregnancy.

Patients with a more negative perception of the consequences of CML, higher perception of CML-related symptoms, and negative emotional response to CML were more often dissatisfied with information on potential problems of nilotinib treatment. Patients with an ambivalent attitude towards nilotinib were also more often dissatisfied with this information compared to patients with an accepting attitude. These patients differ with regard to their concerns [25]. Although the relationship between patient beliefs about medication and satisfaction with information is known from previous studies, the results of these studies are inconsistent [15–17]. Nevertheless, HCP should inquire after the patient's beliefs about CML and medication (such as the beliefs of the necessity of taking their medication and the possible concerns), and offer targeted counseling.

Dissatisfaction with information appeared not related to self-reported nonadherence to nilotinib. This is in contrast with other studies [6–13]. This could be explained by the generally high level of satisfaction with information found in the present study. In addition, only few patients were dissatisfied with information on what to do in the case of a missed dose, while forgetting to take nilotinib was the most frequently reported reason for nonadherence. Practical aids (such as alarm devices and pill boxes) which are particularly relevant to avoid unintentional nonadherence may be more helpful.

The present study has some strength and limitations. It provides a unique overview of the experiences of CML patients with information on nilotinib treatment. The study used several validated questionnaires to assess CML patient satisfaction with information and their characteristics regarding dissatisfaction. Unfortunately, the number of included patients is limited. The study may lack statistical power, the confidence intervals of our odds ratios were wide and a multivariable regression analysis was impossible. It should be noted that CML is a rare disease and a small study population may be inevitable. Second, the study does not provide insight into the way (e.g., verbal, written) or by whom (i.e., physician, nurse, pharmacist) information was delivered to the patients. Dissatisfaction with information does not imply that information was not provided by HCP [15]. In addition, CML patients from one of the hospitals were more often satisfied with information than patients from the other hospitals. It could be useful to explore differences in the actual information provision on CML treatment between the hospitals.

Conclusion

Most patients were satisfied with information on nilotinib treatment. Information on the risk and management of side effects of nilotinib and the possibility of drowsiness and interference of treatment with sex life could receive more attention. Patients reporting occasional nonadherence to nilotinib treatment did not differ in terms of satisfaction with information as compared to adherent patients in our study.

Disclosure statement

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