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Side effects of treatment with tyrosine kinase inhibitors in patients with chronic myeloid leukemia and the occurrence of anxiety symptoms

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Summary

Aim. The study aims to check whether individual side effects of treatment with TKIs in patients suffering from CML may contribute to the occurrence of anxiety symptoms. In addition, it was decided to check whether there were any relationships between age, gender, duration of treatment, and the intensity of anxiety, divided by the occurrence of individual side effects.

Method. The study involved 91 patients and was conducted at the Hematology Clinic of the University Hospital in Krakow. The following questionnaires were used: created by the author, David Goldberg Questionnaire GHQ-28, and the four-dimensional 4DSQ Questionnaire.

Results. The most frequently mentioned side effects of treatment were bone and joint pain, muscle cramps and pain, water retention, and fatigue. The mean duration of the disease was ten years. Our research showed that fatigue, nausea/indigestion, frequent infections, bone and joint pain, abdominal pain, and loss of appetite were the most common side effects of TKI treatment, which resulted in increased anxiety symptoms.

Conclusions. The work of doctors, psychologists, and pharmaceutical companies on reducing/alleviating side effects may in the future affect a better quality of life for these patients. Early detection of severe anxiety and taking appropriate steps can prevent the emergence of more significant disorders. In addition, several years of attempts to discontinue treatment with some TKIs (imatinib and nilotinib) in patients who achieve a profound molecular response may improve their mental condition.

Key words: chronic myeloid leukemia, anxiety, tyrosine kinase inhibitors

Introduction

Chronic myeloid leukemia (CML) is a neoplastic disease of the hematopoietic system; it belongs to myeloproliferative neoplasms. Treatment of chronic myeloid leukemia depends on the phase of the illness, general health, age, and fitness level. Pharmacotherapy is the most often offered treatment, while chemotherapy, radiotherapy and stem cell transplantation are used much less frequently [1].

In the pharmacological treatment of patients with CML, tyrosine kinase inhibitors (TKIs) are used, which are a type of targeted therapy. TKIs are administered as pills, taken orally. Targeted therapy identifies and attacks leukemia cancer cells while causing less harm to normal cells. Treatment with TKIs is aimed at blocking the abnormal activity of bcr-abl1 kinase, which is responsible for the development of CML [2]. The implementation of the treatment with tyrosine kinase inhibitors showed much better results in terms of survival, reduction of side effects and improvement of the patients' quality of life compared to conventional cytotoxic chemotherapy [3].

Currently, the most commonly used TKI drugs in Poland are imatinib, second-generation TKIs: dasatinib, bosutinib, and nilotinib, and third-generation TKI: ponatinib [4]. The number and type of side effects depend on the specific drug and dose. The most frequently occurring side effects of treatment with TKIs include: neutropenia (resulting in an increased risk of infection), thrombocytopenia (causing bruising and hematomas), anemia (weakness), swelling, muscle cramps, fatigue, nausea, skin changes, loss of appetite, bleeding and diarrhea. Side effects may develop at the beginning and during the treatment, and they may be short-term or chronic over months or years. However, regardless of the type of side effects and treatment, they can all harm a patient's quality of life [5-7].

Fear is a natural, automatic reaction to a real threat, while anxiety is an emotional, inadequate response to an imagined or real threat [8, 9]. Fear, stress, and anxiety are related to the fight-or-flight response, i.e., preparation to fight the danger or run away from the unknown [10]. Anxiety manifests psychological, behavioral, and vegetative-somatic symptoms in the clinical picture [11].

Approximately 10% of cancer patients are diagnosed with anxiety disorders, and less than 40% – with mood disorders [12]. There are many possible reasons for the appearance of anxiety symptoms in cancer patients, from the information about the disease itself, through its duration, lack of support and resources, and multiple hospitalizations, to side effects of treatment and the influence of drugs on the possibility of appearance of psychiatric disorders [13]. Their intensity is influenced, among others, by the type of cancer, duration of the disease, the stage of therapy, and the side effects of treatment [14, 15].

Many studies in the literature are devoted to the side effects of cancer therapy (mainly chemotherapy) and the impact of disease and treatment on anxiety disorders. However, little research has been conducted so far on the effects of individual side effects of TKI treatment on the possibility of the appearance of anxiety symptoms. A similar topic is discussed in research on the quality of life of cancer patients [16, 17], where the most frequently described are patients who undergo or have undergone chemotherapy or radiotherapy.

The study aims to check whether individual side effects of treatment with TKIs in patients suffering from CML may contribute to the occurrence of anxiety symptoms. In addition, it was decided to check whether there were any relationships between age, gender, duration of treatment, and the intensity of anxiety, divided by the occurrence of individual side effects.

The research focused on examining the possibility of developing anxiety disorders, not on their diagnosis.

Material and methods

The study involved 91 adult patients with CML treated with tyrosine kinase inhibitors, consecutively admitted to the outpatient Hematology Department of the University Hospital (SU) in Krakow. The selection of patients was purposeful, and the patients were examined once. The patients'current mental state was assessed.

The following inclusion criteria were applied: a diagnosis of chronic myeloid leukemia, treatment with tyrosine kinase inhibitors, age > 18, and no previous diagnosis of an anxiety disorder.

The study used the following questionnaires: its own questionnaire, David Goldberg's GHQ-28 questionnaire adapted by Zofia Makowska and Dorota Merecz [18], and the four-dimensional 4DSQ questionnaire measuring four dimensions of the mental condition [19].

The constructed questionnaire included questions about the illness and the side effects of treatment. The results of research by Hartmann et al. [5] were used in creating the list of side effects.

Two questionnaires were used to assess the intensity of anxiety symptoms: GHQ-28 and 4DSQ. Each of them consists of four dimensions. In the GHQ-28 questionnaire, these are somatic symptoms, anxiety and insomnia, social dysfunction, and symptoms of depression, while the 4DSQ questionnaire includes: distress, anxiety, depression, and somatization. Only the anxiety (4DSQ) / anxiety and insomnia (GHQ-28) subscales were used in the study. In the case of the GHQ-28 scale, the results were presented using the modified Likert scale (0-3).

To verify the hypotheses formulated as part of the study, statistical analyses were carried out using the IBM SPSS Statistics version 26 package. A frequency analysis, basic descriptive statistics analysis, a series of multivariate linear regression analyses performed with the stepwise method of selecting predictors, a series of correlation analyses with Spearman's rho coefficient, and a series of chi-square independence tests were performed. The level of significance was $\alpha = 0.05$.

First, the basic descriptive statistics of the variables analyzed later in the work were calculated. Mean values were presented with standard deviations for quantitative variables and for nominal variables – frequency of occurrence.

The Bioethics Committee of the Jagiellonian University Medical College granted its approval to conduct the research (No. 1072.6120.113.2020).

Results

The study examined 91 patients with CML treated with tyrosine kinase inhibitors. The study sample consisted of 53 women and 38 men, with a mean age of 57 years (SD: 12.46; range 20 – 82 years). The most frequently mentioned side effects of treatment were bone and joint pain (68.1%), muscle cramps and pain (68.1%), water retention (64.8%), and fatigue (53.8%). The mean duration of the disease was ten years. Detailed data of the study group are presented in Table 1.

Table 1. **Basic descriptive statistics**

Variable	M	SD
Duration of treatment (years)	10.35	5.46
Age	57.15	12.46
Number of side effects	4.33	2.35
Side effects	n	%
Water retention	59	64.84
Frequent infections	19	20.88
Fatigue	49	53.85
Bruising	18	19.78
Diarrhea	26	28.57
Loss of appetite	15	16.48
Pleural effusions	4	4.40
Diabetes	5	5.49
Lipid disorders	10	10.99
Bone and joint pain	62	68.13
Nausea, indigestion	27	29.67
Abdominal pain	20	21.98
Muscle cramps and pain	62	68.13
Skin rash, itching	18	19.78

M – average*; SD* – standard deviation; *n* – number of patients

In examining the influence of side effects on the level of anxiety symptoms measured by the GHQ questionnaire (Table 2), the regression algorithm reached the final solution in step four. The model was well fitted to the data – $F(4, 86) = 7.54$; $p < 0.001$ and allowed to explain 23% of the variance of the dependent variable ($R^2_{adj.} = 0.23$). Based on the regression coefficients presented in Table 2, it was found that fatigue, nausea/indigestion, frequent infections, and bone and joint pain were side effects that statistically significantly influenced the level of anxiety. All predictors were positively associated with the dependent variable.

Table 2. **Standardized and non-standardized coefficients of the linear regression model to predict the impact of side effects on the level of anxiety symptoms measured by the GHQ questionnaire**

		B	SE	β	t	p
1	Constant	4.60	0.58		7.96	<0.001
	Fatigue	2.77	0.79	0.35	3.52	0.001
2	Constant	4.17	0.58		7.16	<0.001
	Fatigue	2.33	0.78	0.29	2.99	0.004
	Nausea, indigestion	2.22	0.85	0.26	2.61	0.011
3	Constant	3.95	0.58		6.79	<0.001
	Fatigue	2.16	0.77	0.27	2.80	0.006
	Nausea, indigestion	1.92	0.85	0.22	2.26	0.026
	Frequent infections	1.92	0.94	0.20	2.04	0.045
4	Constant	2.96	0.75		3.96	<0.001
	Fatigue	2.00	0.76	0.25	2.62	0.010
	Nausea, indigestion	1.72	0.84	0.20	2.05	0.043
	Frequent infections	1.99	0.93	0.20	2.15	0.035
	Bone and joint pain	1.66	0.80	0.20	2.08	0.041

B – non-standardized coefficient; *SE* – standard error; β – standardized coefficient; *t* – result of the *Student's t-test; p* – statistical significance

In the analysis of the impact of side effects on the level of anxiety symptoms measured with the 4DSQ questionnaire (Table 3), the regression model reached the final solution in the second step and was well fitted to the data – $F(2, 88) = 17.26$; $p < 0.001$. This model allowed to explain 27% of the variance. Based on the results presented in Table 3, it was found that abdominal pain and loss of appetite were significant predictors of anxiety. All predictors were positively associated with the dependent variable.

Table 3. **Standardized and non-standardized coefficients of the linear regression model to predict the impact of side effects on the level of anxiety symptoms measured by the 4DSQ questionnaire**

		B	SE	β	t	p
1	Constant	1.00	0.34		2.97	0.004
	Abdominal pain	3.25	0.72	0.43	4.52	<0.001
2	Constant	0.70	0.33		2.11	0.038
	Abdominal pain	2.61	0.70	0.35	3.71	<0.001
	Loss of appetite	2.68	0.79	0.32	3.41	0.001

B – non-standardized coefficient; *SE* – standard error; β – standardized coefficient; *t* –result of the *Student's t-test; p* – statistical significance

Based on the results presented in Table 4, a statistically significant, positive, and strong relationship between the age of the respondents and the anxiety measured by the GHQ questionnaire was found among the respondents with lipid disorders. This means that the older the respondent who experienced this side effect of treatment with TKIs, the higher the level of the anxiety. There was also a statistically significant, positive, and moderate linear relationship between the duration of treatment and the occurrence of anxiety measured by the GHQ questionnaire among the patients with skin rash/itching. This means that in this group, the longer the patients were treated, the higher the level of anxiety they experienced. The other correlations turned out to be statistically insignificant.

Table 4. **Correlation coefficients between anxiety (measured by GHQ and 4DSQ questionnaires) and age and duration of treatment, divided by experienced side effects of treatment with tyrosine kinase inhibitors**

Side effects	Anxiety symptoms	Age	Duration of treatment
Water retention	GHQ	0.23	0.07
	DSQ	-0.07	0.01
Frequent infections	GHQ	0.25	-0.07
	DSQ	-0.15	-0.01
Fatigue	GHQ	0.27	0.15
	DSQ	-0.11	-0.05
Bruising	GHQ	0.11	0.40
	DSQ	0.04	0.40
Diarrhea	GHQ	0.38	0.09
	DSQ	0.08	0.06
Loss of appetite	GHQ	-0.04	0.02
	DSQ	-0.33	-0.03
Pleural effusions	GHQ	0.65	-0.83
	DSQ	-	-
Diabetes	GHQ	0.71	0.80
	DSQ	-0.06	0.82
Lipid disorders	GHQ	0.69*	0.40
	DSQ	-0.28	0.55
Bone and joint pain	GHQ	0.24	0.04
	DSQ	-0.04	-0.02
Nausea, indigestion	GHQ	0.08	-0.07
	DSQ	-0.14	0.18

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Abdominal pain	GHQ	0.36	-0.08
	DSQ	-0.15	0.05
Muscle cramps and pain	GHQ	0.22	0.09
	DSQ	0.01	0.04
Skin rash, itching	GHQ	0.45	0.48*
	DSQ	-0.31	-0.32

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

The analysis of the impact of side effects of treatment with tyrosine kinase inhibitors on the level of anxiety measured by the GHQ and 4DSQ questionnaires separately for women and men showed that in the case of women surveyed with the GHQ questionnaire, the regression algorithm achieved the final solution in the first step. The model turned out to be well fitted to the data – $F(1, 51) = 7.31$; $p = 0.009$ and allowed to explain 11% of the variance of the dependent variable ($R^2_{adj.} = 0.11$). Based on the results presented in Table 5, it was found that fatigue was a significant predictor of anxiety measured with the GHQ questionnaire. This predictor was positively related to the explained variable.

Table 5. **Standardized and non-standardized coefficients of the linear regression model for predicting the impact of side effects on the level of anxiety measured by the GHQ questionnaire among female respondents**

	B	SE	β	t	p
Constant	5.68	0.86		6.63	<0.001
Fatigue	3.03	1.12	0.35	2.70	0.009

B – non-standardized coefficient; *SE* – standard error; β – standardized coefficient; *t* – result of the *Student's t-test; p* – statistical significance

In women examined with the 4DSQ questionnaire (Table 6), the regression algorithm reached the final solution in the second step. The model turned out to be well fitted to the data – $F(2, 50) = 13.69$; $p < 0.001$ and allowed to explain 33% of the variance of the dependent variable ($R^2_{adj.} = 0.33$). Abdominal pain and loss of appetite were significant predictors in this model. Both predictors were positively related to the dependent variable.

Table 6. **Standardized and non-standardized coefficients of the linear regression model to predict the impact of side effects on the level of anxiety measured by the 4DSQ questionnaire among female respondents**

		B	SE	β	t	p
1	Constant	1.46	0.53		2.73	0.009
	Abdominal pain	4.32	1.04	0.50	4.16	<0.001

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2	Constant	1.00	0.53		1.89	0.064
	Abdominal pain	3.50	1.02	0.41	3.43	0.001
	Loss of appetite	3.00	1.08	0.33	2.79	0.007

B – non-standardized coefficient; *SE* – standard error; β – standardized coefficient; *t* – result of the *Student's t-test; p* – statistical significance

In the case of men tested with the GHQ questionnaire, the regression algorithm reached the final solution in step three. The model was well fitted to the data – $F(3, 34) = 7.55$; $p = 0.001$ and allowed to explain 35% of the variability in anxiety measured with the GHQ questionnaire ($R^2_{adj.} = 0.35$). Based on the results presented in Table 7, it was found that the presence of abdominal pain, fatigue, and bruising were significant predictors of anxiety. Only the occurrence of bruises was negatively associated with the dependent variable. This means that the more this side effect occurred, the less anxiety the male respondents felt.

Table 7. **Standardized and non-standardized coefficients of the linear regression model for predicting the impact of side effects on the level of anxiety measured by the GHQ questionnaire among male respondents**

		B	SE	β	t	p
1	Constant	3.78	0.43		8.88	<0.001
	Abdominal pain	2.55	1.07	0.37	2.38	0.023
2	Constant	2.83	0.54		5.25	<0.001
	Abdominal pain	2.87	1.00	0.42	2.87	0.007
	Fatigue	1.91	0.73	0.38	2.61	0.013
3	Constant	3.04	0.50		6.03	<0.001
	Abdominal pain	2.55	0.93	0.37	2.74	0.010
	Fatigue	2.23	0.69	0.44	3.24	0.003
	Bruising	-2.96	1.12	-0.36	-2.64	0.012

B – non-standardized coefficient; *SE* – standard error; β – standardized coefficient; *t* – result of the *Student's t-test; p* – statistical significance

Next, an analysis analogous to the previous one was performed, this time for men surveyed with the 4DSQ questionnaire (Table 8). The regression algorithm reached the final solution in the first step. The model turned out to be well fitted to the data – $F(1, 36) = 4.48$; $p = 0.041$ and allowed to explain 9% of the variance of the dependent variable ($R^2_{adj.} = 0.09$). Based on the results presented in Table 8, it was found that diarrhea was a significant predictor of anxiety. This variable was positively related to the regression model.

Table 8. **Standardized and non-standardized coefficients of the linear regression model to predict the impact of side effects on the level of anxiety measured by the 4DSQ questionnaire among male respondents**

	B	SE	β	t	p
Constant	0.35	0.13		2.71	0.010
Diarrhea	0.65	0.30	0.33	2.12	0.041

B – non-standardized coefficient; *SE* – standard error; β – standardized coefficient; *t* – result of the *Student's t-test; p* – statistical significance

Discussion

The prevalence of anxiety disorders in the general population is estimated at approx. 3-15% [20], while in the case of cancer patients and patients with chronic myeloid leukemia it is approx. 10% [12, 21–23]. In our study, the influence of individual side effects of treatment with tyrosine kinase inhibitors on the appearance of anxiety symptoms in patients with CML was assessed. Early recognition of anxiety symptoms may consequently prevent the emergence of this type of disorder.

Our research showed that fatigue, nausea/indigestion, frequent infections, bone and joint pain, abdominal pain, and loss of appetite were the side effects of TKI treatment that resulted in an increased level of anxiety symptoms (Tables 2 and 3). Jiang et al. [24], in a study on the concerns of patients and hematologists regarding treatment with tyrosine kinase inhibitors in chronic myeloid leukemia, showed that both patients and hematologists are concerned about treatment with the use of TKIs due to the occurrence of adverse effects. There are many international studies in the literature devoted to the side effects of TKI therapy [22, 25-29] and the impact of the disease itself on the occurrence of anxiety disorders [23, 30, 31]; however, no attempts have been made yet to identify the relationship of these factors together, except for several studies that have focused on quality of life in patients treated with TKIs. In the study of Yu et al. [21] assessing the variables related to symptoms reported by patients with CML and receiving TKIs and their impact on quality of life, 1142 patients treated with: imatinib (Glivec, Imatinib Teva), nilotinib (Tasigna), and dasatinib (Sprycel) were examined. At least one side effect of TKI treatment was observed in 97% of the respondents, the most frequent being: fatigue (77%), periorbital and lower limb edema (72%), chest pain and shortness of breath (61%), memory impairment (54%), skin color change (44%), alopecia (44%), muscle spasms (42%), weight gain (42%), musculoskeletal pain (42%) and itchy skin (38%). Additionally, the study confirmed that some side effects of treatment had a negative impact on health-related quality of life [21]. The presence of side effects of treatment with TKIs may lead to changes in the treatment method or complete discontinuation of therapy [32] and may also contribute to the development of anxiety symptoms. The occurrence of anxiety disorders may also overlap with various somatic symptoms; however, the relationship between physical symptoms and anxiety is complex [33]. Some studies indicate such a cor-

relation [34], while others indicate that physical symptoms may occur independently of anxiety symptoms [35].

The verification of the relationship between the age of the respondents and anxiety divided by the perceived side effects of TKI treatment showed that one side effect in the form of lipid disorders turned out to be statistically significant. The older the patients with lipid disorders, the greater the anxiety they experienced (Table 4). In our study, it was expected that more than one side effect would be related to the age of the respondents and anxiety, as the results of some studies indicate that age is important in the occurrence of anxiety symptoms in cancer patients [30, 36, 37]. A study by Linden et al. [36] on anxiety and depression after cancer diagnosis showed that younger patients with hematological neoplasms are more than twice as likely to report a clinical level of anxiety as the elderly. Although no analyses of the relationship between the age of the respondents and anxiety divided by the perceived side effects of treatment have been conducted so far, it was assumed that the results would be similar to the studies presented above. Perhaps the results will be different when the research group is enlarged, where the number of people suffering from particular side effects will be greater. In addition, the type of oncological disease, the method of treatment, and the experienced side effects may be important.

The results of our research on the relationship between the duration of treatment and anxiety divided by experienced side effects of TKIs showed that in the group of patients with skin rash/itching ($n = 18$), the longer the patients were treated, the greater the anxiety they experienced (Table 4). No relationships were observed in the remaining 13 groups. The study by Shi et al. [23] compared the anxiety symptoms reported by patients before and during TKI therapy. The researchers did not find significant changes in the Self-Rating Anxiety Scale (SAS) scores during treatment. The severity of anxiety symptoms was the same both before and during treatment with TKIs [23]. Similarly, studies by Jadoon et al. [38] on the assessment of depression and anxiety in adult cancer outpatients and Malekian et al. [39] on anxiety and depression in cancer patients also indicate a lack of correlation between the duration of treatment and the occurrence of anxiety symptoms. Perhaps due to the adaptive functionality of anxiety, patients develop an appropriate defense strategy along with the course of the disease and experience of possible treatment side effects. From an existentialist perspective, moderate anxiety is an appropriate response as an adaptive function to specific events or threats in life. This anxiety can be used as a motivation to change oneself or to adapt to a situation. Along with the duration of a given event, we get used to the new situation we are in, and adaptation occurs in a properly functioning defense system [40].

The results of our research on the relationship between gender and the severity of anxiety measured with both used questionnaires, divided by the occurrence of individual side effects, showed that the two groups did not differ significantly from each other. It was observed that in both women and men, the occurrence of three side effects influenced the appearance of anxiety symptoms: fatigue and abdominal pain in both sexes, loss of appetite in women, and the occurrence of diarrhea in men (Tables 5-8). In the study of Yu et al. [21], it was observed that in women, the symptoms of TKI treatment appeared more often and in a greater number. In other studies [21, 23, 41, 42],

anxiety symptoms in patients with chronic myeloid leukemia were analyzed without dividing by the occurrence of individual side effects. Most studies show that women have higher anxiety levels than men. Our differing results may have been caused by the introduction of a division in terms of the occurrence of TKI treatment side effects, a difference in the sample size and the use of other research tools. The study by Shi et al. [23] examined 1169 patients with CML; in the study by Yu et al. [21], there were 1142 such patients, and in the study by Efficace et al. [41] – 417. Each of these studies used different research tools.

Our research has some limitations. We did not analyze the impact of the disease itself on the severity of anxiety symptoms, so it should be considered that the mere fact of fighting the disease may affect their occurrence. The study also did not analyze the patient's mental condition before starting the therapy, so we could not compare whether the patient's condition had changed since the diagnosis. Additionally, self-descriptive questionnaires were used in the study, which do not indicate the occurrence of anxiety disorders, but the intensification of anxiety symptoms. The diagnosis of an anxiety disorder can only be made based on an interview, which takes into account the diagnostic indicators ICD-11 or DSM-5. It is also challenging to determine whether all the side effects reported by the patient are due to treatment with TKIs or other factors such as comorbidities, taking other medications, mental state, patient's resources, etc. that may have an impact on the presented results.

Conclusions

Anxiety is a common symptom in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. However, it can also be part of adaptation to disease or treatment side effects. Some side effects of TKI treatment increase anxiety symptoms in patients with CML. A minimal relationship was observed between the age of the respondents and the duration of treatment, and the severity of anxiety symptoms divided by the occurrence of side effects of TKI therapy. The occurrence of one side effect impacted the severity of anxiety symptoms in the relationship between the age of the respondents and the duration of treatment. In the analysis of the relationship between gender and the severity of anxiety, non-significant differences between the groups were found.

Our research shows the importance of the side effects of TKI treatment for the appearance of anxiety symptoms. The work of doctors, psychologists, and pharmaceutical companies on reducing/alleviating side effects may in the future affect a better quality of life for these patients. In addition, several years of attempts to discontinue treatment with some TKIs (imatinib and nilotinib) in patients who achieve a profound molecular response [43, 44] may improve their mental condition.

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