Original paper

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

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Introduction: The aim of the study was to check whether individual side effects of treatment with tyrosine kinase inhibitors (TKI) in patients suffering from chronic myeloid leukaemia (CML) contribute to the occurrence of depressive symptoms. In addition, it was decided to check whether there is any correlation between the age, sex, and duration of treatment and the intensity of depressive symptoms, in relation to the occurrence of individual side effects.

Material and methods: The study included 91 patients with CML treated with TKI. The following questionnaires were used: a questionnaire created by the author, David Goldberg's general health questionnaire-28 (GHQ-28), and the four-dimensional symptom questionnaire (4DSQ).

Results: Our research showed that fatigue ($\beta = 0.27$; $p = 0.007$), nausea/indigestion ($\beta = 0.26$; $p = 0.008$), bone and joint pain ($\beta = 0.21$; $p = 0.033$), and abdominal pain ($\beta = 0.33$; $p \leq 0.001$) were the most common side effects of TKI treatment resulting in increased depressive symptoms. Age and duration of treatment had a significant impact on the severity of depressive symptoms in patients experiencing specific side effects of TKI treatment.

Conclusions: The results indicate the influence of the occurrence of TKI treatment side effects on the development of depressive symptoms. Patients' quality of life can be improved with the cooperation of medical staff in reducing/alleviating the side effects.

Key words: chronic myeloid leukaemia, depressive disorders, tyrosine kinase inhibitors.

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Introduction

Chronic myeloid leukaemia (CML) belongs to the group of myeloproliferative neoplasms. At a molecular level, the disease results from a reciprocal translocation between chromosomes, resulting in an abnormal BCR/ABL fusion gene. There are 3 phases in CML: chronic, accelerated, and blast. Treatment depends on the phase of the illness as well as the patient's age, general health, and comorbidities. Currently, the most common treatment is using tyrosine kinase inhibitors (TKI), which have radically and irreversibly changed the treatment of CML [1, 2]. Many studies indicate that the troublesome side effects of TKI treatment may influence discontinuation of treatment [3–6]. The most common side effects of TKI treatment separated by the drugs of the first (imatinib), second (dasatinib, nilotinib, bosutinib), and third generations (ponatinib) are presented in Table 1 [4, 7–10].

Depending on the type of research tools used, diagnostic criteria, type of cancer, phase of the illness, and type of therapy, approximately 8–50% of oncological patients are diagnosed with clinical depression [1–4]. The possible impact of side effects of the treatment on the emergence of depressive disorders is often taken up by researchers in analyses on the quality of life of patients with cancer [5–8]. Patients who are undergoing or have undergone chemotherapy or radiotherapy are most commonly analysed and described.

In patients with CML treated with TKI, the quality of life is described as worse when compared to healthy patients. Moreover, taking various TKI drugs (first, second, and third generation) differentiates the individual groups [9–11]. In addition, patients with CML are at risk of developing depressive symptoms [12, 13].

Information about possible mental disorders in patients undergoing cancer treatment may be important in the context of identifying the patients' needs during further medical care.

The aim of the study was to analyse whether the individual side effects of treatment with TKI drugs (first, second, and third generation) may contribute to the occurrence of depressive symptoms. Additionally, it was decided to check whether additional factors, such as sex, duration of treatment, and age, would affect the obtained results.

The aim of the study was not to diagnose depressive disorders, but to check the possibility of their development during TKI treatment.

The Bioethics Committee at the Jagiellonian University in Kraków approved the study (No. 1072.6120.113.2020). Each participant obtained information about the study and patient confidentiality, and gave their written consent to participate.

Table 1. Frequency of side effects of tyrosine kinase inhibitors treatment

Adverse reactions	TKI				
	Imatynib [11] (Glivec)	Dasatynib [12] (Sprycel)	Nilotynib [13] (Tasigna)	Bosutynib [14–16]	Ponatynib [15, 16] (Iclusig)
Neutropaenia	***	***	***	***	***
Thrombocytopaenia	***	***	***	***	***
Fluid retention/oedema	***	**	*	*	*
Muscle pain	***	**	*	*	**
Fatigue	***	**	*	*	**
Headache	**	**	**	*	**
Skin changes/rash	***	**	***	**	***
Diarrhoea	*	*	*	***	*
Anaemia	**	**	**	**	**
Abdominal pain	**	*	**	**	**
Fever	*				*
Hypertension					***
Pleural effusions		**			

TKI – tyrosine kinase inhibitors
*Frequency * 7–20%, ** 20–30%, *** > 30%*

Material and methods

The study is a retrospective analysis of adult CML patients treated with TKI. Respondents for the study were recruited from patients successively admitted to the outpatient Haematology Department of the University Hospital in Kraków. The selection of patients was purposeful. The patients were examined once. The patients were informed about the purpose of the study, and their consent was obtained.

Patients were excluded from the study if they met the exclusion criteria: attending psychiatric or psychological (psychotherapeutic) treatment during the examination period or up to 3 months before its start, discontinuation of TKI treatment or switching to another drug, initiation of TKI treatment during the examination or up to 3 months before starting treatment, or feeling similar symptoms to those mentioned in the questionnaire at least one month before starting treatment with TKI. Eight patients were excluded from the study, ultimately enrolling 91 patients (53 women and 38 men). The mean age in the research group was 57 years (20–82 years) (SD = 12.46).

In order to assess the patients' mental health, the following questionnaires were used: the author's own questionnaire, David Goldberg's general health questionnaire-28 (GHQ-28) [14], and the four-dimensional symptom questionnaire (4DSQ) [15]. The general health questionnaire-28 and 4DSQ questionnaires are often used in studies of cancer patients [16–20].

The author's questionnaire included questions regarding the patient's sociodemographic variables, the duration of the illness, and the side effects of treatment. The questionnaire lists the 14 most common side effects of TKI, listed in Table 1. Patients could also enter a side effect that was not included in the list.

Using GHQ-28, it is possible to detect psychological disorders in 4 subscales: somatic symptoms, anxiety/insomnia, social dysfunction, and symptoms of depression. The general health questionnaire-28 is used as a tool to measure emotional stress and detect mental disorders [21].

The final tool used in the study is the 4DSQ, which measures 4 dimensions of mental health: distress, anxiety, depression, and somatisation.

Only the subscale of depressive symptoms was used in the study. In the case of the GHQ-28 scale, the results are presented using a Likert scale.

Statistical analyses were performed using the IBM SPSS Statistics 28 package. It was used to perform a frequency analysis, an analysis of basic descriptive statistics, a series of multivariate linear regression analyses performed using the stepwise predictor selection method, a series of correlation analyses with Spearman's Rho coefficient, and a series of χ^2 independence tests. The significance level was $\alpha = 0.05$.

Results

Detailed characteristics of the occurrence of individual side effects of TKI treatment in all studied patients are presented in Table 2.

All patients who participated in the study ($n = 91$) experienced side effects of TKI treatment.

The regression coefficients in Table 3 revealed that fatigue, nausea/indigestion, as well as bone and joint pain were the side effects that had a significant influence on the level of depressive symptoms. All predictors were positively associated with the dependent variable.

Based on the results presented in Table 4, it was found that abdominal pain was a significant predictor of depressive symptoms. The predictor was positively related to the dependent variable.

The next analysis examined whether there were any correlations between age, duration of treatment, and severity of depressive symptoms, according to experienced side effects.

Table 2. The occurrence of individual side effects of treatment with tyrosine kinase inhibitors

Side effects	*n*	%
Fluid retention/oedema	59	64.84
Frequent infections	19	20.88
Fatigue	49	53.85
Bruising	18	19.78
Diarrhoea	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
Cramps, muscle pain	62	68.13
Skin rash, itching	18	19.78

Table 4. Standardised and non-standardised coefficients of a linear regression model to predict the impact of side effects on the level of depressive symptoms measured by the four-dimensional symptom questionnaire

	Parameters	B	SE	β	*t*	*p*
1	Constant	0.54	0.21		2.58	0.011
	Abdominal pain	1.47	0.44	0.33	3.31	< 0.001

B – non-standardised coefficient, β – standardised coefficient, p – statistical significance, SE – standard error, t – the result of Student's t-test.

Based on the results presented in Table 5, statistically significant correlations were found between the age of the respondents and the occurrence of depressive symptoms measured by the GHQ. Strong and moderate positive correlations were found in patients who experienced the following side effects of TKI: fluid retention/oedema (*rs* = 0.33), fatigue (*rs* = 0.30), diarrhoea (*rs* = 0.47), lipid disorders (*rs* = 0.76), bone and joint pain (*rs* = 0.29), cramps and muscle pain (*rs* = 0.28), as well as skin rash and itching (*rs* = 0.51). The older the person who experienced this side effect of treatment with TKI, the higher the level of the depressive symptoms. Additionally, a statistically significant moderate positive linear relationship was found between the duration of treatment and the level of depressive symptoms measured by the GHQ among patients with skin rash and itching (*rs* = 0.67). In this group, the longer the patients were treated, the higher the level of depressive symptoms. The other correlations turned out to be statistically insignificant.

The analysis of the impact of side effects of treatment with TKI on the level of depressive symptoms measured by the GHQ and 4DSQ was measured separately for women and men.

Based on the results presented in Tables 6 and 7, it was found that fatigue, cramps, and muscle and abdominal pain were significant predictors of the level of depressive symptoms for women. These predictors were positively related to the dependent variable.

Table 3. Standardised and non-standardised coefficients of a linear regression model to predict the impact of side effects on the level of depressive symptoms measured by the general health questionnaire

	Parameters	B	SE	β	*t*	*p*
1	Constant	3.93	0.60		6.54	< 0.001
	Fatigue	2.77	0.82	0.35	3.50	0.001
2	Constant	3.44	0.60		5.73	< 0.001
	Fatigue	2.36	0.81	0.29	2.93	0.004
	Nausea/indigestion	2.57	0.88	0.29	2.92	0.004
3	Constant	2.36	0.77		3.01	0.003
	Fatigue	2.19	0.79	0.27	2.77	0.007
	Nausea/indigestion	2.36	0.87	0.26	2.72	0.008
	Bone and joint pain	1.81	0.84	0.21	2.17	0.033

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

Table 5. Correlation coefficients between the level of depressive symptoms (measured by the general health questionnaire and four-dimensional symptom questionnaire) and both age and duration of treatment, divided by side effects of treatment with tyrosine kinase inhibitors

Side effects	Depressive symptoms	Age	Treatment duration
Fluid retention/oedema	GHQ	0.33*	0.61
	DSQ	0.95	–0.11
Frequent infections	GHQ	0.21	0.06
	DSQ	–0.04	–0.15
Fatigue	GHQ	0.30*	0.10
	DSQ	–0.05	–0.01
Bruising	GHQ	0.18	0.37
	DSQ	0.06	0.36
Diarrhoea	GHQ	0.47*	0.02
	DSQ	0.13	–0.13
Loss of appetite	GHQ	0.07	–0.03
	DSQ	–0.06	–0.18
Pleural effusions	GHQ	0.77	–0.70
	DSQ	–	–
Diabetes	GHQ	0.58	0.77
	DSQ	0.45	–0.70
Lipid disorders	GHQ	0.76*	0.37
	DSQ	–0.51	0.24
Bone and joint pain	GHQ	0.29*	0.07
	DSQ	0.15	–0.10
Nausea, indigestion	GHQ	0.18	–0.17
	DSQ	–0.01	0.11
Abdominal pain	GHQ	0.44	–0.09
	DSQ	0.16	–0.16
Cramps. muscle pain	GHQ	0.28*	0.04
	DSQ	0.10	–0.09
Skin rash, itching	GHQ	0.51*	0.32
	DSQ	0.36	0.67**

DSQ – dimensional symptom questionnaire, GHQ – general health questionnaire
*** p < 0.01; * p < 0.05*

Table 6. Standardised and non-standardised coefficients of the linear regression model for predicting the impact of side effects on the level of depressive symptoms measured by the general health questionnaire among the surveyed women

	Parameters	B	SE	β	*t*	*p*
1	Constant	4.77	0.90		5.31	< 0.001
	Fatigue	3.20	1.18	0.36	2.72	0.009
2	Constant	3.06	1.21		2.53	0.015
	Fatigue	3.13	1.14	0.35	2.74	0.008
	Cramps and muscle pain	2.52	1.22	0.26	2.06	0.045

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

Table 7. Standardised and non-standardised coefficients of the linear regression model to predict the impact of side effects on the occurrence of depressive symptoms measured with the four-dimensional symptom questionnaire among the surveyed women

	Parameters	B	SE	β	*t*	*p*
1	Constant	0.74	0.34		2.20	0.032
	Abdominal pain	1.69	0.66	0.34	2.56	< 0.013

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

Based on the results presented in Tables 8 and 9, it was found that the presence of abdominal pain, fatigue, diabetes, and bruises were significant predictors of depressive symptoms for men. Only the occurrence of bruises was negatively associated with the dependent variable. The more prevalent this side effect, the less depression felt by the respondents.

Discussion

The results of some studies indicate that depression is a disorder that occurs in patients with chronic myelogenous leukaemia treated with TKI [12]. In our study, we assessed the impact of the occurrence of individual side effects of TKI treatment on the appearance of depressive symptoms in patients with CML.

The results of our research showed that fatigue, nausea/indigestion, bone and joint pain, and abdominal pain were the side effects of TKI treatment which caused the occurrence of depressive symptoms (Tables 3, 4). Many studies are concentrated on the side effects of TKI therapy [22–24]. In a study by Phillips *et al*. on the quality of life of patients with chronic myelogenous leukaemia treated with TKI, a group of patients treated with imatinib, nilotinib, and dasatinib was compared with a group of healthy patients. Studies have shown that patients with CML treated with TKI ($n = 62$) obtained significantly higher scores than the control group ($n = 62$) in such variables as fatigue (measured with the FSI questionnaire), depression (measured with the CES-D scale), skin changes, nausea, diarrhoea, swelling, itching, dizziness, and changes in appearance (symptoms measured by MSAS-SF) [25]. Similar results were attained in a study by Shi *et al*. on the variables associated with self-reported symptoms of anxiety and depression in patients with chronic myelogenous leukaemia treated with TKI. The results of the above studies confirmed the presence of depression in 37% of the respondents [12]. In contrast, in a study by Efficace *et al*. on the health-related quality of life of patients with chronic myelogenous leukaemia receiving long-term imatinib therapy compared to the general population, fatigue was identified as the predominant side effect of imatinib treatment among CML patients [26].

In existing literature, we can find some connections between fatigue, abdominal pain, and depression. Walter's study on the relationship between abdominal pain, anxiety, and depression found that the intensity of depressive symptoms was higher in people reporting abdominal pain compared to those who did not report it ($p < 0.0005$) [27]. However, Yu's study of 1142 CML patients treated with TKI for at least 3 months confirmed that side effects such as fatigue and abdominal pain were associated with significantly lower scores on the physical component summary scale in the health related quality of life questionnaire [28]. Ozminkowski *et al*. also confirmed that abdominal pain in a patient may lead to the development of depressive disorders [29]. The impact of these 2 side effects of TKI treatment on the development of depressive symptoms can be justified by the assumption that the patient has greater difficulty adapting to abdominal pain (and pain overall) and fatigue than to the other side effects of TKIs. Perhaps they

Table 8. Standardised and non-standardised coefficients of a linear regression model for predicting the impact of side effects on the appearance of depressive symptoms measured by the general health questionnaire among male respondents

	Parameters	B	SE	β	*t*	*p*
1	Constant	3.41	0.50		6.85	< 0.001
	Abdominal pain	2.76	1.25	0.35	2.21	0.034
2	Constant	2.38	0.64		3.73	< 0.001
	Abdominal pain	3.10	1.19	0.39	2.62	0.013
	Fatigue	2.05	0.87	0.35	2.37	0.023
3	Constant	2.63	0.60		4.38	< 0.001
	Abdominal pain	2.73	1.11	0.34	2.46	0.019
	Fatigue	2.42	0.82	0.42	2.97	0.005
	Bruises	–3.44	1.33	–0.36	–2.58	0.014

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

have a greater impact on the patient's mental state, especially when the duration of the side effects is prolonged.

The verification of the relationship between age and the occurrence of depressive symptoms, according to the side effects of TKI treatment, showed that the statistically significant side effects were fluid retention/oedema, fatigue, diarrhoea, lipid disorders, bone and joint pain, muscle pain/cramps, and skin rash/itching. The older the patient with these side effects, the more often the depressive symptoms would occur (Table 5). Research emphasises that the risk of side effects associated with TKI treatment, in particular fluid retention, increases after the age of 65 years [30–32]. Some studies also analyse the relationship between the age of cancer patients and the occurrence of depression. The results indicate that depressive symptoms in elderly cancer patients are related to the side effects of the disease and its treatment, comorbidities, lack of acceptance of the disease, changes or failures in the treatment, or poor social support [1, 33, 34]. Some research results on haemato-oncological patients indicate that younger patients are more likely to suffer from depression compared to older patients [35, 36]. The differences may result from the analysed group; in some studies, these are cancer patients, and in others, haemato-oncology patients. The type of cancer, and thus the methods of treatment, can significantly affect the results.

The results of our research on the relationship between the duration of TKI treatment and the occurrence of depressive symptoms, according to the experienced side effects, showed that in the group of patients with skin rash/itching (n = 18), the longer the patients were treated, the greater the possibility of developing depressive symptoms (Table 5). Studies confirm that the above-mentioned side effects of TKI are common in patients undergoing treatment for CML. In 2- and 4-year observational studies on the side effects of treatment using bosutinib, the incidence of skin rash in patients was approximately 35% [37, 38]. In addition, studies by Shi *et al*. show a relationship between the duration of treatment and the possibility of developing depression. In the analysis of variables related to self-reported symptoms of anxiety and depression in patients with CML receiving TKI, the researchers showed a significant correlation between the duration of treatment (1–3 years and > 5 years) with more severe symptoms of depression (2.426–3.020; p = 0.032 and 0.003) [12]. In contrast, other studies indicate that a longer duration of treatment with second-generation TKIs is associated with less frequent and milder side effects [26, 39–41]. According to the data in Table 1, the type of TKI treatment taken may affect the differences in the results.

The results of our research on the relationship between sex and the occurrence of depressive symptoms measured by both questionnaires, according to the occurrence of individual side effects, showed that the 2 groups did not differ significantly from each other. It has been observed that in both women and men, the occurrence of five side effects contributes to the occurrence and development of depressive symptoms: fatigue and abdominal pain in both sexes, cramps and muscle pain in women, and bruising and diabetes in men (Tables 6–9). The obtained results are slightly different from those mentioned in other studies. For example, Rakshith *et al*.'s study of differences in drug effects and/or toxicity in oncology depending on the sex of the patients points to particular discrepancies; the researchers acknowledge that women and men cope with the disease differently, and that the type of cancer, treatment, side effects occurring during therapy, and biological conditions are important factors differentiating these groups [42]. In a study by Isfort *et al*. on the quality of life of patients treated with bosutinib, women reported more severe symptoms than men, with significant differences being found for fatigue (31 vs. 51, p = 0.01) and insomnia (24 vs. 42, p = 0.04) [43]. Other studies also emphasise that fatigue is one of the most common side effects of TKI treatment, and female sex is associated with more frequent and more severe symptoms of treatment [26, 28, 39, 44]. Only minor correlations can be explained by the fact that the above-mentioned side effects of TKI treatment are so frequent and/or experienced by patients of both sexes that they may affect the possibility of depressive symptoms in a similar way in both groups. In addition, differences in group sizes and intake of various first-, second-, or third-generation TKIs [9–11] may affect the obtained results.

Table 9. Standardised and non-standardised coefficients of the linear regression model to predict the impact of side effects on the level of depressive symptoms measured with the four-dimensional symptom questionnaire among the studied men

Parameters	B	SE	β	*t*	*p*
Constant	0.24	0.15		1.59	0.121
Diabetes	1.52	0.46	0.48	3.32	0.002

B – non-standardised coefficient, β – standardised coefficient, p – statistical significance, SE – standard error, t – the result of Student's t-test
More statistics on the above results are presented in the supplementary data

The above findings confirm that certain treatment side effects influenced the development of depressive symptoms in CML patients during TKI therapy.

Our study has some limitations: despite the initial interview, it is difficult to determine whether the side effects of TKI treatment and their relationship with depressive symptoms are the effect of the disease, worse coping with the disease, or a side effect of the therapy. Another limitation is the use of questionnaires that are not used to diagnose depressive disorders, but to measure the severity of depressive symptoms. The diagnosis of depressive disorders should be based on an interview, which should consider the diagnostic indicators of ICD 11 or DSM V.

Conclusions

Individual side effects of TKI treatment in patients with chronic myelogenous leukaemia affect the occurrence of depressive symptoms and are a clear indicator of their severity. In the case of the relationship between age and the duration of treatment according to side effects, in patients experiencing fluid retention/oedema, fatigue, diarrhoea, lipid disorders, bone and joint pain, muscle pain/spasm, and skin rash/itching, the younger the patient, the lower the severity of depressive symptoms. In patients experiencing a side effect in the form of skin rash/itching,

the longer the duration of treatment, the greater the severity of depressive symptoms.

As mentioned above, it is difficult to determine whether the side effects of TKI treatment and their relationship with depressive symptoms are the result of the disease, worse coping, or a side effect of the therapy. The above study is an introduction to further research into the relationship between various treatment methods and their side effects, and the mental state of oncological patients.

In chronically treated patients, special attention should be paid to the occurrence of severe and long-lasting side effects. The risk of developing depressive disorders in the group of patients with CML is high; therefore, there is a need for special psychological, psychiatric, and educational care. Healthcare professionals working with CML patients could discuss the possible side effects of treatment with the patients and give advice on how to deal with them. Patients' knowledge and awareness of potential side effects before starting the treatment process could reduce their anxiety and the risk of developing depressive symptoms.

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