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ORIGINAL RESEARCH ARTICLE

Comparison of depressive, anxiety, and somatic symptoms in patients with Philadelphia negative chronic myeloproliferative neoplasms treated with interferon alpha

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Abstract

Introduction: The study aims to analyze the occurrence of depression, anxiety, and somatic symptoms in patients with chronic myeloproliferative neoplasms (essential thrombocythemia, polycythemia vera, and myelofibrosis) and to check whether individual side effects of interferon alpha treatment may contribute to the occurrence of depression, anxiety, and somatic 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.

Material and methods: The study involved 84 patients and was conducted at the Hematology Clinic of the University Hospital in Krakow and the Clinic of Hematology, Blood Cancer and Bone Marrow Transplantation in Wrocław. The following questionnaires were used: created by the author, David Goldberg General Health Questionnaire 28 (GHQ-28), and the Four-Dimensional Questionnaire (4DSQ).

Results: The most frequently reported side effects of treatment were abdominal pain, fatigue, and bone and joint pain. Almost 40% of the respondents obtained a moderately and strongly

increased result on the depression scale, less than 50% on the anxiety scale, and over 60% on the somatization scale. Somatic symptoms had the greatest impact on the occurrence of mental disorders, with anxiety symptoms being second in significance. There are differences in the severity of depressive, anxiety, and somatic symptoms depending on the side effects of interferon alpha treatment.

Conclusions: The finding of the above study indicates the need for further research into the importance of detecting depressive, anxiety, and somatic disorders, and to addressing concomitant physical symptoms, both in patients with myeloproliferative neoplasms receiving interferon alpha and treated with other methods. In patients treated chronically, the occurrence of side effects of high intensity and lasting for a long time should alert medical personnel. The collected data on patients with myeloproliferative neoplasms who have to suffered from mental and physical symptoms of the disease or its treatment justifies the need for caring psychological, psychiatric, and educational care.

Key words: depresson, anxiety, somatization, myeloproliferative neoplasms, essential thrombocythemia, polycythemia vera, myelofibrosis, interferon alpha

Introduction

Chronic myeloproliferative neoplasms (MPNs) are a heterogeneous group of disorders characterized by the overproduction of mature cells from one or more myeloid lineages. The most common are polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis (primary; PMF, or post-ET-MF or post-PV-MF), and chronic myeloid leukemia (CML), which is treated separately due to the presence of the Philadelphia chromosome and different treatments [1].

In most patients with myeloproliferative neoplasms without the Philadelphia chromosome, mutations in the *JAK2* [2], *MPL* [3, 4] or *CALR* genes [5] are detected.

In the initial phase of the disease, a significant proportion of patients do not develop any clinical symptoms, and the disease is usually detected via routine blood tests. The exception is myelofibrosis, where, in more than half of cases, symptoms may appear in the form of significant weakness, bone and muscle pains, fever, itching of the skin, night sweats or discomfort in the abdominal cavity. The peripheral blood count of patients with MPN may include leukocytosis, thrombocythemia, or/and an increase in the number of erythrocytes, hemoglobin, and hematocrit. Typically, this type of cancer develops slowly and can affect

people of all ages, but the most common age at incidence is between 50 and 70 years. In Poland, the annual incidences are: of polycythemia vera 2.5/100,000 population [men suffer more often than women (1–2:1)]; of essential thrombocythemia 1.5/100,000 of the population; of primary myelofibrosis 0.5–1.5/100,000 population; and of CML 0.7/100,000 population. The treatment used depends on the type of myeloproliferative disorder and on the presence of risk factors [6–10].

In the pharmacological treatment of PV, ET, and MF, interferon alpha (IFNα) [11–13] is often used, mainly in the form of peginterferon alpha-2a (Pegasys®) [14, 15] or ropeginterferon alpha-2b (Besremi®) [16]. Interferon alpha was introduced to the treatment of patients with myeloproliferative neoplasms without the Philadelphia chromosome more than 30 years ago [17]. This medication also has antiviral properties; therefore it is also used in the treatment of viral diseases such as hepatitis B and C and Kaposi's sarcoma [18].

The side effects of interferon alpha in patients suffering from myeloproliferative neoplasms have been widely reported in the literature [19–21]. Apart from hematological, neurological, and rheumatological symptoms, the most common side effects include fatigue, loss of appetite, nausea, diarrhea, muscle pain, skin rash, headaches, and abnormal triglyceride levels [22–27].

Both cancer itself (with its mental and physical comorbidities) [28] and the side effects of treatment can contribute to the development of depression and anxiety symptoms [29]. Many researchers have presented this topic in their work on the occurrence of anxiety and depression among patients with myeloproliferative neoplasms, analyzing the influence of the disease (its symptoms) on the occurrence of depression or anxiety [30–34]. Many studies have also focused on the side effects of treatment with various forms of interferon alpha in MPN [35], and some indicate that depression is one of them [23, 35–37]. Raison et al. [38] indicated that significant depressive symptoms occur in 21–58% of patients receiving non-pegylated IFNα, with symptoms usually appearing within the first few months of treatment, and may be due to high medication dose, female gender, history of depression, and duration of treatment.

It is noteworthy that due to the use of different definitions of depression in research and various diagnostic tools and interviews, the word 'depression' can encompass various psychiatric or neurological symptoms not necessarily related to clinical depression.

The literature does not provide studies that analyze the coexistence of anxiety, depression, somatic symptoms, and side effects of MPN treatment together. Usually, the influence of chronic myeloproliferative neoplasms (including its symptoms) on the

occurrence of depression and/or anxiety or the general side effects of the drug (where depression is one of the side effects) have been examined. However, it has not been investigated whether possible side effects of the drug (e.g. fatigue, diarrhea) may contribute to the emergence of anxiety/depression. One of the difficulties may be determining whether a particular disease symptom is a side effect of treatment, or a somatic symptom of the disease. To our best of our knowledge, only a study by Padrnos et al. [34] on symptoms of depression in patients with myeloproliferative neoplasms drew attention to the relationship between depression and other variables. It showed that side effects may influence the development of depressive disorders [34].

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

The aim of our study was to analyze the occurrence of depression, anxiety, and somatic symptoms in patients with chronic myeloproliferative neoplasms (ET, PV, and PMF) and to check whether individual side effects of interferon alpha treatment may contribute to the occurrence of depression, anxiety, and somatic symptoms. In addition to this, we decided to check for a relationship between the age and the sex of the patient as well as the duration of the treatment and the severity of depressive, anxiety, and somatic symptoms; the data was divided depending on the occurrence of the individual side effect. The aim of the study was not to diagnose depressive or anxiety disorders, but instead to check the possibility of their development during IFN alpha treatment.

Material and methods

The study was carried out at the Hematology Clinic of the University Hospital in Kraków and the Clinic of Hematology, Blood Cancer and Bone Marrow Transplantation in Wrocław, Poland. The study involved 105 adult patients on interferon alpha treatment for a minimum of three months who gave their written consent. The patients were diagnosed with essential thrombocythemia, or polycythemia vera, or primary myelofibrosis. 21 patients were excluded from the study because they met our exclusion criteria i.e.: psychiatric or psychological (psychotherapeutic) treatment during the study period or the three months before its start, discontinuation of interferon alpha treatment or switching to another drug, initiation of interferon alpha treatment during the study or up to three months before starting treatment, feeling similar symptoms to those mentioned in the questionnaire, and the presence of anemia

or disorder of the thyroid gland at least one month before starting treatment with alpha interferon. Ultimately, 84 patients (65 women and 19 men) were enrolled into the study. Data on the prevalence of anemia or hypothyroidism was collected from laboratory test results performed on the day of the questionnaire. The mean age in the research group was 39 [standard deviation (SD) = 10.199] years. Median IFNα dosing was 45 μg/week, with a minimum value of 45 μg/week and a maximum of 180 μg/two weeks. Detailed characteristics of the study group are set out in Table I.

Table I. Description of study group

Variable		**Me ± SD**	**(min–max)**
Age (years)		37.50 ± 10.199	(20–65)
Treatment time (years)		9.50 ± 6.185	(1–23)
Number of side effects		4.00 ± 2.781	(0–11)
Type of MPN		**N**	**%**
Essential thrombocythemia		32	38.1
Polycythemia vera		28	33.3
Primary myelofibrosis		24	28.6
Variable		**N**	**%**
Sex	Female	65	77.4
	Male	19	22.6
Education	Basic vocational education	1	1.2
	Secondary	36	42.9
	Higher	47	56.0
Place of residence	City	63	25.0
	Village	21	75.0
Residence status	Living alone	5	6.0
	Living with family	79	94.0

Me — median; SD — standard deviation; MPN — myeloproliferative neoplasm; N — number of patients

Research tools

1. Sociodemographic questionnaire, which includes questions about age, sex, place of residence, marital status, education, type of MPN (ET, PV, PMF, and others), duration of the disease, side effects of interferon alpha treatment divided into periods and their duration. The list of side effects of interferon alpha treatment was prepared based on the results of studies on its effects and toxicity [22, 23, 27].
2. Goldberg's General Health Questionnaire 28 (GHQ-28) [39] questionnaire was used to assess mental health in adults. This questionnaire is sometimes used as a screening tool to detect people at risk of developing mental disorders and to analyze four symptoms of

mental disorders: depression, anxiety, somatic and social dysfunction. In this study, the general, current mental state of the respondents and three dimensions of mental health: depressive, anxiety, and somatic symptoms, were analyzed. Additionally, the focus was on identifying people who may be at risk of developing mental disorders.
Two scoring methods were used in the study: 1) the GHQ method, in which a dichotomous scale is used to identify people with a mental disorder, the cut-off point in this method being 6 points; and 2) a modified Likert scale from 0 to 3 points, which is used to check the general mental state of the respondents and to analyze three mental health factors: depressive, anxiety and somatic symptoms. Each scale contains seven questions, and a maximum of 21 points can be obtained. Sten norms were used to assess the results of general mental state.

3. Four-Dimensional Symptom Questionnaire (4DSQ), measuring the severity of current depressive symptoms (six questions), anxiety (12 questions), somatic (16 questions), and distress (16 questions) [40]. This study focused on analyzing three out of four dimensions: depression, anxiety, and somatic symptoms. In the case of depressive symptoms, the maximum number of points that can be obtained is 12, for anxiety symptoms — 24, and for somatic symptoms — 32. The cut-off points for individual scales are presented in Table II.

Table II. Cut-off points for individual scales of the Four-Dimensional Symptom Questionnaire

Factor	Distress	Depression	Anxiety	Somatization
Moderate	>9	>2	>3	>10
High	>20	>5	>9	>20

The names of the scales in both questionnaires: depression, anxiety, and somatization should be treated as depressive, anxiety and somatic symptoms, respectively. The above tests are used as screening tests or for identifying people who may be at risk of developing mental disorders, and by themselves do not diagnose disorders. The diagnosis of depressive, anxiety, or somatic disorders requires the fulfillment of specific diagnostic criteria of the International Statistical Classification of Diseases and Related Health Problems 11th revision (ICD-11) or

Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) classification. In the presented study, depressive symptoms are not equivalent to the terms “depression” or “depressive disorder”.

Statistics

Statistical analyzes were performed using IBM SPSS Statistics version 26. It was used to perform a frequency analysis, basic descriptive statistics analysis, a series of multivariate linear regression analyses, a series of correlation analyses with Spearman's rho coefficient, and a one-way ANOVA with repeated measures along with a post hoc test with Benferroni correction. The normality of the distribution was verified by the Kolmogorov-Smirnov test. The level of significance was $\alpha = 0.05$.

Firstly, the basic descriptive statistics of the variables analyzed later in the work were calculated. For quantitative variables, mean values were presented with standard deviations, and nominal variables — with the frequency of occurrence.

Results

The most frequently reported side effects of treatment were abdominal pain (82.1%), fatigue (66.7%), and bone and joint pain (61.9%). Detailed data is set out in Table III.

Table III. Occurrence of side effects with division into time of their appearance and duration

Side effect	**PLT**	**PLNT**	**L3T**	**L3NT**	**TOTAL TR**	**TOTAL W**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Water retention	25 (29.8)	11 (13.1)	8 (9.5)	1 (1.2)	33 (39.3)	45 (53.6)
Frequent infections	15 (17.9)	3 (3.6)	–	–	15 (17.9)	18 (21.4)
Fatigue	45 (53.6)	6 (7.1)	5 (6.0)	–	50 (59.5)	56 (66.7)
Bruising	31 (36.9)	7 (8.3)	–	–	31 (36.9)	38 (45.2)
Diarrhea	9 (10.7)	19 (22.6)	–	5 (6.0)	9 (10.7)	33 (39.3)
Loss of appetite	25 (29.8)	14 (16.7)	–	–	25 (29.8)	39 (46.4)
Bone and joint pain	34 (40.5)	9 (10.7)	6 (7.1)	3 (3.6)	40 (47.6)	52 (61.9)
Nausea, indigestion	27 (32.1)	7 (8.3)	–	8 (9.5)	27 (32.1)	42 (50.0)
Abdominal pain	44 (52.4)	19 (22.6)	6 (7.1)	–	50 (59.5)	69 (82.1)
Cramps, muscle aches	30 (35.7)	8 (9.5)	5 (6.0)	5 (6.0)	35 (41.7)	48 (57.1)

Skin rash, itching	28 (33.3)	20 (23.8)	–	3 (3.6)	48 (57.1)	48 (57.1)
Anemia	18 (21.4)	2 (2.4)	1 (1.2)	1 (1.2)	19 (22.6)	21 (25.0)
Hypothyroidism	13 (15.5)	1 (1.2)	1 (1.2)	1 (1.2)	14 (16.6)	16 (19.0)

PLT — treatment side effects that appeared early in treatment and are still ongoing; PLNT — treatment side effects that started at the onset of treatment but are no longer present; L3T — treatment side effects that started three months after onset of treatment and are still ongoing; L3NT — treatment side effects that started three months after onset of treatment but are no longer present; TOTAL TR — treatment side effects that appeared at the beginning of treatment and are still ongoing (PLT) and treatment side effects that appeared three months after onset of treatment and are still ongoing (L3T); TOTAL W — sum of all side effects of treatment; N — numer of patients

As the next step, the side effects that persisted until the day of the study (TOTAL TR) were analyzed.

The general mental state of the respondents was checked using the GHQ-28 questionnaire and GHQ scoring (0 — no symptom, 1 — symptom occurrence). Thirty patients (35.71%) at risk of developing mental disorders were identified. These people exceeded the threshold of 6 points, which is the cutoff point for identifying people with mental disorders. Tables IV and % present the results of the 4DSQ and GHQ-28 questionnaires.

Table IV. Incidence of depressive, anxiety and somatic symptoms measured with the Four-Dimensional Questionnaire (4DSQ)

	All patients (n = 84)					
4DSQ	**Depression**		**Anxiety**		**Somatization**	
	N	**%**	**N**	**%**	**N**	**%**
Moderate	24	28.6	31	36.9	43	51.2
High	8	9.5	10	11.9	19	22.6

Analysis of the occurrence of depressive, anxiety and somatic symptoms in patients with chronic myeloproliferative neoplasms showed that almost 40% of the respondents obtained a moderately or strongly increased result on the depression scale, less than 50% on the anxiety scale, and over 60% on the somatic symptoms scale (Table IV).

Using the GHQ-28 questionnaire and the 4DSQ questionnaire, the general mental state of the respondents and the influence of individual disorders on their severity were checked (Table V).

Table V. Overall score and score for individual scales of General Health Questionnaire 28 (GHQ-28) and the Four-Dimensional Questionnaire (4DSQ)

Questionnaire	Overall score		Somatization		Anxiety		Depression		
	M	SD	M	SD	M	SD	M	SD	F
GHQ-28	24.48	11.575	6.96[a]	3.338	6.10[b]	4.041	2.93[b]	3.104	70.577*
4DSQ	–	–	11.24[a]	7.996	3.29[b]	4.694	1.74[c]	2.523	138.988*

[a, b, c]different indices mean statistically significant differences at level of p <0.001; *p <0.001; M — medium; SD — standard deviation

The overall result of the GHQ-28 test showed an average mental condition of the patients. Analysis with the use of a one-way analysis of variance in the intergroup scheme showed that somatic symptoms had the greatest impact on the occurrence of mental disorders, with anxiety symptoms being second in significance. Similar results were observed using the 4DSQ.

As the next step, the severity of depressive, anxiety, and somatic symptoms were checked, and divided into side effects of interferon alpha treatment, using the 4DSQ and GHQ-28 questionnaires (Table VI).

Table VI. Depressive, anxiety, and somatic symptoms divided by side effects of interferon alpha treatment

Side effect		Somatization		Anxiety		Depression		F
		M	SD	M	SD	M	SD	
Water retention	GHQ	7.48[a]	3.28	5.88[b]	3.91	3.24[c]	3.55	25.74*
	DSQ	12.00[a]	7.76	3.67[b]	5.10	1.85[c]	2.69	65.31*
Frequent infections	GHQ	10.73[a]	2.87	8.73[a]	3.60	4.53[b]	3.38	22.10*
	DSQ	15.80[a]	8.49	4.47[a]	5.44	2.87[b]	2.97	43.20*
Fatigue	GHQ	8.20[a]	2,85	7.46[a]	4.02	3.62[b]	3.24	42.79*
	DSQ	12.52[a]	7.51	3.42[b]	4.38	1.80[c]	2.30	105.10*
Bruising	GHQ	8.23[a]	3.77	7.10[b]	4.11	3.19[c]	2.99	38.40*
	DSQ	12.39[a]	7.82	3.81[b]	4.59	2.32[b]	2.88	59.10*
Diarrhea	GHQ	9.11[a]	3.14	8.22[b]	3.14	3.67[c]	3.80	70.58*

Loss of appetite	DSQ	12.44[a]	8.31	1.78[b]	1,56	1.67[c]	2.00	138.98*
	GHQ	8.56[a]	3.34	7.84[a]	3.35	5.08[b]	3.14	23.01*
Bone and joint pain	DSQ	12.36[a]	7.80	3.76[b]	4.48	2.36[b]	3.07	50.84*
	GHQ	8.13[a]	3.66	7.05[b]	3.80	3.83[c]	3.47	33.91*
Nausea, indigestion	DSQ	12.85[a]	8.42	3.73[b]	4.41	2.08[c]	2.56	72.17*
	GHQ	7.93[a]	3.03	8.26[a]	3.28	4.41[b]	3.43	28.71*
Abdominal pain	DSQ	11.07[a]	6.87	3.67[b]	4.28	1.85[b]	2.69	54.78*
	GHQ	8.30[a]	2.94	7.58[a]	3.24	4.14[b]	3.39	44.60*
Cramps, muscle aches	DSQ	12.34[a]	7.57	3.68[b]	4,18	1.92[c]	2.47	140.88*
	GHQ	8.86[a]	3.02	8.00[a]	3.33	4.51[b]	3.51	24.90*
Skin rash, itching	DSQ	13.66[a]	7.62	3.86[b]	4.59	2.34[b]	2.66	85.78*
	GHQ	6.69[a]	3.37	5.67[b]	4.39	3.54[c]	3.55	23.36*
Anemia	DSQ	12.42[a]	9.10	3.48[b]	5.46	2.04[b]	2.77	72.99*
	GHQ	6.81[a]	0.90	5.75[b]	1.16	2.25[b]	0.72	13.44*
Hypothyroidism	DSQ	10.31[a]	1.93	2.44[a]	1.16	1.38[b]	0.65	34.27*
	GHQ	8.48[a]	0.61	8.14[b]	0.47	6.43[b]	0.64	8.405*
	DSQ	16.19[a]	1.84	5.24[a]	1.20	2.27[b]	0.74	47.19*

[a, b, c]different indices mean statistically significant differences at level of $p < 0.001$; *$p < 0.001$; M — medium; SD — standard deviation

With the use of a one-way analysis of variance in the intergroup scheme, it was shown that there are differences in the severity of depressive, anxiety, and somatic symptoms depending on the side effects of interferon alpha treatment. In the case of the study with the GHQ-28 questionnaire, in most of the experienced side effects of interferon alpha treatment, the greatest influence on the occurrence of psychological disorders were somatic symptoms, followed by anxiety and anxiety-related insomnia. Only in the cases of side effects of nausea and indigestion was anxiety the leading factor in inducing mental disorders.

The side effects with the greatest severity of somatic symptoms were hypothyroidism-related symptoms, frequent infections, diarrhea, muscle cramps, and pain. Similar results were obtained for the deterioration of anxiety symptoms, but additional side effects with high scores were nausea and indigestion. In the case of depressive symptoms, the side effects

obtaining the greatest results were: loss of appetite, frequent infections, and muscle pain. The 4DSQ survey showed that all experienced side effects of treatment were associated with increased levels of somatization and anxiety. In the case of depressive symptoms, elevated levels were observed, in order of severity: hypothyroidism-related symptoms, frequent infections, loss of appetite, muscle cramps and pain, bruising, diarrhea, bone, and joint pain, skin rash, and itching.

The next analysis examined whether there was any relationship between age and duration of treatment and the severity of depressive, anxiety, and somatic symptoms, divided by individual side effects (Table VII).

Table VII. Spearman's correlation coefficients between anxiety, depressive and somatic symptoms [measured by General Health Questionnaire (GHQ) and Four-Dimensional Questionnaire (4DSQ)] and age and duration of treatment by perceived side effects of interferon alpha treatment

Side effect	**Variables**	**Somatization**		**Anxiety**		**Depression**	
		GHQ	**DSQ**	**GHQ**	**DSQ**	**GHQ**	**DSQ**
Water retention	Age	0.93	0.21	0.08	–0.03	–0.21	–0.02
	Treatment time	0.11	–0.14	–0.25	–0.04	0.02	–0.17
Frequent infections	Age	0.26	–0.04	–0.19	–0.33	–0.18	0.13
	Treatment time	0.13	0.43	0.25	–0.12	0.01	0.03
Fatigue	Age	–0.25	0.21	0,15	0.17	–0.09	0.17
	Treatment time	–0.11	0.08	–0.02	0.08	–0.30*	–0.08
Bruising	Age	0.08	–0.09	0.31	0.29	–0.01	0.24
	Treatment time	0.03	0.08	0.36*	0.40	0.02	–0.02
Diarrhea	Age	–0.21	0.05	–0.03	0.13	–0.18	0.08
	Treatment time	0.04	–0.01	0.16	0.03	0.04	0.02
Loss of appetite	Age	–0.55**	–0.08	–0.09	0.18	–0.23	0.01
	Treatment time	–0.57**	–0.12	–0.45**	–0.22	–0.62**	–0.23
Bone and joint pain	Age	–0.27	0.18	–0.03	–0.05	–0.24	–0.06
	Treatment time	–0.24	–0,08	–0,13	–0,20	–0,37*	–0.27
Nausea, indigestion	Age	–0.34	–0,01	0,04	0,18	–0,08	0.11
	Treatment	–0.41	–0,08	–0,07	–0,02	–0,45*	–0.10

	time						
Abdominal pain	Age	–0.38**	0.04	0.15	0.17	–0.23	0.18
	Treatment time	0.01	0.17	0.09	0.06	–0.07	0.05
Cramps, muscle aches	Age	–0.19	0.25	0.09	–0.17	0.15	–0.01
	Treatment time	–0.08	0.15	0.04	–0.05	–0.35*	–0.14
Skin rash, itching	Age	–0.18	0.03	0.17	0.07	–0.18	–0,07
	Treatment time	0.11	–0.08	–0.10	–0.23	–0.10	–0.37*
Anemia	Age	–0.10	0.37	–0.07	–0.65	–0.27	–0.18
	Treatment time	0.00	0.48*	0.06	0.10	–0.46*	–0.20
Hypothyroidism	Age	–0.13	–0.40	–0.42	–0.17	–0.03	–0.27
	Treatment time	–0.07	–0.38	–0.33	–0.36	–0.17	–0.38

*p <0.05; **p <0.01

Significant, high or moderate correlations occurred between the occurrence of anxiety (r_s = –0.57), depression (r_s = –0.45) and somatic (r_s = –0.67) symptoms and the time of treatment. In these patients, the longer the treatment duration, the lower the intensity of depression, anxiety, and somatic symptoms. Additionally, in this group of respondents, there was a negative, high correlation (r_s = –0.55) between the occurrence of anxiety symptoms and age. The older the person was, the lower the level of anxiety. There were also moderate negative correlations between the occurrence of individual symptoms of mental disorders and the age and duration of treatment in patients who experienced the following side effects of interferon treatment: fatigue, bone, and joint pain, nausea and indigestion, muscle cramps and pain, and skin rash and itching and anemia. Two positive correlations occurred between depressive symptoms and the duration of treatment (r_s = 0.36), in people experiencing the side effect of bruising, and between anxiety symptoms and the duration of treatment in patients experiencing anemia (r_s = 0.48).

The results of the analysis of the relationship between the severity of anxiety, depression, and somatic symptoms measured with the GHQ-28 questionnaire and age, gender, place of residence, number of side effects, and duration of treatment are set out in Table VIII.

Table VIII. Multidimensional relationships between severity of anxiety, depression, and somatic symptoms and age, gender, place of residence, number of side effects, and duration of treatment

Variables	B*	*p*
Somatization		
Duration of treatment	0.009	0.849
Age	–0.024	0.408
Number of side effects	0.760	<0.001
Sex (male vs female)	1.222	0.063
Place of residence (village vs city)	1.899	0.004
Adjusted R^2 = 0.447 (F = 14.438)		
Anxiety		
Duration of treatment	0.049	0.470
Age	–0.082	0.046
Number of side effects	0.749	<0.001
Sex (male vs female)	0.329	0.718
Place of residence (village vs city)	1.234	0.177
Adjusted R^2 = 0.262 (F = 6.904)		
Depression		
Duration of treatment	–0.031	0.537
Age	–0.009	0.768
Number of side effects	0.635	<0.001
Sex (male vs. female)	–1.377	0.043
Place of residence (village vs city)	–0.312	0.640
Adjusted R^2 = 0.323 (F = 8.937)		

*Crude regression coefficients

In the analysis of the impact of the side effects of treatment on the severity of somatic, anxiety, and depression symptoms measured with the GHQ-28 questionnaire, regression models made it possible to explain to explain 45%, 27% and 32% of the variance.

Based on the results presented in Table VIII, we found that the number of side effects was a common predictor of the occurrence of somatic, anxiety, and depressive symptoms. The more the patient experienced them, the greater the severity of all symptoms of mental disorders.

Place of residence also turned out to be an important predictor of somatic symptoms. People living in the city felt more anxious than those living in the countryside. In the case of

anxiety symptoms, age was also an important prognostic factor. The older the person was, the lower the intensity of anxiety symptoms. The analysis also showed that the female gender was an unfavorable prognostic factor for the occurrence of depressive symptoms.

In the study of the relationship between the severity of anxiety, depression, and somatic symptoms measured with the 4DSQ questionnaire and age, gender, place of residence, number of side effects and duration of treatment, neither model was statistically significant.

Next, a regression analysis was performed to verify the relationship between the severity of anxiety, depression and somatic symptoms measured by the GHQ-28 questionnaire and the incidence of side effects of interferon alpha treatment (Table IX).

Table IX. Relationships between severity of anxiety, depression, and somatic symptoms measured with General Health Questionnaire 28 (GHQ-28) and side effects of interferon alpha treatment

Side effect	**B***	***p***
Somatization		
Water retention	1.096	0.108
Frequent infections	3.240	<0.001
Fatigue	1.667	0.012
Bruising	0.717	0.296
Diarrhea	0.308	0.767
Loss of appetite	1.361	0.113
Bone and joint pain	–0.779	0.271
Nausea, indigestion	–0.117	0.879
Abdominal pain	0.641	0.417
Cramps, muscle aches	1.670	0.031
Skin rash, itching	–1.452	0.017
Anemia	–1.161	0.835
Hypothyroidism	0.695	0.335
Adjusted R^2 = 0.481 (F = 6.917)		
Anxiety		
Water retention	–0.690	0.462
Frequent infections	2.229	0.068
Fatigue	2.036	0.027
Bruising	–0.066	0.946
Diarrhea	0.467	0.746
Loss of appetite	–0.869	0.463
Bone and joint pain	–0.638	0.515
Nausea, indigestion	2.694	0.013
Abdominal pain	1.056	0.336

Cramps, muscle aches	1.309	0.219
Skin rash, itching	–1.309	0.039
Anemia	1.042	0.335
Hypothyroidism	0.973	0.330
Adjusted R^2 = 0.317 (F = 3.967)		
Depression		
Water retention	0.039	0.948
Frequent infections	0.422	0.588
Fatigue	–0.207	0.724
Bruising	–0.753	0,220
Diarrhea	–1.007	0.281
Loss of appetite	1.787	0.021
Bone and joint pain	–0.530	0.402
Nausea, indigestion	–0.089	0.897
Abdominal pain	1.939	0.007
Cramps, muscle aches	0.743	0.279
Skin rash, itching	1.173	0.031
Anemia	3.000	<0.001
Hypothyroidism	0.262	0.684
Adjusted R^2 = 0.519 (F = 7.877)		

*Crude regression coefficients

The analysis showed that the prevalence of somatic symptoms was: frequent infections, fatigue, muscle cramps, and pain, as well as skin rash and itching. All side effects, with the exception of skin rash and itching (B = –1.452, p = 0.017), were positively associated with the response variable. Three side effects were predictors of anxiety symptoms: fatigue (B = 2.036, p = 0.027), nausea and indigestion (B = 2.694, p = 0.013), and skin rash and itching (B = –1.309, p = 0.039). In the case of depressive symptoms: loss of appetite (B = 1.787, p = 0.021), abdominal pain (B = 1.939, $p \leq 0.007$), skin rash and itching (B = 1.173, p = 0.031), and anemia (B = 3.000, $p \leq 0.001$) were significant predictors of the development of depressive disorders. All side effects of treatment were positively associated with the response variable.

In regression analysis between the severity of anxiety, depression, and somatic symptoms — measured with the 4DSQ questionnaire and divided by side effects — neither model was statistically significant.

Discussion

Many scientific studies have been devoted to side effects occurring during treatment with various types of interferon alpha.

The incidence and type of side effects of interferon alpha treatment reported in the literature and observed in our analyzed group of patients were similar.

Fatigue and flu-like symptoms (headache, muscle pain, back, and joints, fever, chills) were most frequently reported [35, 40, 41]. Skin rash, abdominal pain or hypothyroidism-related symptoms are side effects less common in people with myeloproliferative neoplasms, but they occur in other conditions treated with interferon alpha [42–46]. An analysis of the incidence of side effects of interferon alpha treatment depending on the period of their appearance and persistence showed that the most common side effects occurred at the beginning of treatment and are still ongoing, followed by those that occurred at the beginning of treatment, but do not exist anymore (Table III). The most common side effects in these groups were fatigue, skin rashes, and itching, and abdominal pain. Analysis of the occurrence of depressive, anxiety, and somatic symptoms in patients with chronic myeloproliferative neoplasms showed that, on average, every second person has at least one symptom of a mental disorder in the form of somatic, anxiety or depression symptoms, with the highest indication being of somatic symptoms, followed by anxiety symptoms (Tables IV, V).

These results suggest that these patients may develop a somatic disease, and additionally they may be affected by physiological symptoms of the disease and/or in some people there may be a tendency to somatize the symptoms of the disease. The obtained results do not differ from those presented in the literature; somatic, anxiety, or depressive symptoms are common in cancer patients [30, 31, 47]. Studies by Scherber et al., McFarland et al. and Brochmann et al. have indicated that depression or anxiety symptoms appear in 13–31% of patients with MPN [30, 33, 48].

In our study, somatic symptoms were the most frequent and severe symptoms in the study group. These results may indicate that the side effects of alpha interferon treatment may resemble typical somatic symptoms e.g. nausea, fatigue, abdominal pain, diarrhea, weight loss, and loss of appetite. Some of them could be aggravated by alpha interferon-induced hypothyroidism. In addition, the disease itself may also be characterized by similar symptoms, and the coexistence of anxiety or depressive disorders may indicate somatic symptoms. In a study by Katon et al. [49], in which patients suffered from diabetes, lung disease, heart disease, and arthritis, it was found that the presence of comorbid depression or anxiety disorders is associated with an increased burden of somatic symptoms in patients with chronic disease. On the other hand, the results of Akechi et al. [50] suggest that individual somatic

symptoms in cancer patients differ in nature and that, for example, symptoms related to appetite and reduced thinking ability can be used to diagnose depression, while sleep disturbances and fatigue can not be used.

It is difficult to determine whether the somatic symptoms in patients with myeloproliferative neoplasms are related to the disease itself and the side effects of its treatment or to the accompanying anxiety or depressive symptoms. For this reason, subsequent analyzes attempted to determine to what extent the side effects of treatment may contribute to the development of somatic, anxiety, or depressive disorders.

Our study showed that individual side effects of interferon alpha treatment contribute to the occurrence and development of mental health disorders, and some of them (frequent infections, muscle cramps and pain, fatigue, nausea and indigestion, loss of appetite, abdominal pain, anemia and skin rash and itching) are prognostic factors for the occurrence of somatic, anxiety or depression symptoms (Tables VI and IX). The literature confirms that the numerous and troublesome side effects of interferon alpha treatment can contribute to the deterioration of the quality of life of patients [40, 51, 52] and the emergence of depressive and anxiety symptoms [53].

The study conducted into the relationship between the age of the patient, duration of the treatment, and the severity of depressive, anxiety and somatic symptoms, which was divided by the occurrence of individual symptoms, showed that patients experiencing side effects such as loss of appetite, bone and joint pain, nausea and indigestion, cramps and muscle pain as well as skin rashes and itching of the skin, were more likely to experience less severe mental disorder symptoms the longer the disease persisted.

On the other hand, among patients experiencing side effects such as loss of appetite and abdominal pain, the older the person is, the less frequent the occurrence of anxiety symptoms and the less severe. In patients who develop anemia as a result of interferon alpha treatment, the longer the patients were treated, the higher the occurrence of depressive symptoms (Table VII).

The results show that the group of patients experiencing certain side effects adapts better to the ongoing disease and more easily achieves the appropriate defense strategy. Numerous studies have emphasized that chronic disease and health problems resulting from it are a constant source of stress for patients, and various coping strategies (based on, among others, religion, meditation, trust in medical staff, positive attitude, patient’s own resources or social support) may contribute to effective adaptation in chronically ill people [54–59]. In contrast, in a study by Trask et al. [60] on the course of depression, fatigue, and quality of life

before and during interferon therapy in patients with melanoma, it was observed that somatic complaints, depression, and fatigue as a side effect of interferon treatment increased significantly during therapy, and that the patient's quality of life decreased in the areas of physical and functional well-being and additional symptoms [60]. These differences may be due to the type of interferon used, the duration of treatment, the dose administered, and/or the nature of the disease.

Our results on the variables that can influence the appearance of anxiety, depression, and somatic symptoms showed that the number of side effects was an important predictor of mental disorders (Table VIII). Similarly, in the study by Trask et al. [60], it was shown that fatigue, which is one of the main and most common side effects of interferon alpha treatment, can contribute to the development of mental health disorders. Another study by Brandberg et al. [61] on health-related quality of life in patients with melanoma taking interferon alpha-2b indicated a deterioration in the quality of life and several side effects associated with this treatment. The cited study did not analyze the relationship between these two variables but only focused on identifying side effects and quality of life during the treatment period [61]. The results of the studies in the analyzed group of patients are not surprising, as the occurrence of side effects of almost any treatment usually affects the quality of life of patients, but their number, type, duration, and coping strategy may significantly affect the presence of mental disorders.

Age was a predictor of anxiety symptoms. The older the person, the lower the intensity of anxiety symptoms. In a study by Brown et al. on the relationship between age and anxiety and depression symptoms in quality of life, 443 adults aged 30–98 years were examined. It showed that there is no difference between the psychological and social quality of life and age, while the environmental quality of life increases and the physical quality decreases with age [62]. Nickel's studies [63] of depression and anxiety in patients with chronic heart disease showed that younger patients (under 65) experienced more anxiety and depression symptoms than patients over 65. Other studies have shown that the ability to adapt to changes increases with age [64, 65], and our own results confirm this.

Another analysis showed that women were more likely to develop depressive disorders; the results are identical to most of the data available in the literature, which indicate that women are more likely to develop anxiety or depressive disorders [47, 63, 66] or are more often diagnosed with depression [67]. However, some studies show no such relationship [33, 68].

The differences may be caused by the influence of additional variables on the obtained results, such as the homogeneity of the studied groups, the type of disease, the age of the patient, the duration of the treatment, taking antidepressants, quantity, and severity of the experienced side effects and their duration, social situation or the process of adaptation to the disease. There are some studies that suggest that women perceive and construct social reality differently than men; they play a protective role in relationships and are more sensitive, often at the expense of their own emotional stability [69–71].

Study limitations

The conducted research has some limitations. Despite the initial history of the side effects of treatment (whether they occurred before the drug was introduced or arose later), it is difficult to say with 100% certainty whether, for example, fatigue or diarrhea and its relationship with depressive, somatic, or anxiety symptoms are the effects of the disease itself (MPN), a side effect of the drug, or a depressive, anxiety or somatization disorder.

Another limitation of the study was the use of a non-validated symptom burden measurement tool (self-survey). Our rationale was to use the same questionnaire used in several previous studies in a different group of patients, which will be compared with the currently studied. The study was based on the most common side effects in patients with chronic myeloproliferative tumors and lymphoproliferation.

Another limitation was the use of self-description questionnaires, which are not used to diagnose depression or anxiety disorders but are only used to indicate the possibility of certain symptoms of mental disorders. To diagnose these disorders, the diagnostic criteria of ICD 11 or DSM 5 should be used. Therefore, the obtained results are exploratory and require further research.

Clinical implications

A questionnaire-based examination of the mental state of patients, both newly diagnosed with myeloproliferative neoplasms and those already undergoing treatment, may be an option that could be offered to patients; if the results of the questionnaire exhibited depressive, anxiety and/or somatic symptoms, the patient could then be offered psychiatric treatment and/or psychological support.

Another option that could be introduced is having the medical professionals consult with the patients about the possible side effects of the treatment as well as how to deal with them,

which could increase the patient's overall understanding of the process and in turn reduce possible depressive, anxiety and somatic symptoms.

Conclusions

Some of the side effects of interferon alpha treatment in patients with chronic myeloproliferative neoplasms influence the occurrence of depression, anxiety, and somatic symptoms and are a clear indicator of their severity. Somatic symptoms had the greatest impact on the occurrence of mental disorders, with anxiety symptoms being second in significance.

In the case of the relationship between the age of the respondents and the duration of treatment, divided by individually occurring side effects, patients experiencing the side effect in the form of loss of appetite, the person was younger and the duration of treatment was shorter, the severity of anxiety symptoms was lower.

In the case of all disorders of the mental sphere, significant predictors were the number of side effects, in addition to somatic symptoms — the place of residence (city), anxiety symptoms — age (younger person), and depressive symptoms — gender (woman).

The findings of our study indicate the need for further research into the importance of detecting depressive, anxiety, and somatic disorders, and addressing concomitant physical symptoms, both in patients with myeloproliferative neoplasms receiving interferon alpha and those treated with other methods.

In patients treated chronically, the occurrence of side effects of high intensity and lasting for a long time should alert medical personnel.

The collected data on patients with myeloproliferative neoplasms who have suffered from mental and physical symptoms of the disease or its treatment justifies the need for caring psychological, psychiatric, and educational care.

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