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ANXIETY AND DEPRESSION IN PATIENTS WITH ACUTE LEUKAEMIA TREATED WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION

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SUMMARY

Background: *Acute leukemia and hospitalization for hematopoietic stem cell transplantation (HCT) are the great psychological stressors. The aim of this study was to assess anxiety and depression associated with such conditions and their psychophysical predictors before and after HCT.*

Subjects and methods: *We conducted a longitudinal study using self-descriptive tools. The questionnaires: LOT-R, AIS, Mini-Mac, CECS, RSCL and HADS were filled by 60 patients with acute leukaemia before and after HCT.*

Results: *Anxiety and depressive symptoms correlated positively with psychological symptom distress. The correlation with depressive symptoms was weak, however, with anxious symptoms was moderate. In both cases, the higher was a level of psychological symptom distress, the higher level of anxiety and depression was observed in patients. The results indicated the weak, positive correlation between onerousness of physical symptoms and a level of anxiety. The greater was the severity of physical symptoms, the higher was the level of anxiety. The negative predictor of anxious symptoms was control of anxiety but it was weakly associated with a lower level of the explained variable. The negative predictor of anxious symptoms was also dispositional optimism whose high level accompanied the lower severity of the explained variable. However, the positive predictor of anxious symptoms was the variable of onerousness of symptoms whose high level accompanied the higher severity of anxious symptoms in the examined group*

Conclusion: *Patients with acute leukemia who are hospitalized for HCT require detailed monitoring of their psychological distress to introduce the proper psychological and pharmacological interventions that reduce anxiety as well as boost "dispositional optimism" and mechanisms of control.*

Key words: *hematopoietic stem cell transplantation - anxiety - depression - dispositional optimism*

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INTRODUCTION

Hematopoietic stem cell transplantation (HCT) is acknowledged as an invasive but nowadays a front-line conventional therapeutic method in many hematological malignancies. It is associated with distressing physical symptoms resulting from toxicity of the treatment as well as emotional and psychological problems during the transplant (e.g. Pidala et al. 2009, Prieto et al. 2005). Its efficacy in acute leukemia is limited by higher mortality associated with treatment in a case of allogenic hematopoietic transplants or higher risk of relapse in a case of autogenic hematopoietic transplants (e.g. Fife et al. 2010, Gooley et al. 2010). The uncertainty of the therapy outcomes requires new strategies for adaptation and draws attention of clinicians and medical staff members to its psychosocial consequences, mainly assessed in terms of life quality understood as a functional result of illness and its treatment perceived by a patient (e.g. Braamse et al. 2012). According to the American Society for Blood and Marrow Transplantation, one of the most important issues affecting patients treated with HCT is psychological distress (e.g. Majhail et al. 2012). Despite many limitations in conclusions of research studies, transplant clinicians agree with the general opinion that the highest degree of distress is experienced by patients during hospitalization for HCT (e.g. Pidala et al. 2009, Jacobsen et al. 2002).

Anxiety and depressive disturbances are diagnosed in 5 to more than 40% patients with hematological malignancies (e.g. Mosher et al. 2009). It has been proved in prospective studies of depression in patients treated with HCT that the highest risk of depression occured just before or shortly after transplantation procedures (e.g. Goetzmann et al. 2006, Prieto et al. 2005, Illescas-Rico et al. 2002). Some studies have indicated that depression and anxiety can become chronic years after the transplantation (e.g. Syrjala et al. 2004, Andrykowski et al. 2005). The deterioration of mental state during and after transplant hospitalization may be a consequence of the fact that patients experience it as „the traumatic event" leading to the development of psychological distress.

Past research has identified factors such as personal resources, social support and disease- related or transplantation-related complication as the potential predictors of further mental state and life quality (e.g. Braamse et al. 2012).

In this study, we sought to describe whether anxiety and depression affects the course of hematopoietic stem cell transplantation. Second, we investigated whether

mental state may be influenced by the symptoms associated with treatment and the personality predispositions. Third, we tried to assess the personal resources as predictors of anxiety and depression.

SUBJECTS AND METHODS

Study Population

This longitudinal study was performed with approval of the Committee of Bioethics at the Medical School of Silesia in Katowice in Poland. All study participants had acute myeloblastic or lymphoblastic leukemia and underwent bone marrow transplantation. They had to satisfy the following recruitment criteria: consent to participation in the study, age from 18 to 70, absence of hallucinations and delusions, absence of cognitive disturbances, ability to fill self-report questionnaires.

The patients completed the following questionairres during hospitalization by admission and discharge.

The following self-report questionnaires were used in the study:

- The Acceptance of Illness Scale (AIS) developed by Felton et al. (1984), adapted to the Polish language by Juczyński (2001) is applied to measure the degree of acceptance of illness. It consists of 8 items, that describe negative consequences of undesirable health. A participant assumes his/her attitude to particular 5-degree items, where 1 means "strongly agree" and 5 means "strongly disagree". The higher a scale results is, the better the patient accepts his/her illness and adapts more suitably to the illness with lower feeling of psychological discomfort. The AIS has satisfactory psychometric properties. The Cronbach's *alpha* for the Polish version is 0.82.
- The Courtald Emotional Control Scale (CECS) developed by Watson and Greer (1983), adapted to the Polish language by Juczyński (2001) consists of three 7-item subscales, which refer to various ways of anger, depression and anxiety expression. A participant assumes his/her attitude to particular items describing a frequency of use of emotional expression ways, where 1 means "almost never" and 4 means "almost always". The tool allows to measure rates for the particular subscales as well as the general rate of emotional control, which is a sum of all subscales and reflects the participant's own opinion about own capacity to control own reactions in a situation, when negative emotions are experienced. The higher result is achieved by the participant, the greater tendency to suppress negative emotions is shown. The Cronbach's *alpha* coefficients are estimated as: 0.80 for the control of anger, 0.77 for the control of depression, 0.78 for the control of anxiety and 0.87 for the common coefficient of emotional control.
- The Life Orientation Test (LOT-R) developed by Scheier et al. (1994), adapted to the Polish language by Juczyński (2001) assesses generalized optimism. The questionnaire consists of 10 items and 6 of them refers to generalized optimism. A participant assumes his/her attitude to a particular 5-degree statement. The higher result, the higher level of generalized optimism. The Cronbach's *alpha* coefficient is estimated as 0.76.
- The Mental Adjustment to Cancer (MAC) developed by Watson et al. (1994), adapted to the Polish language by Juczyński (2001) as (Mini-Mac) is a tool, which allows to measure coping reactions in patients with cancer. The questionnaire consists of 29 items referring to various strategies of coping with cancer. A participant assumes his/her attitude to particular 4-degree statements about currently used coping strategies, where 1 means "definitely no" and 4 means "definitely yes". The Polish version of the tool allows to measure rates for four coping reactions: "anxious preoccupation", "fighting spirit", "helplessness-hopelessness" and "positive redefinition". The scale "positive redefinition" in the Polish version is an equivalent of the scale "fatalism" in the original version, and the strategy originally called "cognitive avoidance" corresponds the strategy called "fighting spirit" in the Polish version. The higher result is in each scale, the more dominating the particular strategy is. The Cronbach's *alpha* coefficients are estimated as: 0.92 for the helplessness-hopelessness, 0.90 for the fighting spirit, 0.89 for the anxious preoccupation and 0.87 for the positive redefinition.
- The Rotterdam Symptom Checklist (RSCL) developed by de Haes et al. (2012), adapted by Majkowicz (2000) is a self-report tool to assess the quality of life in patients with cancer. The tool consists of 39 items forming 4 subscales: physical symptom distress (23 items), psychological symptom distress (7 items), activity level (8 items) and overall valuation of life (1 item). A participant assumes his/her attitude to particular 4-degree statements about severity of a particular symptom. The only exclusion is the scale called "overall valuation of life", which is the 7-degree Likert's scale. The higher result of physical and psychological symptoms, the worse the patient's state. However, the high result in the scales called "activity level" and "overall valuation of life" reflects better functioning of a particular patient. The coefficients of inner consistency based on the Polish studies conducted on a group of terminal patients were estimated as: *alpha*=0.86 for physical symptoms, *alpha*=0.83 for psychological symptoms and *alpha*=0.87 for activity.
- The Hospital Anxiety and Depression Scale (HADS) developed by Zigmond and Snaith (1983), adapted by Majkowicz (2000) detects states of anxiety and depression. The questionnaire consists of 7 items for anxiety and 7 items for depression. A participant assumes his/her attitude to particular 4-degree statements about a frequency of negative emotions. The higher result, the greater severity of anxiety or

depression. The questionnaire is a commonly used tool and the result more than 8 points in each subscale means, that the particular patient is in a risk group of the clinical anxiety or depressive disturbances. The inner consistency (Cronbach's *alpha*) measured at the stage of the first treatment is estimated as 0.79 for the scale of anxiety and 0.83 for the scale of depression.

Statistical Analysis

Statistical analyses were performed using STATISTICA version 12.5. Descriptive statistics were summarized for quantitative variables as mean ± standard deviation or for qualitative variables as frequency and percentage.

The questionnaires' results achieved before and after HCT were compared using Wilcoxon test. Correlation between examined variables was accessed using a co-factors' analysis of tau-b Kendall correlation.

A likelihood of depressive decompensation was estimated using an analysis of logistic regression. The fact of depressive symptom intensification in reference to a result achieved in HADS scale before HCT was established as a dependent variable. The coping strategies with illness, acceptance of illness, control of emotions and severity of symptoms after HCT (high results with a lower limit calculated through addition a half of standard deviation to mean value or results below 7th sten) and the presence of objective complications after HCT and the sex (male) were introduced as the predictors.

RESULTS

A total of 63 patients with acute myeloblastic and lymphoblastic leukemia were included. Of those, 60 completed all questionnaires. Average age of this cohort was 39.62±12.80. There were observed complications associated with HCT in 60% patients; mainly inflammatory complications 40% more rarely toxic 11.7%, thrombotic 8.3% or hemorrhagic 6.7% complications. Table 1 illustrates the sociodemographic and medical characteristics of the examined patients.

Table 1. Characteristics of participants in reference to sociodemographic and medical data

Characteristics	N	%
Gender		
Female	34	56.7
Male	26	43.3
Level of education		
Primary	2	3.3
Vocational	17	28.4
Secondary	20	33.3
University	21	35.0
Employment status		
Unemployed	5	8.3
Retired	22	36.7
Student	3	5.0
Physical work	12	20.0
White-collar work	18	30.0
Marital status		
Married	41	68.4
Widowed	2	3.3
Divorced	2	3.3
Single	15	25.0
Having children (yes)	39	65.0
Type of leukemia		
Acute lymphoblastic leukemia	19	31.7
Acute myeloblastic leukemia	41	68.3
Type of transplantation		
Allogeneic	47	78.3
Allogeneic sibling	13	21.7
Risk level		
Intermediate	11	18.3
High	49	81.7
Complications (yes)	36	60.0

The average severity of anxiety at admission to hospital was 6.53 (*SD* 4.08) and at discharge 6.35 (*SD* 4.19). The average severity of depression at admission to hospital was 3.93 (*SD* 3.42) and at discharge 4.07 (*SD* 3.91).

The analysis of line regression was conducted to check whether there were the significant predictors of anxious symptoms among the psychological variables. The predictors were introduced simultaneously to the model. Table 2 shows the results of the analysis.

Table 2. Psychological predictors of anxiety symptoms in patients after hematopoietic stem cell transplantation

Model	Non-standardized coefficients		Standardized coefficients	t	Significance
	B	SE B	Beta		
Constant of regression	4.712	7.532		0.626	0.534
Acceptance of illness	-0.017	0.093	-0.022	-0.179	0.859
Control of anger	0.182	0.115	0.221	1.582	0.120
Control of depression	0.103	0.138	0.114	0.746	0.459
Control of anxiety	-0.242	0.123	-0.319	-1.967	0.040
Dispositional optimism	-0.230	0.125	-0.222	-1.830	0.048
Anxious preoccupation	0.085	0.112	0.092	0.757	0.453
Fighting spirit	-0.257	0.162	-0.185	-1.587	0.119
Helplessness/hopelessness	0.090	0.138	0.072	0.651	0.518
Positive redefinition	0.058	0.176	0.035	0.329	0.743
Onerousness of symptoms	0.182	0.061	0.375	2.987	0.004

Tabele 3. Onerousness of symptoms experienced by patients after HCT and its association with the severity of depressive symptoms

Onerousness of symptoms (RSCL)	Severity of symptom		Association with severity of depressive symptoms		Association with severity of anxiety symptoms	
	M	SD	tau-b	p	tau-b	p
The physical symptom distress	32.92	6.490	0.180	0.058	*0.199*	*0.033*
lack of appetite	1.70	0.830	0.189	0.077	0.107	0.308
tiredness	1.95	0.723	*0.225*	*0.035*	0.202	0.054
sore muscle	1.55	0.746	-0.004	0.971	0.064	0.549
lack of energy	1.78	0.715	0.200	0.062	0.110	0.295
low back pain	1.58	0.809	-0.084	0.437	-0.002	0.988
nausea	1.50	0.813	0.167	0.125	0.149	0.163
difficulty sleeping	1.52	0.701	*0.232*	*0.033*	*0.255*	*0.017*
headaches	1.30	0.530	-0.068	0.540	-0.048	0.658
vomiting	1.22	0.585	-0.036	0.747	0.037	0.732
dizziness	1.15	0.481	0.166	0.137	0.213	0.052
decreased sexual interest	1.65	0.971	0.055	0.603	0.057	0.585
abdominal (stomach) pain	1.35	0.709	0.175	0.112	0.187	0.083
constipation	1.30	0.671	0.036	0.746	0.095	0.380
diarrhea	1.12	0.372	0.127	0.258	-0.004	0.970
acid indigestion	1.23	0.427	0.042	0.711	0.095	0.390
shivering	1.35	0.633	0.086	0.432	0.065	0.544
tingling hands or feet	1.32	0.596	-0.002	0.987	0.061	0.576
difficulty concentrating	1.28	0.585	0.158	0.152	0.181	0.094
sore mouth/pain when swallowing	1.23	0.465	0.163	0.146	0.083	0.450
loss of hair	1.53	0.965	0.126	0.244	0.103	0.331
burning/sore eyes	1.37	0.551	-0.044	0.694	-0.085	0.435
shortness of breath	1.23	0.465	0.147	0.190	0.114	0.301
dry mouth	1.70	0.788	-0.068	0.529	-0.030	0.778
The psychological distress scale	11.53	3.780	*0.261*	*0.007*	*0.454*	*<0.001*
irritability	1.72	0.715	0.155	0.151	*0.291*	*0.006*
worrying	2.03	0.823	0.205	0.055	*0.414*	*<0.001*
depressed mood	1.57	0.767	*0.309*	*0.000*	*0.459*	*<0.001*
nervousness	1.68	0.725	0.137	0.206	*0.323*	*0.002*
despairing about the future	1.37	0.610	*0.386*	*0.001*	*0.477*	*<0.001*
tension	1.58	0.696	*0.248*	*0.023*	*0.399*	*<0.001*
anxiety	1.58	0.645	0.146	0.184	*0.355*	*0.001*

The obtained model of regression seemed to match the data well. It explained 43% variability with regard to anxious symptoms, but the real results with regard to the explained variable differed from the expected one averagely on 3.16 point. There was no autocorrelation of the regressive rests (d=1,900) in the model. The regressive rests had the arrangement congruent with the normal one. There was no collinearity of the predictors.

The negative predictor of anxious symptoms was control of anxiety but it was weakly associated with a lower level of the explained variable. The negative predictor of anxious symptoms was also the dispositional optimism whose high level accompanied the lower intensity of the explained variable. However, the positive predictor of anxious symptoms was the variable of the onerousness of symptoms whose high level accompanied the higher intensity of anxious symptoms in the examined group (Table 3).

The results indicated the weak, positive correlation between onerousness of physical symptoms and a level of anxiety. The greater was the intensity of physical symptoms, the higher was the level of anxiety. The analogous tendency of correlation was observed with regard to depressive symptoms, but it was insignificant statistically, although on a border of importance.

Tiredness correlated positively with a level of depression in patients with regard to the physical symptoms. Difficulty sleeping correlated positively with the severity of depression as well as anxiety.

Both groups of the symptoms (depressive and anxious), correlated positively with psychological symptom distress. The correlation with depressive symptoms was weak, however, with anxious symptoms was moderate. In both cases, the higher was a level of psychological symptom distress, the higher level of anxiety and depression was observed in patients.

The specific symptoms (irritation, worrying, nervousness and anxiety) were positively correlated with anxious symptoms. The other symptoms (depressed mood, despairing about the future, tension) were correlated with anxious as well as depressive symptoms, but the association with anxiety was stronger.

DISCUSSION

The statistical analysis used in the study allowed to prove the significant association between anxiety and onerousness of symptoms, especially linked to psychological distress. It was also proven that onerousness of symptoms was a moderate predictor of anxiety. The correlation between depressive symptoms and psychological distress was less significant statistically and associated with a smaller number of symptoms. The results did not allow to estimate a significant association between physical distress and occurrence of anxious and depressive symptoms, what is probably a result of the use of the HADS. The use of the HADS, which does not intentionally assess physical symptoms of depression, allows to avoid physical burdens accompanying such medical treatment as HCT (e.g. Zigmond and Snaith, 1983).

Our results referring to anxiety and depression before and after HCT confirm the similar with other studies prevalence of their symptoms in the group of patients who underwent HCT (e.g. Goetzmann et al. 2006, Prieto et al. 2005, Hjermstadt et al. 2004, Trask et al. 2002). In contrast to other studies, a decrease of anxiety after HCT was not observed (e.g. Fife et al. 2000, Shirinbakhsh Masule et al. 2014). It may be explained by the severity of physical symptoms merely to a small extent because such an association was only in a case of sleep disturbances. The current prospective longitudinal studies have indicated that the transplant hospitalization is experienced by patients as the traumatic event that can lead to the development of posttraumatic stress disorder (e.g. El-Jawahri et al. 2016). However, such a conclusion requires better identification of the factors that boost psychological distress, e.g. coping strategies and social support (e.g. El-Jawahri et al. 2015).

The negative predictors of anxiety were dispositional optimism and control of anxiety what means that their high results were associated with a later smaller intensification of anxious symptoms (e.g. Coyne et al. 2010, Goetzmann et al. 2008). It might be understood that optimistic attitude and control as an adaptive capacity to rationalize own anxiety were these mechanisms protecting against overwhelming fears, especially before HCT (e.g. Herzberg al. 2013, Rasmussen et al. 2009, Schou et al. 2004). In practice, it would mean that all therapeutic interventions boosting the protective mechanisms would allow to reduce general psychological distress after HCT.

Several limitations of the study should be taken into account in the analysis. The first one is associated with the fact that the study was limited only to a period of the transplant hospitalization and there is a lack of further observation of the patients with regard to psychological and physical symptoms and their association with factors occurring in their natural environment. The second limitation is a small number of the patients what decreases representativeness of the population examined in the study.

CONCLUSION

The association of anxiety and to a smaller degree depression with onerousness of symptoms, especially psychological distress, should induce teams of clinicians and medical workers to some interventions. Such interventions should be focused on detailed monitoring of the distress symptoms. In their consequence, all suitable psychological and pharmacological approaches would be introduced to protect the patients against their post-transplantation complications and to improve their post-transplantation adjustment and recovery.

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Contribution of individual authors:

Anna Warchala: design of the study, literature researches and analyses, statistical analyses, interpretation of data, manuscript writing.

Irena Krupka-Matuszczyk: literature researches and analyses, manuscript writing.

Krzysztof Krysta: manuscript writing.

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