ORIGINAL ARTICLE

Heart Rate Variability and Heart Rate Turbulence in Patients with Hematologic Malignancies Subjected to High-Dose Chemotherapy in the Course of Hematopoietic Stem Cell Transplantation

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Background: In hematological malignancies, remissions and cures may be achieved by hematopoietic stem cell transplantation (HSCT) following high-dose chemotherapy (HDC). Cardiotoxicity of such therapy has not yet been fully elucidated. Noninvasive approaches allowing to evaluate an autonomic control of the heart function include analyses of both heart rate variability (HRV) and heart rate turbulence (HRT).

Methods: In 38 patients with hematological malignancies, 24-hour electrocardiography Holter monitoring, with HRV and HRT analysis before HSCT (A test) and after HSCT (B test), was performed.

Results: The 24-hour analysis of HRV demonstrated that SDNN, SDNNi, rMSSD, and pNN50 parameters were significantly lower after HSCT as compared to the results obtained before the transplantation ($P < 0.05$). For period of diurnal activity and for night hours, SDANN, SDNNi, rMSSD, and pNN50 were significantly lower in B test, as compared to the results of A test ($P < 0.05$). The analysis of HRT demonstrated that turbulence onset parameter was significantly higher, and turbulence slope parameter was significantly lower in B test, as compared to A test ($P < 0.05$). The multifactorial stepwise backward regression analysis indicated that administration of cyclophosphamide and carmustine and higher concentrations of blood cholesterol represented risk factors for decreased HRV. Cyclophosphamide and higher triglyceride levels represented independent risk factors for decreased HRT.

Conclusions: In patients with hematopoietic malignancies treated with HSCT, decreased HRV and HRT were observed after chemotherapy and stem cells administration.

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heart rate variability; heart rate turbulence; hematopoietic stem cell
transplantation; high-dose chemotherapy; cardiotoxicity

Cytostatic agents are an essential part of treatment not only in hematology but also in entire oncology. However, therapy using cytostatics is linked to

a pronounced toxicity for normal body cells. As demonstrated up to now, cardiotoxic effects are exerted first of all by anthracyclins. Therapy

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with anthracyclins is associated with a risk of myocardial injury, resulting in development of a systolic dysfunction, signs of heart failure, and even with sudden cardiac death.^{1,2} Also other strategies of antineoplastic therapy may cause cardiotoxicity of a clinical significance, as exemplified by cyclophosphamide treatment in patients with malignant lymphoma.³

Hematopoietic stem cell transplantation (HSCT), an important therapeutic strategy in many hematologic malignancies, significantly prolongs survival in patients. In hematological malignancies, sustained remissions and even cures may be achieved in certain patients by use of HSCT following the high-dose chemotherapy (HDC).^{3,4}

Nevertheless, clinical observations suggest that cardiovascular complications may appear in some patients in a course of peripheral blood (PB) stem cell transplantation and also there is a serious risk of developing some long-term complications. Until now, a detailed range of possible cardiovascular complications and potential cardiotoxic effects of stem cells administration in individual groups of patients remains unknown.

According to current knowledge, pathomechanism of heart disturbances is thought to involve abnormal control exerted by the autonomic nervous system. Useful noninvasive approaches allowing to evaluate autonomic control of heart functioning contain analysis of heart rate variability (HRV) and analysis of heart rate turbulence (HRT).

The present study was aimed at evaluation of HRV and HRT in patients with hematological malignancies subjected to HDC in a course of HSCT.

METHODS

Study Population

To the study, 43 consecutive patients, hospitalized in the Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation at Wrocław Medical University, Poland, were enrolled. Inclusion criteria were, as follows: age above 18 years, hematologic malignancy recognized, achievement of total remission of the disease and qualification of patient for HSCT following HDC based on current standards. However, 5 patients had to be excluded from the study, because of diabetes mellitus (2 patients), ischemic heart disease (1 patient), previous cerebral stroke

Table 1. Clinical Characteristics of the Study Group

Age (years)	42.88 ± 13.49
Gender (%/n)	
Men	60.53/23
Women	39.47/15
Blood neoplasms (%/n)	
Acute myeloid leukemia—AML	28.95/11
Hodgkin's lymphoma—HD	18.42/7
Multiple myeloma—MM	18.42/7
Acute lymphoblastic leukemia—ALL	15.79/6
Non-Hodgkin's lymphoma—NHL	13.16/5
Chronic myeloid leukemia—CML	5.26/2

(1 patient), and arterial hypertension (1 patient), that is, comorbidities that could affect the study results. Thus, the final study group consisted of 38 patients. Clinical characteristics of the study group is presented in Table 1.

Study Protocol

Patients qualified for autologous HSCT (22 patients), around 1 month before the procedure, were subjected to mobilization, a strategy to increase PB stem cells concentration (CD34+ cells), by inducing a rebound of PB stem cell concentration following nonmyelotoxic chemotherapy with administration of granulocyte colony-stimulating factor. After the administration of mobilizing doses, within a few days levels of blood stem cells were examined and, if sufficiently high, the cells were collected. Remaining 16 patients of the 38 of the study group were qualified for allogeneic HSCT.

For performance of HSCT procedure, patients were admitted to the Department in a clinically good condition (described in ECOG scale as 0–1 patients) with no visible signs of infection, normal blood cell count, electrolytes, biochemistry, and level of C-reactive protein (CRP) (see Table 2).

Prior to HSCT procedure, all patients were subjected to echocardiography and to 24-hour Holter monitoring with HRV and HRT analysis (test A). Then, patients were administered a HDC, a type of which was appropriate to the diagnosed malignancy, and a dose of which was calculated for the patient's body weight or body surface area. Conditioning regimens used in HDC included: melphalan for 7 patients, BEAM (BCNU, etoposide, ARA-C, melphalan) for 12 patients, and BuMel (busulfan, melphalan) for 3 patients in auto-HSCT and Flu Bu (fludarabine, busulfan) for

Table 2. Laboratory Characteristics of Patients before HSCT

RBC (mln/ml)	3.85 ± 0.49
Hematocrit (%)	36.04 ± 4.43
Hemoglobin (g/dl)	11.81 ± 2.34
WBC ($\times 10^2$ /l)	6.13 ± 3.22
Platelet count ($\times 10^2$ /l)	159.25 ± 85.15
Sodium (mmol/l)	142.06 ± 2.66
Potassium (mmol/l)	4.08 ± 0.38
Prothrombin activity (%)	94.90 ± 10.52
Fibrinogen (mg/dl)	380.71 ± 72.27
APTT (s)	33.80 ± 5.75
Urea (mg/dl)	31.58 ± 11.01
Creatinine (mg/dl)	0.87 ± 0.24
Uric acid (mg/dl)	5.29 ± 1.36
Glucose (mg/dl)	96.00 ± 24.26
Serum protein (g/dl)	6.80 ± 0.63
Albumin (g/dl)	4.10 ± 0.42
Total cholesterol (mg/dl)	194.09 ± 36.80
Triglyceridy (mg/dl)	128.67 ± 46.50
Aspartate aminotransferase (U/l)	19.81 ± 7.95
Alanine aminotransferase (U/l)	29.21 ± 24.77
Lactate dehydrogenase (U/l)	178.83 ± 29.39
Total bilirubin (mg/dl)	0.79 ± 0.69
C-reactive protein (mg/l)	4.69 ± 3.18

Table 3. Cytostatics Used in High-Dose Chemotherapy (HDC) and Total Body Irradiation (TBI) before HSCT

Cytostatic (%/n)	Percentage/Number of patients
Melphalan	57.89/22
Carmustine – BCNU	34.21/13
Etoposide	34.21/13
Cytarabine – Ara-C	31.58/12
Cyclophosphamide	28.95/11
Busulfan	26.32/10
Fludarabine	13.16/5
Total body irradiation (%/n)	21.05/8

5 patients, Bu Cy (busulfan, cyclophosphamide) for 2 patients, Cy/TBI (cyclophosphamide, total body irradiation) for 8 patients, CBV (BCNU, etoposide, cyclophosphamide) for 1 patient in case of allo-HSCT.

Frequencies of applying cytotoxic agents in HDC and TBI within HSCT procedure irradiation in the study group are shown in Table 3.

After completion of HSCT, around 20 days following the administration of chemotherapy (mean: 22.46 ± 3.19 days), 24-hour Holter monitoring was repeated, with the analysis of HRV and HRT performed once again (test B).

Table 4. Definitions of Time Domain Analysis Parameters of Heart Rate Variability (HRV)

Parameter	Definition
mRR (ms)	Mean of RR intervals
SDNN (ms)	Standard deviation of all normal RR intervals
SDANN (ms)	Standard deviation of the average normal RR interval for all 5-minute segments
SDNNi (ms)	Mean of the standard deviations of all RR intervals for all 5-minute segments of the entire recording
rMSSD (ms)	Root mean square differences
pNN50 (%)	The number of adjacent normal RR intervals differing by more than 50 ms, as a percent of the total number of normal RR intervals

Analysis of HRV

In all examined patients, time domain analysis of HRV was carried out, which was preceded by visual verification of the automatic electrocardiography (ECG) recording. HRV was examined within 24-hour Holter recording and separately for a period of daily activity (6:00–22:00) and for night hours (22:00–6:00). Time domain analysis of HRV included: mRR, SDNN, SDANN, SDNNi, rMSSD, and pNN50. Definitions and abbreviations of the examined time parameters of HRV are listed in Table 4.

Analysis of HRT

The analysis of HRT included standard parameters: turbulence onset (TO) and turbulence slope (TS). Parameters of HRT were considered to be normal when $TO < 0\%$, and $TS > 2.5$ ms/ RR interval. The analysis of HRT indices in the studied groups and subgroups permitted to define proportions of the patients with normal HRT parameters (HRT0), the patients with a single abnormal HRT parameter (HRT1), and the patients with two abnormal HRT parameters (HRT2). Definitions and abbreviations of the studied HRT parameters are listed in Table 5.

Statistical Analysis

Statistic analysis was conducted using the STATISTICA 9 software (StatSoft Polska, Cracow, Poland). For the quantitative variables, arithmetic means (X) and standard deviations (SDs) of

Table 5. Definitions and Parameters of Heart Rate Turbulence (HRT)

Parameter	Definition
TO (%)	The percentage difference between the heart rate immediately following premature ventricular contraction (PVC) and the heart rate immediately preceding PVC Normal TO < 0%
TS (ms/RR)	The steepest slope of the linear regression line for each sequence of five consecutive normal intervals in the local tachogram Normal TS > 2.5 ms/RR interval
HRT0	Normal heart rate turbulence: TO and TS both normal
HRT1	One component of HRT abnormal: TS or TO
HRT2	TO and TS abnormal

estimated parameters were calculated in the studied groups. Distribution of the variables was examined using tests of Lilliefors and W-Shapiro-Wilk. For the dependent qualitative variables of the normal distribution, the *t*-test for linked variables was applied. For the dependent quantitative variables of the normal distribution, the *t*-test for linked variables was applied. In cases of quantitative dependent variables manifesting the distribution distinct from normal, the pair sequence test of

Wilcoxon was applied. Results for qualitative variables were expressed in a form of percentages. For the dependent qualitative variables, a statistical analysis involved the McNemar's or Cochran's test. In order to define a relationship between the studied variables, analysis of multifactorial regression was performed. Parameters of the model obtained in regression analysis were estimated using a technique of least squares. Results at the level of $P < 0.05$ were assumed to be of statistical significance.

RESULTS

Analysis of 24-hour HRV demonstrated that SDNN, SDNNi, rMSSD, and pNN50 parameters were significantly lower after HSCT (B test), as compared to the results obtained before the procedure (the A test) ($P < 0.05$). Comparing parameters of time domain HRV analysis calculated for diurnal activity period and for night hours, SDANN, SDNNi, rMSSD, and pNN50 were significantly lower in B test, as compared to the results of A test ($P < 0.05$). On the other hand, SDNN proved to be significantly lower in B test, as compared to A test only during the day ($P < 0.05$) (Table 6).

Analysis of HRT demonstrated that TO parameter was significantly higher and TS parameter was significantly lower in B test, as compared to the

Table 6. Time Domain Parameters of Heart Rate Variability (HRT) in the Study Group

	Test A	Test B	P
24-hour recording (6:00–6:00)			
mRR (ms)	843.13 ± 165.19	837.54 ± 158.94	NS
SDNN (ms)	99.43 ± 19.27	87.29 ± 16.32	$P < 0.05$
SDANN (ms)	56.17 ± 18.48	54.27 ± 17.59	NS
SDNNi (ms)	59.47 ± 22.35	49.98 ± 23.14	$P < 0.05$
rMSSD (ms)	65.12 ± 19.49	58.29 ± 20.01	$P < 0.05$
pNN50 (%)	9.83 ± 3.27	7.15 ± 2.13	$P < 0.05$
Day hours (6:00–22:00)			
mRR (ms)	852.43 ± 149.24	848.23 ± 150.12	NS
SDNN (ms)	103.34 ± 17.34	90.57 ± 15.24	$P < 0.05$
SDANN (ms)	63.94 ± 17.35	55.01 ± 13.32	$P < 0.05$
SDNNi (ms)	63.29 ± 19.87	52.72 ± 19.27	$P < 0.05$
rMSSD (ms)	67.34 ± 14.59	59.21 ± 17.25	$P < 0.05$
pNN50 (%)	11.24 ± 4.29	8.04 ± 2.30	$P < 0.05$
Night hours (22:00–6:00)			
mRR (ms)	829.24 ± 149.27	827.29 ± 148.32	NS
SDNN (ms)	92.37 ± 13.28	86.99 ± 13.98	NS
SDANN (ms)	53.38 ± 17.29	44.18 ± 18.24	$P < 0.05$
SDNNi (ms)	54.97 ± 14.87	45.81 ± 14.01	$P < 0.05$
rMSSD (ms)	62.15 ± 17.59	54.13 ± 16.48	$P < 0.05$
pNN50 (%)	8.84 ± 2.24	6.03 ± 2.02	$P < 0.05$

Table 7. Parameters of Heart Rate Turbulence (HRT) in the Study Group

	Test A	Test B	P
TO (%)	-1.51 ± 0.37	-0.72 ± 0.48	P < 0.05
TS (ms/RR)	6.93 ± 1.78	4.79 ± 1.97	P < 0.05
HRT0 (%)	92.10	78.95	P < 0.05
HRT1 (%)	7.89	18.42	NS
HRT2 (%)	0.00	2.63	NS

Test A = before the high-dose chemotherapy; Test B = after the high-dose chemotherapy.

results obtained in A test ($P < 0.05$). A significantly lower proportion of patients was included to the HRT0 category in B test than in A test ($P < 0.05$) (Table 7).

A multifactorial stepwise backward regression analysis, performed in the whole study group, considering the basic clinical parameters (age, gender, blood cell count, and biochemical parameters), type of hematopoietic tumor (acute myeloblastic leukemia, Hodgkin's lymphoma, multiple myeloma, acute lymphoblastic leukemia, non-Hodgkin's lymphoma, or chronic myeloblastic leukemia), and kind of administered cytostatic drugs for HDC in a course of HSCT procedure (i.e., melphalan, carmustine, etoposide, cytarabine, cyclophosphamide, or busulfan), provided the following models:

$$\begin{aligned} \Delta rMSSD = & 30.13 \text{ cyclophosphamide} \\ & + 12.34 \text{ carmustine} + 0.04 \text{ total cholesterol} \\ & \pm 8.05; \Delta TS = 0.31 \text{ cyclophosphamide} \\ & + 0.02 \text{ triglycerides} \pm 0.21. \end{aligned}$$

The obtained models indicated that in the group of patients with hematopoietic malignancies who experienced HDC in the course of HSCT, administration of cyclophosphamide and carmustine and original higher concentrations of total blood cholesterol represented independent risk factors for the decreased HRV (expressed by the elevated difference between rMSSD in A test and rMSSD in B test).

Moreover, it was demonstrated that administration of cyclophosphamide and higher initial blood triglyceride level in the study group represented independent risk factors for the reduced HRT (expressed by the increased difference between TS in A test and TS in B test).

The results of estimations for the models obtained in a multifactorial retrograde stepwise regression analysis are presented in Table 8.

DISCUSSION

HSCT represents a relatively new, however widely used method of treatment in hematology with multiple advantages. Both autologous and allogeneic PB stem cell transplantation are important therapeutic strategies in many hematologic malignancies. Clinical observations have suggested that within a peritransplant period, some patients, in particular those given a HDC, manifest cardiovascular complications.

In line with current knowledge, dysfunctions in the autonomic nervous system are considered to be a crucial background in several cardiovascular diseases. Analysis of HRV and HRT is accepted as a useful and noninvasive method evaluating autonomic control of the heart rate.

Occurrence of decreased HRV seems to be well documented in patients with various cardiovascular diseases. HRV is a measure of the cyclic variation of normal RR intervals that reflects cardiac autonomic function and may be regarded as a marker of sympathetic and parasympathetic influence on the heart rate modulation. HRV is a useful tool for evaluation of autonomic nervous system functioning in different subsets of patients. Decreased HRV characterizes patients with myocardial infarction and provides an unfavorable prognostic factor in acute coronary syndromes.⁵ In addition, a decrease in HRV has been recognized as pathomechanisms of arterial hypertension, heart failure, cardiomyopathies, diabetes mellitus, supraventricular and ventricular arrhythmias, and sudden cardiac death.⁶⁻¹⁰

Also, another parameter, that is, decreased HRT, seems to be of precious value in patients with various cardiovascular conditions. HRT is defined as a biphasic reaction of sinus node in response to the premature ventricular beat, consisting of early acceleration and subsequent deceleration of the heart mediated by a baroreflex response to the lower stroke volume of the ectopic beat. HRT is an independent and powerful predictor of mortality after myocardial infarction.^{11,12} Blunted HRT reaction was observed in various subgroups of patients, such as those with arterial hypertension, heart failure, and after myocardial infarction.¹²⁻¹⁵

Table 8. Results of Estimation for the Final Models Obtained in the Multivariate Backward Stepwise Regression Analysis

	Model for Δ rMSSD (ms)		
	Cyclophosphamide	Carmustine – BCNU	Total Cholesterol (mg/dl)
Regression coefficient	30.132	1.341	0.037
SEM of Rc	6.195	6.012	0.008
P value	0.003	0.048	0.007
P value for the model		P < 0.009	

	Model for Δ TS (ms/RR)	
	Cyclophosphamide	Triglycerides (mg/dl)
Regression coefficient	0.307	0.024
SEM of Rc	0.092	0.008
P value	0.007	0.008
P value for the model		P < 0.011

Δ rMSSD = difference between rMSSD in test A and rMSSD in test B; Δ TS = difference between TS in test A and TS in test B; cyclophosphamide and carmustine – BCNU = nominal variables, where 1: yes, 2: no; SEM of Rc = standard error of the mean of regression coefficient.

Analysis of the results obtained in the present study shown that a HDC used in patients with hematopoietic malignancies during HSCT procedure may induce in a peritransplant period a decrease in both HRV and HRT. The significant decrease was detected for most parameters of HRV analysis within the time following completion of HSCT procedure, as compared to the test results obtained directly before a HDC, both in the whole day analysis and in the separate analyses conducted for hours of daily activity and those for night rest.

Moreover, following a completion of HSCT, changes typical for the decreased HRT were observed, that is, elevation of TO and reduction of TS, as compared to the test results obtained directly before HDC. Also, the significantly lower proportion of the patients with normal HRT, that is, with HRT0 in the second test after HSCT, in comparison with the test directly preceding the HDC, pointed out a presence of the decreased HRT as connected to therapy in hematopoietic malignancies.

In order to define independent factors of risk for decreases in HRV and HRT values resulting from HSCT, a procedure multifactorial regression analysis was performed. The models obtained in the regression analysis enabled to find out that in the group of patients with hematopoietic malignancies subjected to a HDC in the course of HSCT, application of cyclophosphamide and carmustine as well as higher original blood level

of total cholesterol represented independent risk factors for the reduced HRV, whereas administering cyclophosphamide and higher initial blood triglyceride concentrations represented independent risk factors for the reduced HRT. In 24-hour-HRV analysis, application of cyclophosphamide resulted in decrease in rMSSD averagely by 30.13 ms and in reduction of TS in HRT analysis by the mean of 0.31 ms/RR, whereas application of carmustine resulted in a decrease in rMSSD in 24-hour-HRV analysis by the mean of 12.34 ms.

The results obtained in this study provided some new knowledge about chemotherapy effects in a course of transplantation procedure on the circulatory system functioning, which until now was not fully investigated using HRV and HRT methods in a peritransplant period.

According to Kupari et al., cardiac complications are generally not a major problem in bone marrow transplantation (BMT), but they may have serious consequences for individual patients and, therefore, should be carefully monitored, especially in persons undergoing allogeneic BMT.¹⁶ Nowadays, PB stem cells transplantation in many hematological diseases is a procedure of the first choice, but many studies were carried out earlier, when BMT was the first line therapy.

Some authors declare that clinically significant heart involvement affects 5–10% of patients undergoing BMT after pretreatment with cyclophosphamide and TBI.³ Conventional diagnostic methods, like electrocardiography and

echocardiography, lack a satisfactory sensitivity in prediction of cardiotoxicity in these patients.³

Gardner et al. reported that positron emission tomography scanning may be a useful adjunct in evaluating cyclophosphamide cardiotoxicity.³ In turn, Lehmann et al. also examined the effect of HSCT on cardiac function in patients with various hematological malignancies undergoing either allo- or auto-HSCT.¹⁷ They found no serious changes in left ventricular ejection fraction (LVEF) measured by radioventriculography in any of the diagnostic subgroups in allogeneic or autologous recipients.

Cyclophosphamide (CTX) is an alkylating agent with major toxicities of bone marrow, rarely inducing also cardiomyopathy, and in our regression model it has been proved to be a risk factor for the decrease of both HRV and HRT. Cardiomyopathy is reported more often as reversible, but in some cases it is followed by a serious fulminant heart failure and fatal outcome.¹⁸

It was suggested by the American College of Cardiology and American Heart Association (ACC/AHA) that patients receiving chemotherapy can be considered to represent the A group of heart failure.¹⁹ The most clinically evident cardiotoxicity and the best recognized is the adverse effect of anthracyclines.²⁰ Castel et al. claims that the most serious cardiac complications of cancer therapies include heart congestive failure, mainly due to the use of anthracyclines, cyclophosphamide, and trastuzumab, usually at high doses.²⁰ The other side effects, not so common, may include arterial hypotension or hypertension, thromboembolic complications, arrhythmias and conduction disturbances, pericarditis, myocarditis, myocardial infarction and cardiomyopathy.^{20,21}

Complications may occur during treatment or shortly after that or may not be apparent until months and even years after completion of chemotherapy.²⁰

Many risk factors may predispose a patient to cardiotoxicity, such as cumulative dose of anthracyclines, total dose administered during a day or a course, rate of administration, schedule of administration, female gender, concurrent administration of cardiotoxic agents, prior anthracycline chemotherapy, history of or preexisting cardiovascular disorders, and electrolyte imbalances, such as hypokalemia and hypomagnesemia.²⁰⁻²⁵

In our study group, the patients were treated first by standard chemotherapy including an-

thracyclines, with traditional CHOP regimen (cyclophosphamide, hydroxydaunorubicin, Oncovin, i.e., vincristine and prednisone).

Pai claims that the patients may be almost asymptomatic, with scanty manifestations, such as electrocardiographic changes. As a method of choice in prevention of cardiotoxicity, the quoted author reasonably suggested the need for a continuous cardiac monitoring, baseline and regular electrocardiographic and echocardiographic studies, with the possible use of other methods.²¹

Summing up, a review of the up-to-date reports, apart from cardiotoxic effects of anthracyclins, pointed also to toxic effects of cyclophosphamide and carmustin, which goes in line with a reduction of HRV and HRT documented also in this study that could reflect the potential cardiotoxic effect.^{20,21}

Mechanisms of reduced HRV after HSCT seems to be a complex matter, because it involves probably both neural and nonneural mechanisms. Reduced HRV, especially SDNN, according to Lombardi and Stein, is induced by inability of the heart to decrease the rate at night, which reflects an impaired vagal activity.²⁶ However, it is proposed by many authors that both a diminished vagal and increased sympathetic modulation of the sinus node may be reflected by the HRV reduction.²⁶⁻³¹

The abnormalities observed in our study could result from the transplantation procedure, however an influence of chemotherapy itself was also probable for some chemotherapy regimens were proved to be independent risk factors for the decreased HRV. To clarify this point, an additional test should be carried out just between the time of chemotherapy and transplantation. However, it would give three tests including HRV analysis. It was rather impossible in the patients after transplantation because of leukopenia and life threat.

Limitations of the present study involve a relatively heterogeneous nature of the study group, and therefore using various protocols of HDC before transplantation of stem cells. Also a quite small number of patients included to the study group may be a weak point of the study. However, the other authors encountered similar problems. This issue reflects specificity of treatment in hematological patients, long duration of the procedure due to a need of stem cells mobilization in autotransplantation and preparation including a

search for the suitable donor in allogeneic stem cells transplantations.

The authors intend to follow up the study patients subjected to HSCT procedure in about a year's time with echocardiography and Holter monitoring including HRV and HRT analysis to check if the autonomic dysregulation is correlated with development of incipient cardiomyopathy.

CONCLUSIONS

- (1) In the patients with hematopoietic malignancies treated with HDC in the course of HSCT, decreased HRV and decreased HRT were observed after completion of the HDC, as compared to the tests performed directly before this treatment.
- (2) In the patients with hematopoietic malignancies subjected to HSCT, application of cyclophosphamide and carmustine and higher initial total cholesterol blood levels represent independent risk factors for the decreased HRV, while application of cyclophosphamide and higher initial triglycerides blood levels seems independent risk factors for the decreased HRT.

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