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ПРЕДИКТОРЫ СНИЖЕНИЯ МИНЕРАЛЬНОЙ ПЛОТНОСТИ КОСТНОЙ ТКАНИ У ПАЦИЕНТОВ С ЛИМФОМОЙ ХОДЖКИНА, АССОЦИИРОВАННЫЕ С ПАТОГЕНЕТИЧЕСКОЙ ТЕРАПИЕЙ

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Predictors of Bone Mineral Density Reduction in Patients with Hodgkin's Lymphoma Associated with Pathogenetic Therapy

Резюме

Лимфома Ходжкина чаще встречается в популяции молодых пациентов. Увеличение общей и безрецидивной выживаемости увеличивает вероятность развития постцитостатических осложнений в виде снижения минеральной плотности костной ткани и связанных с этим низкоэнергетических переломов. **Целью работы** является оценка факторов риска снижения минеральной плотности костной ткани у пациентов с лимфомой Ходжкина после стандартной полихимиотерапии и аутологичной трансплантации гемопоэтических стволовых клеток. **Материал и методы.** В исследование включены 118 человек, из них 88 человек — пациенты с лимфомой Ходжкина и 30 человек — группа контроля. Исследуемая группа пациентов с лимфомой Ходжкина разделена на 2 группы: пациенты, получившие стандартную полихимиотерапию, и пациенты, получившие стандартную полихимиотерапию и аутологичную трансплантацию гемопоэтических стволовых клеток. Для всех пациентов измерения минеральной плотности кости проводились с использованием сканера HologicDiscovery QDR (США) в поясничном отделе позвоночника (L2 — L4) и в области бедра (общая площадь бедра и шейки бедра). Были выбраны минимальные измерения минеральной плотности костной ткани и Т-критериев в области бедра и шейки бедра, для молодых пациентов подсчитан Z-критерий. **Результаты.** По результатам денситометрии в обеих исследуемых группах не наблюдалось снижение минеральной плотности костной ткани ниже возрастной нормы. У 13 пациентов (30 %), получивших аутологичную трансплантацию гемопоэтических стволовых клеток, выявлено снижение Т-критерия, что соответствует остеопении и остеопорозу. В группе стандартной ПХТ снижение Т-критерия наблюдается у 6 пациентов (14 %): до остепении — у 3 пациентов (7 %), до остеопороза — у 3 пациентов (7 %). Все пациенты с лимфомой Ходжкина, включенные в исследование, получали высокие дозы глюкокортикостероидов. Не выявлено зависимости снижения МПК, Z-критерия и риска низкоэнерге-

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тического перелома от стадии и варианта заболевания. **Заключение.** Высокая частота встречаемости снижения плотности костной ткани с учетом благоприятного прогноза для жизни пациентов с лимфомой Ходжкина указывает на необходимость разработки схем профилактики развития остеопороза и остеопении.

Ключевые слова: *Лимфома Ходжкина, денситометрия, остеопороз, минеральная плотность костной ткани*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Hodgkin's lymphoma is more common in the younger patient population. An increase in overall and recurrence-free survival increases the likelihood of developing post-cytostatic complications in the form of a decrease in bone mineral density and associated low-energy fractures. **The aim of the work** is to evaluate risk factors for bone mineral density decrease in patients with Hodgkin's lymphoma after standard polychemotherapy and autologous hematopoietic stem cell transplantation. **Material and Methods:** The study included 118 people, of which 88 people were patients with Hodgkin's lymphoma and 30 people were the control group. The study group of patients with Hodgkin's lymphoma was divided into 2 groups: patients who received standard polychemotherapy and patients who received standard polychemotherapy and autologous hematopoietic stem cell transplantation. For all patients, measurements of bone mineral density were performed using the HologicDiscovery QDR scanner (USA) in the lumbar spine (L2–L4) and in the thigh region (total area of the thigh and femoral neck). The minimum measurements of bone mineral density and T-scores in the hip and femoral neck were selected, and the Z-score was calculated for young patients. **Results:** According to the results of densitometry in both study groups, there was no decrease in bone mineral density below the age norm. In 13 patients (30 %) who received autologous hematopoietic stem cell transplantation, a decrease in T-score was found, which corresponds to osteopenia and osteoporosis. In the standard PCT group, a decrease in the T-criterion was observed in 6 patients (14 %): to stagnation — in 3 patients (7 %), to osteoporosis — in 3 patients (7 %). All patients with Hodgkin's lymphoma included in the study received high doses of glucocorticosteroids. There was no correlation between the decrease in BMD, Z-criterion and the risk of low-energy fracture on the stage and variant of the disease. **Conclusion:** The high incidence of bone density reduction, taking into account a favorable prognosis for the life of patients with Hodgkin's lymphoma, indicates the need to develop schemes for the prevention of osteoporosis and osteopenia.

Key words: *Hodgkin's lymphoma, densitometry, osteoporosis, bone mineral density*

Conflict of interests

The authors declare no conflict of interests

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aHSCT — autologous hematopoietic stem cell transplantation, BMD — bone mineral density, CR — complete response, DXA — dual-energy x-ray absorptiometry, GCs — glucocorticosteroids, HL — Hodgkin lymphoma, PCT — polychemotherapy, PD — progression of disease, PR — partial response, SD — stabilization of disease

Introduction

Hodgkin lymphoma (HL) is a malignant disease of lymphatic system that develops in the impaired lymphopoiesis of B-lymphocytes in a lymph node and is characterized by typical lymphogenous metastasis [1]. This disease develops in people of any age group, with the peak incidence at the age of 20–35 years [2].

In recent years, the morbidity rate of HL has not changed significantly, however, the mortality rate has decreased along with the increased life expectancy of patients [3]. Survival prognosis for this disease is relatively favorable if advanced methods of treatment are used. Most patients can be cured after a standard first-line polychemotherapy (PCT) [2].

An advanced and very effective treatment method for relapsed or refractory HL is autologous hematopoietic stem cell transplantation (aHSCT) associated with the increased number of cured patients. However, the increased survival rate in HL is associated with increased possibility of complications (including

disabling and life-threatening) of previous cytostatic therapy. Many delayed complications of PCT and aHSCT include the pathological condition of musculoskeletal system that develops as a result of metabolic bone lesions — osteoporosis and the associated low-energy fractures [2, 3]. The mechanisms of osteoporosis development in patients with HL are poorly known. Several literature sources describe decreased bone mineral density (BMD) as a consequence of impaired formation and destruction of bone tissue, as well as increased bone resorption due to such factors as cytostatic agents, glucocorticosteroids (GCs), nutritional deficiency, sedentary lifestyle [3, 4]. In this context, the issues of diagnosis and preventing osteoporosis seem to be very relevant for oncohematology.

Objective of the study: to evaluate risk factors for BMD decrease in patients with Hodgkin lymphoma after standard PCT and aHSCT.

Materials and Methods

The retrospective study included 118 individuals, 30 of them were enrolled in the control group and 88 patients were admitted to the Department of Hematology, Chemotherapy and Bone Marrow Transplantation of the Sverdlovsk Regional Clinical Hospital No. 1 with confirmed HL.

The patients with proven diagnosis were divided into two study groups with equal number of participants (n = 44): group 1 — patients who received standard PCT (15 males (34 %), 29 females (66 %), median age 32.5 years), group 2 — patients who received standard PCT and aHSCT (22 males (50 %) and 22 females (50 %), median age 28 years). Group 3 — the control one — included 30 healthy volunteers (12 males (40 %), 18 females (60 %), median age 29 years). These groups were comparable in terms of demographic parameters and morphological characteristics of the disease.

Inclusion criteria were as follows: 1) reliable diagnosis of Hodgkin lymphoma; 2) indications for standard PCT and/or PCT + aHSCT. Exclusion criteria were as follows: 1) endocrine disorders (hypercorticism, thyrotoxicosis, etc.); 2) rheumatic diseases (rheumatoid arthritis, systemic lupus erythematosus); 3) gastrointestinal diseases (malabsorption syndrome, conditions after gastrointestinal surgery, liver failure); 4) history of cancer; 5) alcoholism and drug addiction.

HL was diagnosed based on the results of histological and immunohistochemical tests of biopsied lymph node.

This disease has two morphological forms: classical HL and nodular lymphocyte-predominant Hodgkin lymphoma that develops in only 5 % of total cases [1]. Classical HL, in turn, has 4 histological types with a common immunophenotype: nodular sclerosis (types I and II), mixed cellularity type, lymphocyte-rich classical type, and lymphocyte-depleted type [1]. The types with poor prognosis, i.e., lymphocyte-depleted and type II nodular sclerosis HL develop in no more than 10 % of cases [1, 2].

The patients in the groups were divided depending on the histological type of the disease. Most of them had nodular sclerosis — 40 patients (91 %) in group 1 and 41 patients (93 %) in group 2. There were only few patients with lymphocyte-depleted type — 1 patient (2 %) in group 2, as well as with mixed cellularity type — 4 patients (9 %) and 2 patients (5 %) in groups 1 and 2, respectively. Lymphocyte-rich classical type was not found (Table 1).

Depending on the stage of the disease, distribution in groups was as follows: group 1 — most patients had stage II of the disease; group 2 — most patients had stage III or IV. According to the results of the iliac bone trepanobiopsy in group 1, a tumor lesion of bone marrow

Table 1. *Characteristics in all study groups*

Categories	PCT Group (n=44)	The PCT+autoTGSK Group (n=44)	Control Group (n=30)
Stage			
I	0 (0.0 %)	0 (0.0 %)	–
II	22 (50.0 %)	13 (30.0 %)	
III	7 (16.0 %)	14 (32.0 %)	
IV	15 (34.0 %)	17 (39.0 %)	
A/B			
A	11 (25.0 %)	11 (25.0 %)	–
B	33 (75.0 %)	33 (75.0 %)	
Variant			
nodular sclerosis	40 (91.0 %)	41 (93.0 %)	–
mixed-cell	4 (9.0 %)	2 (5.0 %)	
lymphoid depletion	0 (0.0 %)	1 (2.0 %)	
Gender			
Female	22 (50 %)	29 (66 %)	18 (60 %)
Male	22 (50 %)	15 (34 %)	12 (40 %)

was found in 3 patients (7 %), in group 2 — in 12 patients (27 %).

The ratio of asymptomatic (A) and intoxication forms (B) in both groups was equal and amounted to: 11 individuals (25 %) with A form and 33 individuals (75 %) with B form, respectively. Thus, the predominance of B form in all groups was observed.

The most common first line therapy for patients with advanced HL is ABVD and enhanced BEACOPP regimen — escBEACOPP. Most patients in the aHSCT group received PCT according to BEACOPP regimen — 32 patients (73 %); according to ABVD regimen — 11 patients (25 %); according to COPDAC regimen — 1 patient (2 %). In the PCT group, most patients received treatment according to escBEACOPP regimen — 40 patients (91 %); 3 patients (7 %) — according to ABVD, besides, 1 patient (2 %) received therapy according to Gem-P regimen.

The number of courses was determined depending on the progression of the tumor process and the response to treatment. The average number of treatment courses was 4 (2 to 8). The average duration of PCT was (6 ± 2) months in aHSCT group and (8 ± 2) months in the PCT group. The patients did not receive radiation therapy for residual tumor.

As a result of the first line PCT, more than half of the patients in group 2 — 32 patients (73 %) — demonstrated partial response (PR). Eight patients (18 %) achieved stabilization of the disease (SD). The progression of the disease (PD) developed in 4 individuals in this group (9 %). In group 1, 33 patients (75 %) had complete response (CR) after the first line therapy; 11 patients (25 %) had PR.

After restaging, patients who had no CR received reserve therapy (2 to 7 courses), with the average number of 4 courses; in the PCT group, no reserve therapy was required.

The largest number of patients in group 2 received reserve therapy courses according to the following regimens: DHAP — 34 patients (77 %), escBEACOPP — 10 patients (23 %), DexaBEAM — 4 patients (9 %), Gemzar-including courses — 9 patients (20 %), HdCph, BEACOPP, BEACVPP — 1 patient each (2 %).

Generally, reserve therapy courses have improved treatment results: PR was achieved in 34 patients (77 %); it is 6 % higher compared to the first line of therapy. SD was established in 3 patients (7 %); it is 62 % less compared to the first line. CR was found in 6 patients (14 %); it is 67 % higher compared to the first line. PD was registered in only 1 patient (2 %); it is 75 % less than the previously obtained treatment result.

Currently, aHSCT is indicated as the standard of care for patients with relapsed or refractory HL. All patients of group 2 received this type of treatment. According to several researchers, aHSCT can increase long-term disease-free survival in HL patients from 30 to 65 %. According to our data, aHSCT was accompanied by CR in 29 patients (65 % of cases), and PR in 15 patients (35 % of cases).

All patients of study groups received no osteotropic therapy for osteoporosis as a preventive measures or regimen. Amount of treatment performed was determined in accordance with the response to the basic pathogenetic therapy. The patients received supportive treatment with proton pump inhibitors and diuretics.

The ongoing antineoplastic regimen therapy was associated with several side effects; among these, potential risk factors for decreasing BMD that increase the risk of fractures were analyzed. Development of changes in hormonal status after PCT and aHSCT was demonstrated, in particular, decreased androgenic function in men and decreased fertility in women [5]; there was also the onset of bowel diseases. Moreover, prolonged immobilization after aHSCT and weight loss are the risk factors for bone resorption disorders [3, 4].

Bone tissue disorder is assessed based on the measurement of BMD using dual-energy x-ray absorptiometry method (DXA). The assessment of densitometric parameters and bone tissue was carried out using dual-energy x-ray absorptiometry with HOLOGIC device (Hologic Inc, Bedford). Bone mass is calculated by the content of minerals per bone area unit (BMD, g/cm^2), a percentage of normal values in patients of the corresponding gender and age and peak bone mass [6]. At the same time, Z-score relative to age norm and T-score relative to peak bone mass were also calculated [6].

Values of DXA parameters depend on age, gender, and the onset of menopause. Normal T-score is considered to be ≥ −1.0; decreased BMD, or osteopenia, is T-score from −1.0 to −2.5; osteoporosis is characterized with T-score less than −2.5 standard deviations. In young individuals, normal Z-score is > −2.0; decreased BMD, or osteopenia, is Z-score ≤ −2.0. If young patients have a history of fractures of lower extremities, compression fractures of the spine, two or more fractures of the tubular bones of arms, as well as Z-score ≤ −2.0, it refers to a decrease in BMD and/or osteoporosis development [6].

T-score is recommended for the assessment of osteopenia and osteoporosis in 50+ patients [6], however, several sources admit using this parameter for this purpose in younger patients, if there are additional risk factors for decreased BMD [5, 7]. In patients with hemoblastosis who receive pathogenetic therapy, such factors include decreased androgenic and fertile function, long-term use of glucocorticoids, and cytostatic therapy [7]. In this regard, in the course of this study, T-score was used as an additional parameter characterizing the risk of decreased BMD.

During the study, a questionnaire survey of patients was conducted in order to identify risk factors, namely: previous fractures, hip fractures in parents, smoking, alcohol consumption, a history of diseases that contribute to the development of secondary osteoporosis (diabetes mellitus, hyperthyroidism, hypothyroidism, etc.).

In males 50+ and females in menopause, the signs of osteoporosis are more often found in the area of femoral neck, and in individuals younger than 50, in the area of lumbar spine [3, 8].

Data gathering, the subsequent correction, systematization of source information and visualization of the obtained results were carried out in Microsoft Office Excel (2016) spreadsheets. Statistical processing of the results was carried out using Python 3.8. Built-in functions from modules and Scipy were used for calculations. Quantitative parameters were assessed for compliance with normal distribution. To this end, the Shapiro — Wilk test was used. Samples of quantitative parameters with distribution other than normal were described using the values of median (Me) and the lower and upper quartiles (Q1–Q3) (Me [Q1; Q3]). The Mann — Whitney U test was used to compare independent samples. When comparing several samples of quantitative data with distribution other than normal, the Kruskal — Wallis test was used that is a non-parametric alternative variant to one-way analysis of variance. Nominal data were described with the indication of absolute values and percentages (%). The comparison of nominal data was carried out using the Pearson $\chi 2$ test. When the number of expected observations in any of the cells of the four-field table was less than 10, Fisher's exact test was used to assess the level of significance of the differences. We used the odds ratio (OR) and 95 % CI as a quantitative measure of effect when comparing relative parameters. In order to study the relationship between events represented by quantitative data with distribution other than normal one, a nonparametric method was used — the calculation of Spearman's rank correlation coefficient. The difference between parameters and identified relationships were considered statistically significant at $p \leq 0.05$.

The protocol was approved by the local ethics committee. Written informed consent was obtained from all patients prior to enrollment in the study.

Results

According to the results of densitometry, there was no decrease in BMD below the normal range in both study groups compared with the control group, as shown in Table 2.

In 11 patients (25 %) who received aHSCT, decreased T-score was found that corresponds to osteopenia (T-score in the range −1.0 to −2.5); in 2 patients (5 %) T-score was equal to −2.6 and −3, respectively. In the group of patients who received standard PCT, decreased T-score was found in 6 patients (14 %): in 3 patients (7 %) to osteopenia, and in 3 patients (7 %) to osteoporosis. BMD values in treatment groups demonstrated no statistically significant difference. In the control group, registered BMD, Z-score and T-score were within normal range.

The decrease in BMD in group 2 was 12 % higher than in the comparison group. At the same time, the degree of BMD decrease did not depend on the duration of the disease, the number of PCT courses, however, aHSCT caused significant decrease in BMD.

The relationship between BMI, the number of PCT courses, the dose of GCs, and the number of smoking patients is shown in Table 3.

When analyzing the prevalence of risk factors for decreased BMD, there were no significant differences in BMI and the number of smokers in studied groups (Table 3). Most patients in both groups were with overweight — 21 (48 %) and 24 patients (55 %), respectively. Body weight deficiency was found only in 2 patients (4.5 %) in group 1.

Due to certain differences in the dosing of GCs used to achieve remission in patients with HL, it seemed reasonable to analyze BMD values in groups that differed depending on the total dose of agents used in this group. Unfortunately, in the PCT group, such analysis turned out to be very difficult to perform due to the inclusion of a single case of a total dose of GCs less than 7,000 mg and the difficulty of its comparison with a subgroup of 43 individuals. However, in the group of HL patients who received aHSCT in addition to PCT, the detailing of this issue turned out to be quite consistent and demonstrated a definite aggravation of the decrease in BMD due to GCs in high doses when analyzing this parameter in any of the examined anatomical regions (Table 4).

The results of assessment the correlation of BMD in the examined area L1–L4 with disease stage are shown in Figure 1.

As one can see on Figure 1, no significant correlations could be identified between decreased BMD, Z-score, and the risk of low-energy fractures with the stage of the disease.

As known, the development of menopause is a significant risk factor for decreased BMD. The decrease in fertility in females and of androgenic function in males develops due to cytostatic agents. Alkylating agents (cyclophosphamide, procarbazine) in PCT regimens cause cytostatic damage to the ovaries in women and lead to a decrease in anti-Müllerian hormone level. PCT suppresses ovarian function and leads to secondary menopause [3, 5, 7].

Table 2. *Parameters of bone mineral density in the studied groups*

Parameters	PCT Group	The PCT+autoTGSK Group	Control Group	p
Number of patients	n=44	n=44	n=30	–
BMD (g/sm^2)	1.0 [0.97; 1.05]	0.93 [0.82; 1.03]	1.03 [0.0; 0.0]	–
Z-criterion	-0.4 [-2.8; 0.2]	-1.1 [0.5; -3.2]	-0.3[0.2; -1.9]	p2-1: < 0.001* p2-3: =0.0167* p1-3: =0.056
T-criterion L1-L4	-0.5 [-1.1; -0.2]	-1.27 [-0.4; -3]	0.0 [0.0; 0.0]	p2-1: =0.0235* p2-3: < 0.001* p1-3: =0.0128*
T-criterion hip neck	-0.5 [-1.1; -0.2]	-0.12 [-0.2; -2]	0.0 [0.0; 0.0]	p2-1: =0.025* p2-3: < 0.001* p1-3: =0.0486*
The T-criterion is general	-0.7 [-0.1; -1.2],	-0.39 [-0.1; -1.6]	0.0 [0.0; 0.0],	p2-1: =0.0018* p2-3: < 0.001* p1-3: =0.0414*

Note: p1-2 — reflects the differences between groups 1 and 2, p2-3 — reflects the differences between groups 2 and 3, p1-3 — reflects the differences between groups 1 and 3;
* statistically significant differences were noted at p <0.05

Table 3. *Risk factors for a decrease in BMD in the studied groups*

Factors	PCT Group (n=44)	The PCT+autoTGSK Group (n=44)	Control Group (n=30)	p
Body mass index, kg/m^2	25.28 [22.3; 28.35]	24.82 [22.78; 29.9]	23.71 [21.64; 25.35]	p2-1: =0.3567 p2-3: =0.0391 p1-3: =0.0770
Number of PCT courses	6±2	8±2	–	p1-2: < 0.001*
GCS: up to 7000 мг/mg more than 7000 мг/mg	 1 (2 %) 43 98 %)	 11 (25 %) 33 (75 %)	–	p1-2: =0.0058*
Smokers, people	16(36 %)	13 (30 %)	6 (20 %)	p2-3: =0.1825 p2-3: =0.2885 p1-3: =0.3109

Note: p1-2 — reflects differences between groups 1 and 2, p2-3 — reflects differences between groups 2 and 3, p1-3 — reflects differences between groups 1 and 3;
* statistically significant differences were noted at p <0.05

Table 4. *BMD values in groups of patients with LH in accordance with the total dose of GCS used*

Evaluation Area	Parameter	PCT Group			The PCT+autoTGSK Group		
		Up to 7000мг /mg GCS	More than 7000мг/mg GCS	p	Up to 7000мг /mg GCS	More than 7000мг/mg GCS	p
The number of patients depending on the received dose of GCS		n=1	n=43	–	n=11	n=33	–
Hip neck	**BMD (g/sm^2)**	0.81 [0.81;0.81]	0.82 [0.8;0.94]	0.3182	0.81 [0.76;0.88]	0.72 [0.64;0.78]	0.0122*
General	**BMD (g/sm^2)**	0.91 [0.91;0.91]	0.95 [0.88;0.99]	0.3762	0.91 [0.89; 0.99]	0.86 [0.71;0.91]	0.0167*
L1-L4	**BMD (g/sm^2)**	0.99 [0.99;0.99]	1.0 [0.97; 1.05]	0.4686	0.98 [0.91; 1.07]	0.91 [0.82;1.02]	0.0307*

Note: p1-2 — reflects the differences between groups 1 and 2, p3-4 — reflects the differences between groups 3 and 4; * statistically significant differences were noted at p <0.05

In this connection, we assessed bone density in postmenopausal women (with the absence of menstruation for more than 6 months) in studied groups, as shown in Table 5.

As one can see in Table 5, postmenopausal women in the aHSCT group had a decrease in BMD compared with the standard PCT group. No decrease in Z-score was found in the female patients of the studied groups. T-score levels in the female patients of the studied groups revealed no significant difference. There were no significant differences in the densitometric parameters of lumbar spine area in the groups of menopausal female patients.

The prevalence of osteopenia/osteoporosis based on BMD value in menopausal and non-menopausal women in the studied groups is shown in Figure 2.

As follows from the Figure 2, non-menopausal women in the studied groups more often demonstrated BMD levels within normal range; a decrease in this parameter to the level of osteopenia and osteoporosis was less often. These differences were revealed both in the PCT group and in the aHSCT group.

In the total cohort of enrolled patients, in the standard PCT group, fractures were registered in 11 patients (25 %); 3 of them (7 %) had the fractures of forearm, 8 patients (18 %) had the fractures of radius and ankle

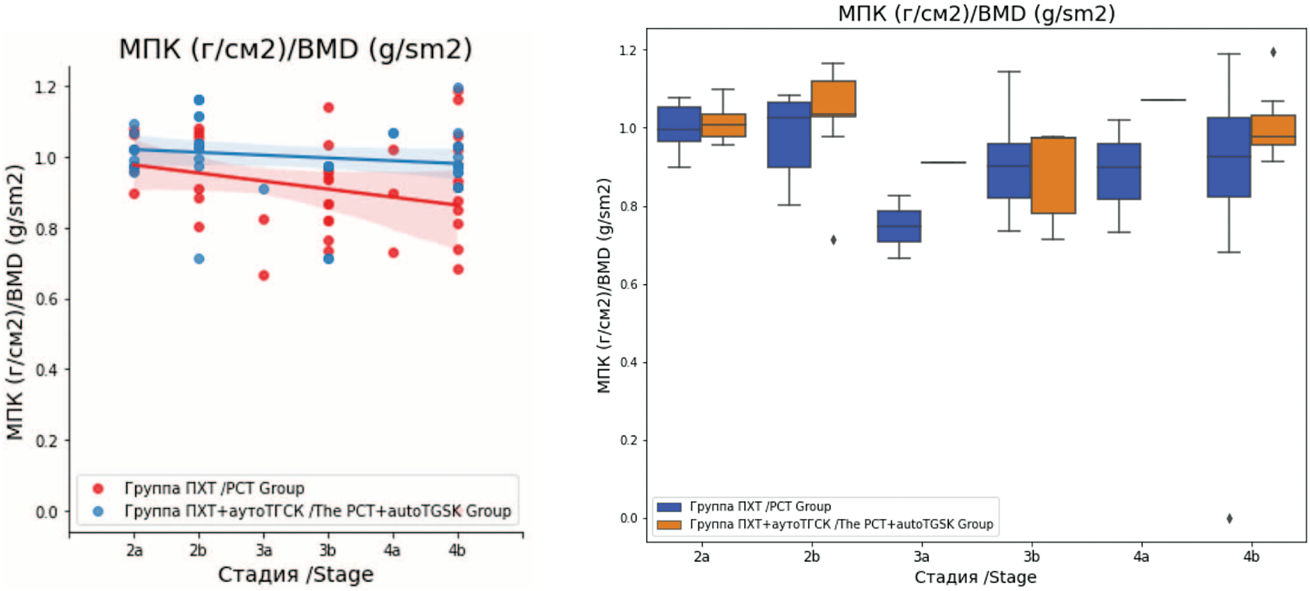

Figure 1. *Correlation between bone mineral density in the studied region of the lumbar spine (L1-L4) and the stage of the disease*

Table 5. *Characteristics of BMD in postmenopausal women in the study groups*

Evaluation Area	Parameter	PCT Group (n=11)	The PCT+autoTGSK Group (n=19)	p
Hip neck	BMD (g/sm²)	0.82 [0.72; 0.88]	0.7 [0.65; 0.78]	0.0509
	T-criterion	0.0 [-1.15; 0.0]	-0.8 [-0.8; -0.8]	0.2755
	Z-criterion	-0.1 [-1.35; 0.35]	-1.2 [-1.7; -0.5]	0.0273*
General	BMD (g/sm²)	0.98 [0.79; 1.04]	0.85 [0.73; 0.91]	0.0194*
	T-criterion	0.0 [-0.84; 0.4]	-0.2 [-0.2; -0.2]	0.2787
	Z-criterion	0.3 [-1.45; 0.7]	-0.7 [-1.6; -0.25]	0.0262*
L1-L4	BMD (g/sm²)	0.97 [0.81; 0.99]	0.9 [0.75; 1.0]	0.2066
	T-criterion	-0.4 [-2.1; 0.0]	-1.0 [-1.0; -1.0]	0.500
	Z-criterion	-0.8 [-1.95; -0.25]	-1.2 [-2.35; -0.15]	0.2518

Note: p1-2 — reflects the differences between groups 1 and 2; * statistically significant differences were noted at p ≤0.05

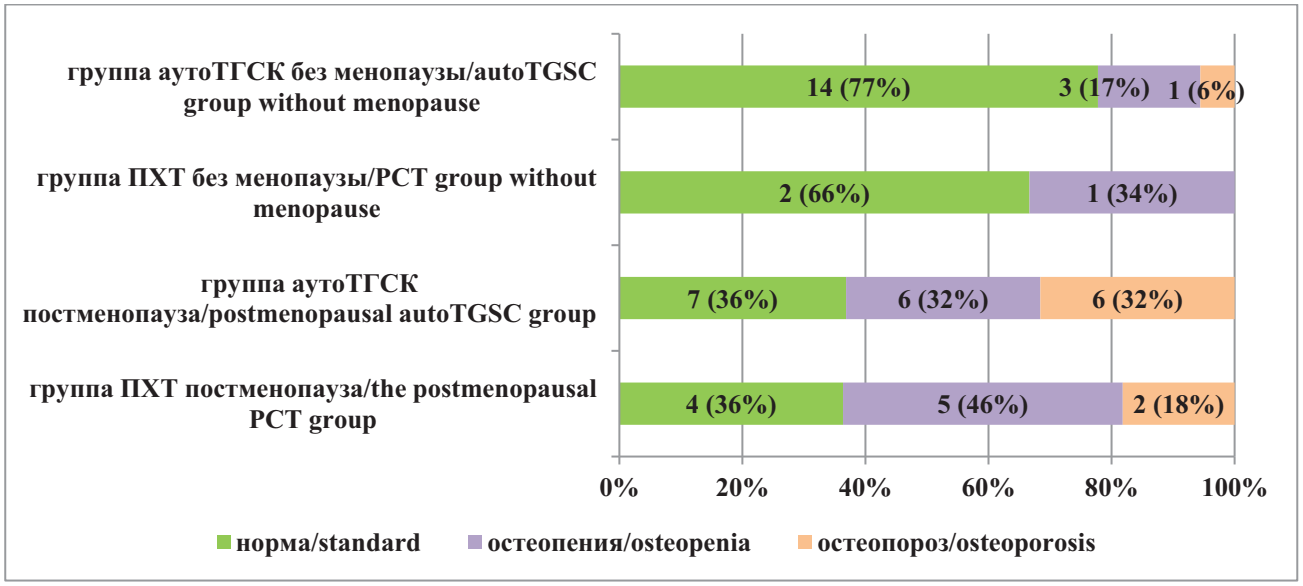

Figure 2. *The prevalence of osteopenia/osteoporosis based on bone mineral density in the study groups of patients without menopause and with menopause*

Note: all differences in the frequency of cases of osteopenia, osteoporosis and the registration of normal values in subgroups of patients with and without advanced menopause are significant at $p < 0.05$ in the groups of PCT and autoTGSK

joint bones. Eleven patients (25 %) in the aHSCT group had the fractures of radius, humerus, and ankle joint bones, and one patient (2 %) had the fractures of forearm bones. X-ray of the spine in lateral view revealed no evidence of compression fractures of vertebrae. All fractures in patients of both groups took place in childhood and adolescence as a result of traumatic injury.

According to the results of the X-ray of bones, avascular necrosis of femoral head was found in 2 patients (4 %) in the standard PCT group and in 3 patients (7 %) in the aHSCT group. Areas of avascular necrosis were in the stabilization phase and required no surgical treatment; patients received non-surgical therapy. Due to the relatively small sample of patients and the fact that this complication was uncommon for the patients in both study groups, it was not possible to analyze the risk of its development in connection with the ongoing pathogenetic therapy.

According to the questionnaire completed by the patients of both groups, only 6 patients (7 %) had no risk factors, 10 patients (11 %) had one risk factor, 28 patients (32 %) had 2 risk factors, and 44 patients (50 %) had three or more risk factors.

Discussion

Questions of the pathogenetic relationship between HL and decreased BMD remain undetermined to a large extent. The clinical relevance of the disease in increasing the risk of osteoporosis and associated fractures appears to be controversial. Pathogenetic therapy is potentially of first importance in this respect.

The regimen management of HL has made it possible to achieve success in the form of more than 90 % cure rate [2, 3]. However, with the reference to improved results of disease management, physicians face the question of ensuring the adequate quality of life for patients, as well as preventing delayed complications of therapy, including osteoporotic changes in bone tissue. In this regard, the issue of routine diagnosis of the state of bone tissue after PCT remains unresolved.

According to the results of the study performed by M. Voitko et al. (2019), PCT and glucocorticoids in high doses lead to a negative effect on bone remodeling in half of patients with HL that is present in impaired collagen renewal in bones and elimination of microcracks, as well as in decreased mechanical properties of collagen and bone tissue [3, 9].

Osteopenia and osteoporosis as the complications of therapy for lymphoproliferative diseases are more common in HL patients [3]. Bone tissue disorders associated with pathogenetic therapy in this category of patients are clinically significant complications [3, 5, 9].

According to different literature sources, bone tissue acquisition takes place at the age of 20–30 years, therefore, patients in this age group are more susceptible to the development of osteopenia and osteoporosis due to ongoing cytostatic and GCs therapy [5, 9, 10].

Delayed effect after polychemotherapy (PCT) remain a considerable problem at the present time. HL develops

predominantly at the age of 16–35 years, that is, during peak bone acquisition. At the same time, impaired development of collagen cartilage of the bone matrix, impaired process of bone renewal, and angiopathy of periosteal vessels after PCT result in impaired quality parameters of bones [11, 12]. The use of cytostatic agents, glucocorticoids, as well as disease onset in the young age are probably the critical factors in osteoporosis development in this group of patients [2, 5, 10].

Main risk factors for a decrease in BMD after standard PCT and aHSCT include high-dose PCT, GCs, prolonged immobilization, low body mass index, nutritional deficiency [3, 5, 10]. The main evidence of the pathogenetic significance of these factors in the development of decreased BMD was demonstrated in the model of primary postmenopausal osteoporosis. This research generally confirms the role of pathogenetic therapy as a risk factor for osteoporotic fractures in HL patients who receive pathogenetic therapy.

At the same time, the most important risk factor for low-energy fractures in bone tissue disorders in HL patients is long-term use of GCs [2, 3, 5]. High doses of corticosteroids used in PCT regimens exacerbate the processes between bone formation and resorption, thus increasing the risk of developing bone tissue disorders. GCs, on the one hand, cause a slowdown in bone formation due to the later maturation of osteoblasts and inhibition of the activity of prostaglandins in relation to growth factors and mature osteoblasts, and on the other hand, they increase bone resorption due to decreased levels of calcitonin and calcium [6].

For patients who frequently receive GCs in high doses, repeated courses of GCs therapy have a negative effect on bone tissue increasing the risk of fractures by 20 % [3, 5, 9]. Modern regimens of PCT and HSCT increase the risk of a decrease in BMD by several times [3].

According to Kanis et al. (2004), previous fractures increase the risk of subsequent fractures with the same frequency in men and women [11]. There is evidence that a fracture in a common location (proximal femur, spine, humerus) significantly increases the risk of subsequent fractures [11]. In the studied groups of patients, previous fractures in individuals who received standard PCT and aHSCT in addition to PCT were found in an equal number of patients (11 individuals, 25 %). All fractures in patients of the studied groups were the result of traumatic injuries in childhood and adolescence.

The decrease in bone density was more pronounced in the aHSCT group than in the standard PCT group indicating a corresponding increase in the risk of osteoporosis. A similar pattern is observed when analyzing the risks of decreased BMD in postmenopausal women [10]. In postmenopausal women on aHSCT, there is a decrease in BMD that is not observed in the standard PCT group. At the same time, it is important to emphasize that, in general, HL patients at different stages of treatment require the analysis of bone tissue during the early period after therapy in order to assess the risk of decreased BMD and timely start the prevention and management of osteoporosis.

Conclusion

HL patients who receive PCT with GCs are at the high risk of osteopenia and osteoporosis. Such known factors as the stage and type of the disease have no effect on the decrease in BMD in HL patients. However, aHSCT significantly increases the risk of BMD decrease. Considering a favorable prognosis, the high incidence of decreased bone density requires the development of osteoporosis- and osteopenia-preventing regimen for this category of patients.

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