ONCOLOGY

Hemogram and Myelogram in Progressing Non-Hodgkin's Lymphomas

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Parameters of hemogram and myelogram were studied in patients with aggressive and indolent non-Hodgkin's lymphomas: the relationships between the parameters recorded before treatment and during remission or progress 6 months after chemotherapy were studied by multifactorial analysis. The progress of indolent non-Hodgkin's lymphomas was associated with changes caused by tumor infiltration of the bone marrow; lymphocytosis in the myelogram or hemogram was associated with a relative decrease in the count of granulocytic hemopoietic stem cells. A sign associated with the absence of remission in aggressive non-Hodgkin's lymphomas was decreased level of hemoglobin and erythroid cells. Changes in myelogram attesting to anemia and suppressed erythropoiesis before chemotherapy are additional prognostic factors indicating obligatory intensification of chemotherapy for patients with aggressive non-Hodgkin's lymphomas.

Key Words: *non-Hodgkin's lymphomas; hemopoiesis; chemotherapy; prediction factors*

Despite great progress in the therapy of non-Hodgkin's lymphomas (NHL) during recent decades, the results of treatment in general cannot be considered as satisfactory. Chemotherapy of NHL prescribed in accordance with the immunomorphological variant and prognostic criteria prolongs the remission and life span, but does not solve the problem of cure [3]. The prognosis is largely determined by the rate of attaining the first remission and its duration. Relapses of aggressive NHL are 3 times less incident in patients in whom complete remission was attained after 2-3 courses of polychemotherapy, than in those in whom complete remission was attained after 5-6 therapeutic courses [7].

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Evaluation of the prognostic value of various clinical and laboratory parameters in NHL patients before and at all stages of therapy is still an actual problem. Correct interpretation of these data is important for selecting the optimal protocol of chemotherapy aimed at rapid attaining and long maintenance of complete remission.

We evaluated prognostic value of hemogram and myelogram parameters recorded in NHL before therapy and essential for attaining the remission after 6-month chemotherapy.

MATERIALS AND METHODS

A total of 87 patients with NHL (53 men and 34 women, mean age 56.7 years) were examined. The patients were divided into groups with aggressive NHL (46 patients) and indolent NHL (41 patients). All patients were observed and treated at State Novosibirsk Regional Clinical Hospital.

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Parameters of the one marrow and peripheral blood were evaluated before and 6 months after chemotherapy. Peripheral blood smears and bone marrow puncture specimens stained by the Romanowsky—Giemsa methods, were examined. The erythroid, granulocytic, and megakaryocytic hemopoietic stems were evaluated using normal ranges of hemogram and myelogram values [2]. Bone marrow involvement was detected in 12 patients with aggressive NHL and 32 with indolent NHL.

Patients with aggressive NHL were prescribed anthracycline-containing chemotherapy protocols (CHOP, CHOEP, BACOD, RACOP) depending on the morphological variant of the tumor and presence of unfavorable prognostic factors. Patients with indolent NHL received cyclophosphamide monotherapy, COP, and CHOP protocols. The efficiency of chemotherapy was evaluated 6 months after the start of treatment according to routine criteria [1].

All patients were divided into groups by the results of cytostatic therapy: patients with aggressive NHL and complete remission (n=20), with aggressive NHL and partial remission (n=8), aggressive NHL with disease progress (n=18), indolent NHL with complete or partial remission (n=24), indolent NHL with disease progress (n=17).

The results were statistically processed using Epi Info 5.00 and SPSS 10.0 software. Variables were compared using Student's t test and ANOVA; nonparametric Kruskal—Wallis test was used in case of non-normal distribution of the sign. Distribution frequency was analyzed using contingency tables, prognostic significance of variables was evaluated using logistic regression model for evaluation of odds ratio (OR) and estimation of 95% confidence interval (CI). Variables at $p \leq 0.1$ were used in the multifactorial analysis model; binary logistic regression method was used. The differences were considered significant at $p<0.05$.

RESULTS

Complete remission was rarely attained in patients with aggressive NHL with hemoglobin content below 90 g/liter and platelet count below 180×10^9/liter in the hemogram, segmented neutrophils in the leukocytic formula below 50%, and with 5% and more atypical lymphocytes, 5% and more blast cells, less than 14.5% erythroid cells in the myelogram (Table 1). Multifactorial analysis showed the following hemogram and myelogram values, associated with the absence of complete remission: platelet count in the hemogram below 180×10^9/liter (p=0.007, OR=13.44, 95% CI 2.04-88.02), less than 14.5% erythroid cells in myelogram (p=0.004, OR=10.19, 95% CI 2.12-48.9).

The progress of NHL (no signs of complete or partial remission after 6 months of therapy) was more often associated with the following hemogram and myelogram values before chemotherapy: hemoglobin below 90 g/liter, platelets in hemogram below 180×10^9/liter, blast forms in myelogram at least 5%, atypical lymphocytes in myelogram at least 5%, erythroid cells in myelogram no more than 14.5% (Table 2).

TABLE 1. Parameters of Hemogram and Myelogram in Patients with Aggressive NHL Attaining and Not Attaining Complete Remission after 6-Month Chemotherapy

Parameter		Group		OR; CI 95%	Significance of differences
		no complete remission (n=26)	complete remission (n=20)		
Hemoglobin	<90 g/liter	7	0	2.05	$p<0.014$
	≥90 g/liter	19	20	(1.40-2.83)	
Hemogram platelets	$<180\times10^9$/liter	14	2	2.19	$p<0.005$
	$\geq180\times10^9$/liter	12	18	(1.36-3.52)	
Segmented neutrophils in hemogram	<50%	14	4	1.81	$p<0.043$
	≥50%	12	16	(1.11-2.97)	
Blast forms in myelogram	≥5%	6	0	2.0	$p<0.029$
	<5%	20	20	(1.47-2.73)	
Atypical lymphocytes in myelogram	≥5%	10	0	2.25	$p<0.002$
	<5%	16	20	(1.56-3.24)	
Erythroid cells in myelogram	<14.5%	19	5	2.49	$p<0.003$
	≥14.5%	7	15	(1.31-4.74)	

Note. Here and in Tables 2-3: 95% CI is shown in parentheses.

According to multifactorial analysis, platelets below 180×10^9/liter (p=0.011, OR=8.42, 95% CI 1.63-43.44) in the hemogram, monocytes in hemogram at least 9% (p=0.04, OR=9.3, 95% CI 1.11-79.49), erythroid cells in myelogram below 14.5% (p=0.009, OR=11.49, 95% CI 1.85-71.42) before chemotherapy indicated the progress of aggressive NHL.

The relationship between hemogram and myelogram values before chemotherapy and anemia requiring blood transfusions during therapy was evaluated in patients with aggressive NHL. Unifactorial regression analysis revealed factors associated with low hemoglobin level (below 80 g/liter) after 6 months of chemotherapy: hemoglobin below 100 g/liter (OR=24.6, 95% CI 1.45-105.12, p=0.02), erythrocyte count in hemogram below 4×10^{12}/liter (p=0.045), erythroid cell count in myelogram below 10% (p=0.004), RACOP chemotherapy courses (OR=24.6, 95% CI 3.12-193.79, p=0.003).

According to multifactorial analysis, courses of RACOP chemotherapy proved to be an independent factor associated with development of anemia (OR= 59.98, 95% CI 4.15-867.39, p=0.003). The disease progressed in all patients with aggressive NHL requiring hemotransfusions after cytostatic therapy (p=0.019). Multifactorial analysis showed that low level of hemoglobin (below 90 g/liter; OR=55.07, 95% CI 2.42-1036.75, p=0.011) and low count of erythroid cells in the bone marrow (below 10%; OR= 49.75, 95% CI 3.92-630.75, p=0.003) were independent fac-

TABLE 2. Parameters of Hemogram and Myelogram in Patients with Aggressive NHL Attaining Complete Remission and with Disease Progress

Parameter		Group		OR; CI 95%	Significance of differences
		progress (n=18)	complete and partial remission (n=28)		
Hemoglobin	<90 g/liter	6	1	2.79	p<0.01
	≥90 g/liter	12	27	(1.59-4.87)	
Hemogram platelets	<180×10^9/liter	11	5	2.95	p<0.007
	≥180×10^9/liter	7	23	(1.42-6.10)	
Blast forms in myelogram	≥5%	5	1	2.56	p<0.028
	<5%	13	27	(1.45-4.54)	
Atypical lymphocytes in myelogram	≥5%	5	0	3.15	p<0.014
	<5%	13	28	(2.01-4.94)	
Erythroid cells in myelogram	<14.5%	14	10	3.21	p<0.013
	≥14.5%	4	18	(1.24-8.29)	

TABLE 3. Hemogram and Myelogram Values Associated with Progress of Indolent NHL

Parameter		Group		OR; CI 95%	Significance of differences
		progress (n=17)	complete and partial remission (n=24)		
Leukocytes in hemogram	≥20×10^9/liter	13	3	5.08	p<0.001
	<20×10^9/liter	4	21	(2.01-12.85)	
Lymphocytes in hemogram	>40%	14	11	2.99	p<0.042
	≤40%	3	13	(1.02-8.77)	
Segmented neutrophils in hemogram	<50%	16	12	7.43	p<0.008
	≥50%	1	12	(1.10-50.18)	
Lymphocytes in myelogram	≥30%	15	8	5.87	p<0.002
	<30%	2	16	(1.54-22.42)	
Segmented neutrophils in myelogram	<10%	10	5	2.48	p<0.031
	≥10%	7	19	(1.20-5.12)	

tors associated with disease progress in this group of patients.

The progress of indolent NHL (no signs of complete or partial remission) was more often observed in in patients with the following hemogram and myelogram values before treatment: hemogram leukocytes 20×10^9/liter and more, hemogram lymphocytes more than 40%, hemogram segmented neutrophils below 50%, myelogram lymphocytes at least 30%, myelogram segmented neutrophils below 10% (Table 3). Multifactorial analysis showed the following independent factors associated with the progress of indolent NHL: hemogram leukocytes above 20×10^9/liter ($p<0.001$, OR=22.7, 95% CI 4.4-118.3), hemogram segmented neutrophils below 50% ($p=0.012$, OR= 15.99, 95% CI 1.8-140.5), myelogram lymphocytes at least 30% ($p=0.002$, OR=15.0, 95% CI 2.7-82.3).

In multifactorial analysis tumor involvement of the bone marrow in the indolent NHL group was an independent factor essential for the disease progress ($p=0.028$, OR=11.4, 95% CI 1.3-100.8). Reduction of erythroid cells (below 10% in myelogram, $p=0.001$) was associated with an increase in the bone marrow lymphocyte count to 65% and more.

It is beyond doubts that treatment efficiency depends on the tumor characteristics (*e.g.*, immunomorphological variant, clinical stage of tumor process) and patient's status. Different models were proposed for predicting treatment efficiency in NHL. The best known of them are the international prognostic index, international index based on age, and tumor scale [13,14]. None of the proposed prognostic models is perfect [5]. Moreover, many parameters proposed as prognostic factors, including IL and TNF levels, activity of the nucleolar organizer area, presence of gene mutations [6,13], are hardly available for practical oncohematology.

Our results indicate that the progress of indolent NHL is associated with changes in hematological parameters caused by tumor infiltration of the bone marrow. Hemogram or myelogram lymphocytosis in patients with indolent NHL is paralleled by a relative decrease in the granulocytic hemopoietic cell count. It was previously shown that the decrease in the volume of indolent NHL in patients receiving cytostatic protocols with low myelotoxicity was not associated with suppression of erythropoiesis; moreover, this treatment was accompanied by an increase in hemoglobin levels and peripheral blood erythrocyte count and was associated with remission [4].

Negative prognostic significance (correlation with disease progress and absence of complete and/or partial remission) of changes in some laboratory values, reflecting disturbances in hemopoiesis and increased content of tumor forms of lymphocytes in the bone marrow, was detected in patients with aggressive NHL. Of the hemogram parameters these were anemia, decreased platelet count and percentage of segmented neutrophils and increased percentage of monocytes (more than 9%) in differential leukocyte count. The myelogram parameters with unfavorable prognostic significance are decreased count of erythroid cells, increased number of blast cells, and presence of more than 5% atypical lymphocytes.

More frequent registration of monocytosis in the hemogram in aggressive NHL progressing during therapy is a fact deserving further investigation. This phenomenon can be explained by hyperactivity of immunocompetent cells in response to tumor process in aggressive NHL.

Of the normal hemopoiesis stems (erythroid, monocytic, granulocytic, megakaryocytic), suppression of erythropoiesis (decreased level of hemoglobin and count of erythroid cells) was associated with ineffective treatment for aggressive NHL.

Anemia is a frequent complication of lymphoproliferative diseases impairing the tolerance of antitumor treatment and patient's quality of life [8]. Presumably, the development of anemia in aggressive NHL is a marker of early progress of the tumor and results from negative effects of the tumor clone on erythropoiesis. Effects of antitumor response cytokines (IL-1, IL-6, TNF-α) on the suppression of early erythroid precursors, the cause of anemia development in malignant tumors, were demonstrated [10].

Our results do not contradict the data that anemia is an additional factor of negative prognosis for relapse-free survival, uneventful survival, and total survival of patients with NHL [11,12].

Many studies demonstrated advantages of high-dose chemotherapy in high-risk (according to the international prognostic index) patients [9]. According to our present findings, evaluation of erythropoiesis parameters in aggressive NHL helps to detect a group of patients with unfavorable prognosis and to determine more accurately the indications for myeloablative courses of cytostatic therapy. Suppression of the erythroid hemopoietic stem observed in patients with aggressive NHL before therapy is an additional factor necessitating evaluation of the efficiency of every therapeutic course and early intensification of therapy, including intensification at the expense of high-dose chemotherapy with transplantation of hemopoietic stem cells.

REFERENCES

1. M. A. Volkova, *Clinical Oncohematology* [in Russian], Moscow (2001).
2. A. I. Vorob'ev, *Manual of Hematology* [in Russian], Moscow (1985).

3. M. L. Gershanovich and M. A. Akimov, *Vopr. Onkol.*, **45**, No. 4, 438-440 (1999).
4. N. P. Domnikova, V. V. Degtyareva, and L. M. Nepomnyashchikh, *Byull. Eksp. Biol. Med.*, **138**, No. 12, 668-673 (2004).
5. A. Hagenbik and A. Novik, *Diagnosis and Treatment of Lymphomas* [in Russian] (2002), pp. 73-136.
6. O. E. Yaguzhinskaya, I. E. Lazarev, E. A. Nikitin, *et al.*, *Ter. Arkhiv*, No. 4, 45-51 (2001).
7. J. O. Armitage, D. D. Weinburger, M. Hutchins, *et al.*, *J. Clin. Oncol.*, No. 4, 160-164 (1986).
8. M. Cazzola, Y. Beguin, J. Kloczko, *et al.*, *Br. J. Haematol.*, **122**, Suppl. 3, 386-393 (2003).
9. A. M. Gianni, M. Bregni, S. Siena, *et al.*, *N. Engl. J. Med.*, **336**, 1290-1297 (1997).
10. R. T. Means and S. B. Krants, *J. Clin. Invest.*, **91**, 416-419 (1993).
11. T. J. Morrow, S. Volpe, S. Gupta, *et al.*, *South Med. J.*, **95**, Suppl. 8, 889-896 (2002).
12. I. Moullet, G. Salles, N. Ketterer, *et al.*, *Ann. Oncol.*, **9**, 1109-1115 (1998).
13. C. Nicolaidas, S. Dimou, and N. Pavlidis, *Oncologist*, No. 3, 189-197 (1998).
14. M. A. Shipp, D. P. Harrington, J. R. Anderson, *et al.*, *N. Engl. J. Med.*, **329**, 987-994 (1993).