wjpmr, 2022,8(3), 11 – 15.

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research article

ISSN 2455-3301

WJPMR

CORRELATION ANALYSIS OF BLOOD PARAMETERS WITH LIVER METASTASES IN BREAST CANCER

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Article Received on 06/01/2022 **Article Revised on 27/01/2022** **Article Accepted on 17/02/2022**

INTRODUCTION

Breast cancer is the leading cause of cancer mortality worldwide.[1] Approximately 50% of all women with breast cancer develop metastases to distant organs, such as the liver, lungs, bones and brain.[2,3] Liver metastases develop in about 50% of all patients with metastatic breast cancer, and in 5-12% of patients liver metastases are the primary site of damage in breast cancer.[4] Metastatic liver damage can cause severe liver dysfunction, which negatively affects the prognosis of breast cancer patients. In the absence of treatment, liver metastases are associated with poor survival and range from 4 to 8 months.[5,6,7] In addition, despite the improvement of systemic treatment, the average life expectancy of patients with metastatic liver damage from the moment of diagnosis varies from 18 to 24 months, and 5-year and 10-year survival is still low - 27% and 13%, respectively.[8,9,10] In this connection, only a personalized approach to the treatment of liver metastases, based on the category of disease prognosis, determines the relevance of this study.

MATERIALS AND METHODS

Our study is based on a retro- and prospective study of 127 patients with breast cancer with liver metastases who underwent treatment on the basis of RSPCOR, from 2016 to March 2021 inclusive. All patients had previously been treated and monitored for a certain long time (from 12 months to five years) (Table 1).

Table 1: Duration of dispensary observation of patients with breast cancer before the appearance of liver metastasis.

№	The timing of the appearance of metastases	Number of patients
1.	Up to year	7 (5,5%)
2.	Up to two years	27 (21,3%)
3.	Up to three years	42 (33,1%)
4.	Up to four years	33 (25,9%)
5.	Under five years of age	15 (11,8%)
6.	More than five years	3 (2,4%)

A malignant tumor, including breast cancer, realizes its main metastatic potential in the first three years after its appearance, in our study, if 76 (59.8%) metastases appeared within three years, then by the end of the third year and at the beginning of the fourth, 109 (85.8%) patients already had metastatic disease.

The average age of the patients included in our study was 41.4±5.1 years. The duration of the patients' anamnesis averaged 8 months (from 1 to 13 months). At the same time, the younger the patient was, the more extensive and aggressive the tumor developed (Table 2.).

Table 2: Distribution of patients depending on the age group.

№	Average age of patients	Number of patients
1.	Under 30 years	6 (4,7%)
2.	31 – 40 years old	39 (30,7%)
3.	41 – 50 years old	48 (37,8%)
4.	51 – 60 years old	25 (19,7%)
5.	Over 61 years old	9 (7,1%)

Peak values of high metastatic potential are observed in the age groups from 31 to 50 years, when women still have high hormonal potential, childbearing functions are preserved, and the body's metabolism is gradually being rebuilt.

Table 2: Clinical and biological characteristics of patients included in the study, breast cancer in primary diagnosis.

№	Clinical characteristics	Number of patients
1.	Stage: T_1 T_2 T_3 T_4	 17 (13,4%) 65 (51,2%) 34 (26,8%) 11 (8,7%)
2.	Regional lymph nodes: N_0 N_1 N_2	 71 (55,9%) 40 (31,5%) 16 (12,6%)
3.	Distant metastases: M_0 M_1	 127 (100%) -
4.	Degree of tumor differentiation: G_1 G_2 G_3 G_4	 11 (8,7%) 39 (30,7%) 52 (40,9%) 25 (19,7%)
5.	Histological variant: Lobular Ductal Mixed* Other**	 25 (19,7%) 68 (53,5%) 28 (22%) 6 (4,7%)
6.	Anatomical localization: Upper-outer quadrant Upper - inner Quadrant Lower - outer Quadrant Lower - inner Quadrant Central location	 43 (33,9%) 30 (23,6%) 17 (13,4%) 19 (14,9%) 18 (14,2%)

Notes: *lobular ductal carcinoma; **mucosal, medullary, papillary carcinoma.

All the patients included in our sample were fully and thoroughly examined, the diagnoses were verified by qualitative morphological research methods. All available visualization methods were used to determine the extent of the spread.

The study of gene expression and immunohistochemical markers enabled oncomorphologists to identify four molecular subtypes of breast cancer. Based on the IHC study, the expression of estrogen and progesterone receptors (ER and PR) by cancer cells, as well as the epidermal growth factor receptor type 2 (Neg2/neu, ErbB2), breast cancer was divided into 4 molecular subtypes, which differ in many prognostic features.

In our study, patients with breast cancer, molecular genetic subtypes of breast cancer, were distributed as follows (Table 3.).

Table 3: Distribution of breast cancer patients included in our study depending on the immunohistochemical phenotype.

IHC phenotype	*Immunohistochemical portrait*			*Number of patients*
	ER	**PR**	**Her2/ neu**	
Luminal A	+	+	–	71 (55,9%)
Luminal B	+	+	+	28 (22%)
HER2+	–	–	+	15 (11,8%)
Triple negative (Basal-like)	–	–	–	13 (10,2%)

In our observation, all patients were divided according to the dominant method of treatment into four groups of patients (Table 4).

Table 4: Distribution of breast cancer patients with liver metastases depending on the treatment.

№	Methods of treatment	Number of patients
1.	Polychemotherapy	13 (10,2%)
2.	Immunotherapy+PCT	15 (11,8%)
3.	Immunotherapy + chemohormonotherapy	48 (37,8%)
4.	Hormone therapy + chemotherapy	51 (40,2%)

27 (21.3%) patients underwent embolization of the lobar or segmental artery of the liver after the main method of treatment.

RESULTS

In the initial stages of the development of liver metastases, patients did not complain. Of 127 patients, 119 liver metastases were an ultrasound finding during the control examination. At the same time, changes in the liver were not suspected, not on the basis of a survey, nor on the basis of a physical examination of patients. Moderate anemia, monocytosis, lymphopenia, acceleration of ESR were noted in blood tests. In biochemical analyses, there is a moderate increase in creatinine and urea. Bilirubin, AlAT and AsAT remained normal for a long time.

In 8 cases, after four (in 5 patients) and five years (in 3 patients) of persistent remission, patients noted severity or mild pain in the liver, poor appetite, weakness, rapid fatigue and palpation showed some liver enlargement, in one case lumpiness of the contours. In blood tests, severe anemia, leuko-, platelet- and lymphopenia, acceleration of ESR. In biochemical analyses, an increase in creatinine, urea, AsAT, AlAT, alkaline phosphatase, LDH, and in some cases bilirubin. All these patients have stopped undergoing mandatory follow-up examination for more than two years due to their satisfactory general condition.

A retrospective study of clinical and biochemical blood tests of patients with breast cancer, who subsequently developed liver metastases, did not reveal any special patterns. When drawing up a graphic picture of the dynamics of changes in the number of lymphocytes, three types of changes in the treatment process emerged (Fig.1). The first type is the downward dynamics, in which in each subsequent study, the number of blood lymphocytes showed a lower content than the previous study (Fig. 1 a.). Stable – the number of blood lymphocytes at each new measurement remained approximately in the same amounts (Fig. 1 b.). Undulating – during treatment, the number of blood lymphocytes changed both in the direction of increase and decrease (Fig. 1 c.).

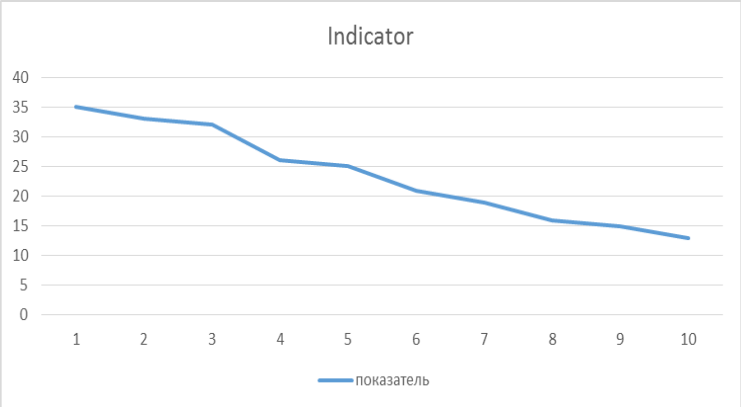

Figure 1: a Top-down view of the dynamics of changes in blood lymphocytes of patients with breast cancer.

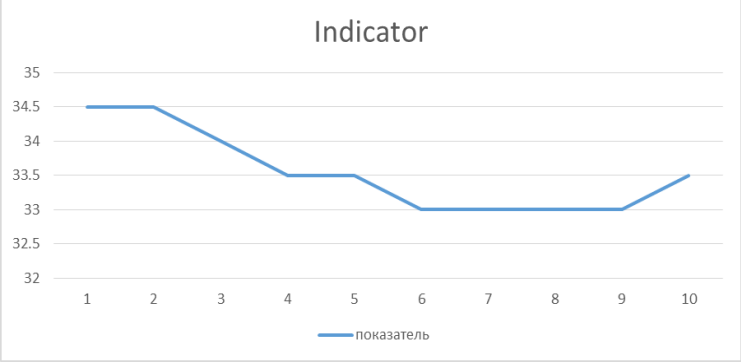

Figure 1.b. Stable view of the dynamics of changes in blood lymphocytes of patients with breast cancer.

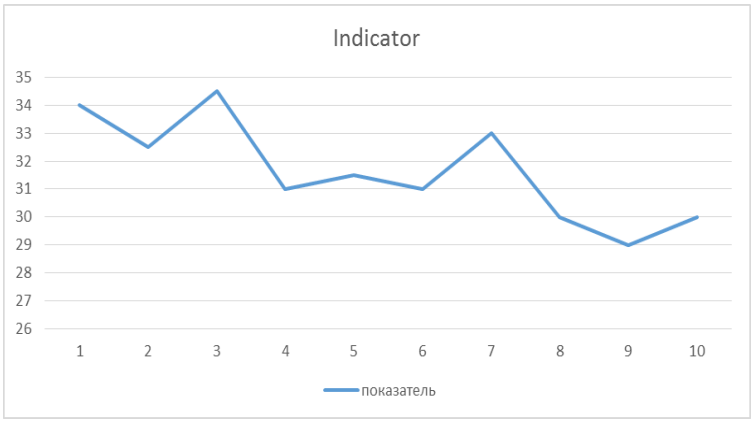

Figure 1: b. Wave-like view of the dynamics of changes in blood lymphocytes of patients with breast cancer.

When comparing the dynamics of changes in blood lymphocytes with the time of occurrence of metastatic lesions in the liver, the following trends were revealed (Table 5).

Table 5: The timing of the development of liver metastases in patients with breast cancer after complex therapy, depending on the dynamics of lymphocytes in the blood.

№	The timing of the appearance of metastases	The number of patients and the dynamics of lymphocytes		
		Descending	Стабильный	Волнообразный
1.	Up to year n=7	7 (17,1%)	-	-
2.	Up to two years n=27	12 (29,3%)	-	15 (29,4%)
3.	Up to three years n=42	19 (46,3%)	8 (22,9%)	15 (29,4%)
4.	Up to four years n=33	3 (7,3%)	13 (37,1%)	17 (33,3%)
5.	Up to five years n=15	-	11 (31,4%)	4 (7,8%)
6.	More than five years n=3	-	3 (8,6%)	-
7.	Total n=127	41 (100%)	35 (100%)	51 (100%)

The worst results were found in patients with a downward view of the dynamics of blood lymphocytes. In these patients, liver metastases developed in the nearest time after complex treatment, and in 38 (92.7%) patients out of 41 with a descending type of dynamics, liver metastases were detected within three years. The best indicators were noted with a stable form of dynamics. In this group of 35 patients, 14 (40%) developed liver metastases from 5 years or more. With wave-like dynamics, 30 (58.8%) patients out of 51 developed liver metastases within three years after completion of treatment.

We also conducted a correlation analysis of the dependence of the volume of liver damage and the dynamics of lymphocytes (Table 6). To do this, we conditionally divided patients with liver metastases into three groups: a group with extensive liver damage, medium (moderate) volume of damage and small volume of damage. Initially, we wanted to measure the volume of the lesion in numbers, but in some cases, due to multiple small metastatic lesions, it was not possible to measure the actual volume.

Table 6: Correlation analysis of the dependence of the volume of liver damage on the dynamics of blood lymphocytes.

№	The volume of liver damage	Type of dynamics of blood lymphocytes		
		Descending	Stable	Undulating
1.	Extensive n=43	22 (53,7%)	4 (11,4%)	17 (33,3%)
2.	Moderate n=55	14 (34,1%)	17 (48,6%)	24 (47,1%)
3.	Small n=29	5 (12,2%)	14 (40%)	10 (19,6%)
4.	Total n=127	41 (100%)	35 (100%)	51 (100%)

Extensive lesion was diagnosed in 43 (33.9%) patients, of which more than half of the patients (22 out of 51.2%) were with descending dynamics of lymphocytes in blood tests. 53.7% of patients with descending dynamics have extensive liver damage, a small tumor volume was detected in only 12.2% of women. With stable dynamics, 40% of patients were diagnosed with a small volume of liver damage. With wave-like dynamics, 47.1% had moderate volumes of secondary tumor ($\chi 2=4,451$; $p>0.001$).

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