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Impacts of Inflammatory Microenvironment on the Development of Cancer Relapse after Combined Treatment

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The purpose of the work was to study the impact of certain elements of the inflammatory microenvironment of the tumor on the development of cancer relapse of main localizations with the amplification of ERBB2 after combined treatment.

Materials and methods. 80 patients, who had been treated for the period from 2016 to 2021 in National Cancer Institute, Kyiv, Ukraine. They were 42-78 (average 60) years old, ECOG 0-2, female. All patients histologically proved adenocarcinoma GIII-GIV. Everyone was studied for the level of chitinase-like proteins, cryoglobulins, tumor-associated macrophages in the preoperative (with the first identified disease for the first time, prior to the beginning of the neoadjuvant chemotherapy) and in the postoperative period.

1st block: with a confirmed mutation of HER-2/neu gene (amplification ERBB2 (3+)): a) inflammatory breast cancer (primary-edema form) – 10 people, b) diffuse-infiltrative stomach cancer – 10 people; c) diffuse-infiltrative esophagus cancer – 10 people; d) diffuse-infiltrative colorectal cancer – 10 people.

2nd block: without a confirmed mutation of HER-2/neu gene: a) inflammatory breast cancer (primary edema form) – 10 people; b) a diffuse-infiltrative stomach cancer – 10 people; c) diffuse-infiltrative esophageal cancer – 10 people; d) diffuse-infiltrative colorectal cancer – 10 people.

Results and discussion. In patients with infiltrative breast cancer, diffuse-infiltrative stomach cancer, and diffuse-infiltrative esophagus cancer, and diffuse-infiltrative colorectal cancer there was a tendency to an increase in the expression of YKL-39 with the ERBB2 amplification during inflammatory tumor infiltration in the stroma. High expression of Stabilin-1 (2.1 ± 0.70 , $n = 22$) was found compared to patient tumors that did not reveal the amplification of ERBB2 (1.46 ± 0.67 , $n = 13$, $p = 0.015$). In most patients with amplification ERBB2, the cryoglobulin content was average (298.6 ± 2.5 mg/l; $1.3 \pm 0.08\%$) – 20 (50%), which corresponds to cryoglobulinemia type II; with conditioned cryoglobulinemia (79.4 ± 1.01 mg/l) in 10 (25%); high content (477.3 ± 48 mg/l; $3.4 \pm 0.2\%$) was recorded in 10 (25%), which indicates the type III of cryoglobulinemia [the hazard ratio (HR) = 0.71, 95%, confidence interval (CI): 0.22-0.83, $p = 0.005$]

Conclusion. Amplification of ERBB2 and macrophages surroundings markers CD68, M2 subpopulation RS1 (Stabilin-1), chitinase-like proteins YKL-39 and SI-CLP independently identified subgroups of patients with inflammatory breast cancer, diffuse stomach and diffuse esophageal, diffuse colorectal cancer with a bad forecast. In patients with the presence of the amplification of ERBB2 in the inflammatory tumor infiltrate, in the stroma, the higher expression of the chitinase-like protein YKL-39 and M2-polarization RS1 of the marker Stabilin-1, was detected compared to the patient's tumors without amplifying ERBB2. This study shows an important role of quantitative values associated with the tumor phenotype and macrophages in tumor progression, depending on the presence of ERBB2 gain. In patients with cryoglobulinemia with inflammatory cancer the secondary immunodeficiency is developed. This is determined by anomalies in the cell and humoral immune system, and leads to the development of postoperative inflammatory complications and relapses.

Keywords: cancer, breast, stomach, esophagus, colorectal, relapse.

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Introduction. Relapse remains one of the most serious problems for patients with cancer diseases [1] and extremely contributes to the deterioration of the quality of life [2]. Many factors, including the remaining cancer cells along the edge of resection after surgery and the resistance of the tumor to treatment, contribute to the return of cancer [3, 4]. Resistance to antitumor drugs occurs due to the characteristics of the inflammatory microenvironment in cancer infiltration Go-Betweens [5, 6]. Several mechanisms of resistance associated with cancer microenvironment are well recognized [7,8] as the hereditary type of cancer cells, which are activated because of a violation of metabolic processes, starting the attack of precursors that contribute to the development of the tumor [9,10]. We consider postoperative complications and cancer

recurrence the main problematic issues after surgery. The interaction between postoperative complications and the weakening of the protective defences of the body against the background of the use of aggressive treatment techniques in inflammatory forms among patients who have suffered an operation on cancer, the dogma has already been proven [11-15].

Everybody knows that the operation is a method of choice in the treatment of cancer. But without the use of modern chemotherapy schemes, the treatment complex is simply impossible. Therefore, we consider changes in the tumor microenvironment precisely after combined treatment (chemotherapy and operational treatment). Introducing antitumor drugs, of course, has a direct impact on the development of inflammatory changes in the cancer process [16, 17]. Despite the potentially radical surgical treatment of cancer with the appointment of modern chemotherapy and/or radiation therapy, in 40% of patients there is a refund of the disease [18]. The results of 2 randomized studies of various variants of organ-breaching treatment have shown that in patients receiving combined treatment (operation + radiation therapy + chemotherapy), the frequency of local recurrences ranged from 0.3% to 8%, while after only the operations local recurrence ranged from 10% to 34% [19, 20].

Inflammatory microenvironment is an essential component in most tumors. The potential for metastasizing the tumor depends on complex and dynamic interactions between cancer cells, inflammatory cells, immune cells and stromal elements in tumor tissue from which they occur. Thus, the complex bond between cancer cells, elements of the immune system and inflammatory cells regulates the progression of the tumor and the relapse of the disease [21, 22, 23].

No doubt, the assessment of cell and humoral immunity, as a prognostic factor for recognizing carcinogenesis paths (especially inflammatory and infiltrative forms of malignant neoplasms), is an essential link in the prevention, diagnosis, and treatment of cancer [24, 25].

There are interesting data about the development of recurrence of cancer of the main localizations in the presence of hypercryoglobulinemia at the time of the beginning of a special treatment [26, 27].

There is forming each of the various phenotypic subtypes of tumor associated macrophages (TAM) under the impact of a plurality of specific cytokine actions in the tumor microenvironment. They illustrate the antitumor effect of macrophages for cancer, where the presence of tumor-associated macrophages correlates with longer survival of patients [28].

The presence of chitinase-like proteins in circulating blood is associated with increased aggressiveness of the course of the disease with various

infiltrative and inflammatory tumors and a high risk of recurrence of the disease. Here, macrophages are a source of chitinase-like proteins, as well as targets for their regulatory effects. Recent studies have concluded the most important role of the tumor microenvironment in cancer progression and metastasis – demonstrated that the tumor microenvironment is rich in pro-inflammatory cytokines, chemokines, and growth factors [29].

It is important to provide modern methodological approaches in the diagnosis and early detection of malignant neoplasms, in order to predict the course of the disease and ways of influencing the oncological process within the tumor environment, considering changes in tumor-associated immunocompetent cells, and not only localization, morphological structure, molecular-biological characteristics of the tumor [24].

Naturally, the intensive study of the connection of inflammatory markers in the peripheral blood and the forecast of the flow and treatment of malignant tumors of the main localizations is critical to the provision of current information to clinicians [30].

Considering the systemic approach to the control of the minimum residual phenomena of cancer, it is possible to identify new opportunities to reduce the risk of relapse after the combined treatment of cancer of various localization at an early stage [15].

Despite the radical operation, cancer is often developing again at the site of operational intervention with all its inherent clinical manifestations. This shows that cancer cells have a high potential of aggressiveness from their primary «organ focus». The potential for relapse of cancer cells keeps depending on cancer microenvironment. The aggravation launched by cancer can be blocked by reducing the inflammatory environment and, as a result, reducing the likelihood of a relapse of the disease. Despite the various work showing the close relationship between cancer of various localities and its microenvironment, it is unpleasant to recognize that the percentage of cancer relapses of various localizations remains fairly high, through the starting mechanisms, the status of which must be generalized according to the relationships with the cancer relapse.

According to various authors, local relapses (LR) for one year after the start of special treatment are recorded in 2.1-10.9% of patients [31, 32, 33].

In this article, we combined the results of our observations, which indicate the relationship between the primary inflammation and the cancer relapse after combined treatment. We tried to focus on specific, and so far, few of the inflammation indicators and predictors of cancer relapses and their use in relation to each other, with main types of cancer and their clinical significance.

Breast cancer

Breast cancer is one of the most malignant tumors; the most recent studies indicate a close relationship between inflammation and progression of malignant tumors. Inflammation is the principal component in the tumor microenvironment, and changing the status of pro-inflammatory components can block anti-cancer immunity. Peripheral blood indicators at the time of the formulation of the primary diagnosis of cancer, as well as in the early postoperative period, may reflect the condition of the local and general inflammatory response of the body. Evaluation of such peripheral blood parameters as the level of cryoglobulins, the number of lymphocytes and monocytes, is proposed as predictive factors for many malignant tumors [34].

Molecular mechanisms associated with inflammation are considered an important component on the development of breast cancer, which is the leading cause of death among women. Programmable cytokines change the biology of cell tumors and contribute to the promotion of cancer and metastasis, activating the stromal cells in the tumor microenvironment, including tumor-related, hypercryoglobulinemia, and especially, in the presence of such aggressive factors, as the mutation of HER-2/neu gene with breast cancer [35].

However, biological processes that cause relapse or maintain residual disease during treatment can differ completely from those that contribute to the primary tumor formation. Analysis of the comparison of molecular characteristics and the location of primary and recurrent tumors detect a degree to which inflammation contributes to the formation of the primary tumor, recurrence of diseases, the development of micrometastases, or the appearance of completely new malignant neoplasms. Intratumoral angiogenesis is associated with inflammation, immune reactions, and metastatic recurrence in breast cancer. Although the direct correlation between inflammation in the primary tumor and cancer recurrence was not detected, there may be a relationship through angiogenesis and have an important role in the relapse of the tumor [36].

Esophageal carcinoma

Although esophageal cancer is less common than other cancers, a wide range of lesions of other areas related to the neck, breast, and belly [37] characterizes it. The principles of surgical treatment include a decrease in surgical injury, contributing to the restoration of patients, and improving treatment safety based on the premise of complete resection of the tumor and adequate lymph dissection [38]. Given that patients with postoperative recurrent or metastasis lose the possibility for surgical treatment, conservative methods, such as chemotherapy, radiation therapy, and biotherapy, can be the most effective

approach in such cases [39]. Studies show that about 40% of patients with esophagus cancer, who are subject to surgical treatment, have early postoperative recurrences for 1 year, and there are still no standard treatment regimens for the postoperative recurrence of esophagus cancer. With recent changes in the lifetime of people, the incidence of esophageal cancer has shown a clear tendency to increase in young people. Therapy cells inhibit immunity directly, suppressing the initialization of the tumor-overwhelming immune response or indirectly stimulating the activation of regulatory immune cells, such as M2-tumor-associated macrophages [40].

Stomach cancer

Stomach cancer is the fifth most common cancer and the third leading cause of mortality in the world [41]. Some immunity and inflammation agents based on prognostic estimates, such as hyperglobulinemia, have been developed as predictors of survival and relapse in various types of cancer, including stomach cancer. Currently, the operation is the treatment of choice for early stomach cancer. Even after therapeutic resection, relapse or metastasis occurs in approximately 35-70% of patients for 5 years [42, 43]. Over the past few decades, they have tested various adjuvant chemotherapy schemes, hoping to monitor postoperative recurrences. Patients with advanced stomach cancer benefit from fluoropyrimidin chemotherapy, while those with locally expanded stomach cancer could achieve an improved overall survival when introducing a monosheme Capecitabine or Platinium. Moreover, patients whose tumors relapsed may have the best forecast when chemotherapy is combined with targeted therapy. However, approximately 50% of all stomach cancer does not react to treatment, and only a few patients achieve a stable state of diseases or partial response to treatment [44].

Colorectal cancer

Although radical mesorectal resection and neo-adjuvant therapy improved the prediction of patients with rectal cancer, locally recurrent rectal cancer after complete resection still occurs in 5-10% of patients [45, 46]. The operation remains the only option to improve the control of symptoms, quality of life, and long-term survival among those who have no locally recurrent rectal cancer. Resection is an important prognostic factor for improving long-term survival in locally recurrent rectal cancer [47, 48]. However, given that radical surgery is very invasive, complications occur with a high level [49]. Previous studies have demonstrated that inflammation is associated with malignant cell proliferation and survival [50, 51].

The purpose of the study is to study the impact of certain elements of the inflammatory microenvironment of the tumor on the development of cancer

relapse of main localizations with the amplification of ERBB2 after combined treatment.

Materials and methods. The material of the clinical records was 80 patients, who were treated for the period from 2016 to 2021 in National Cancer Institute, Kyiv, Ukraine. They were 42-78 (average 60) years old, ECOG 0-2, female. All patients histologically proved adenocarcinoma GIII-GIV.

1st block: with a confirmed mutation of HER-2/neu gene (amplification ERBB2 (3+)), which, naturally, is a confirmation of the pronounced aggressiveness of the malignancy of the cancer process: a) inflammatory breast cancer (primary-edema form) – 10 people; b) diffuse-infiltrative stomach cancer – 10 people; c) diffuse-infiltrative esophagus cancer – 10 people; d) diffuse-infiltrative colorectal cancer – 10 people, who have been revealed during one year a relapse of the disease after a combined treatment (operation with a neoadjuvant course of chemotherapy).

2nd block: without a confirmed mutation of HER-2/neu gene: a) inflammatory breast cancer (primary edema form) – 10 people; b) a diffuse-infiltrative stomach cancer – 10 people; c) diffuse-infiltrative esophageal cancer – 10 people; d) diffuse-infiltrative colorectal cancer – 10 people who during one year were not revealed by a relapse of the disease after the combined treatment (operation with a neoadjuvant chemotherapy rate).

Everyone was studied for the level of chitinase-like proteins, cryoglobulins, tumor-associated macrophages in the preoperative (with the first identified disease for the first time, prior to the beginning of the neoadjuvant chemotherapy) and in the postoperative period.

We carried the identification of ERBB2 amplification out using hybridization fluorescence (FISH) and immunohistochemical (IHC). We performed the further characteristic of the amplification of DNA using digital drip PCR (DDPCR) and a low coating of a whole-genome (LCWGS).

Determining the level of cryoglobulins serum, i.e. immunoglobulins that are inversely repulsed at temperatures below 370 °C. The selection of cryoglobulins from serum was produced according to the technique of A.E. Kalovidoris. The concentration of cryoglobulins was estimated spectrophotometrically on the SF-46 apparatus in the dynamics on the 3rd, 5th, 7th days.

All enrolled patients signed patient informed consent. The study was conducted in accordance with the Helsinki Declaration of the World Medical Association, the Statute of the Ukrainian Bioethics Association, the standard provisions on ethics of the Ministry of Health of Ukraine No. 66 dated February 13, 2006. All patients signed an informed consent to participate in the study and all measures to ensure anonymity of patients were taken.

Research results. Terms of observation of patients were in the range from 4 days to 60 months, the median observation was 36 months (Fig. 1).

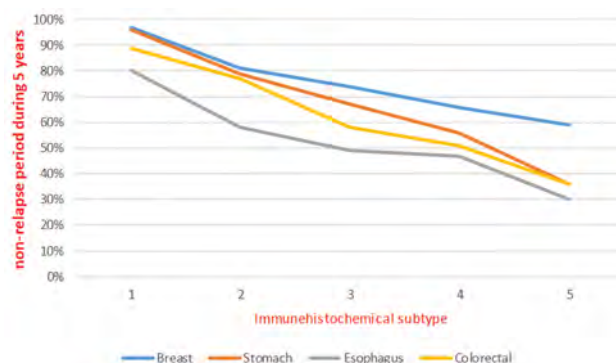


Figure 1. A non-relapse period in patients in the 2nd block for 5 years

According to the level of tumor invasion, patients with invasion of tumor T3 – 34 people prevailed in the entire examination of the group (41.1%). According to the morphological studies, patients of the 1st block with metastases in lymph nodes were absent in 37 patients (92.5%), and in patients of the 2nd block the metastases regional lymph nodes were diagnosed in 35 patients (87.5%) (Table 1).

Table 1 – Distribution of patients depending on the stage

| Stage | 1 st block n (%) | 2 nd block n (%) | P |
|---------------------------|--------------------------------|--------------------------------|--------|
| I (T1N0M0) | 2 (5.1±0.3%) | 14 (33.1±2.2%) | P<0.05 |
| II A (T1N1M0, T2N0M0) | 13 (32.5±4.1%) | 7 (28.4±2.3%) | P<0.05 |
| II B (T2N1M0, T3N0M0) | 7 (28.4±3.7%) | 11 (27.8±1.8%) | P<0.05 |
| III A (T2N2M0) | 17 (41.1±2.4%) | 17 (41±0.9%) | P<0.05 |
| III B (T4N0M0, T4N1M0) | 1 (2.5±0.07%) | 1 (2.5±0.6%) | P<0.05 |
| Total | 40 (100.00) | 40 (100.00) | |

In patients with infiltrative breast cancer, diffuse-infiltrative stomach cancer, diffuse-infiltrative esophagus cancer, and diffuse-infiltrative colorectal cancer there was a tendency to an increase in the expression of YKL-39 with the ERBB2 amplification during inflammatory tumor infiltration in the stroma. High expression of Stabilin-1 (2.1±0.70, n = 22) was found compared to patient tumors that did not reveal the amplification of ERBB2 (1.46±0.67, n = 13, p = 0.015) (Table 2).

In most patients with amplification ERBB2, the cryoglobulin content was average (298.6±2.5 mg / l; 1.3±0.08%) – 20 (50%), which corresponds to cryoglobulinemia type II; with conditioned cryoglobu-

Table 2 – Average expression score of CD68, Stabilin-1, YKL-39, SI-CLP in tumor tissue culture in blocks with amplification ERBB2 and its absence

| Investigated indicators | Average expression score M±SD (N) in a group with amplification erBb2 (3+) (40 patients) | Average expression score M±SD (N) in a group without amplification erBb2 (40 patients) |
|-------------------------|--|--|
| CD68 | 2.96±0.81 (N=11) ^ | 2.26±0.82 (N=12) ^ |
| YKL-39 | 2.35±0.99 (N=7) ^ | 2.24±0.72 (N=9) ^ |
| SI-CLP | 2.63±1.24 (N=2) * | 2.23±0.77 (N=6) |
| Stabilin-1 | 2.94±1.01 (N=22) | 2.0±0.79 (N=13) * |

Notes: reliable differences from the indicator: * – healthy tissue; ^ – tissue of the peritumoral zone (p <0.05).

linemia (79.4±1.01 mg/l) in 10 (25%); high content (477.3±48 mg/l; 3.4±0.2%) was recorded in 10 (25%), which indicates the type III of cryoglobulinemia [the hazard ratio (HR) = 0.71, 95%, confidence interval (CI): 0.22-0.83, p = 0.005] (Fig. 2).

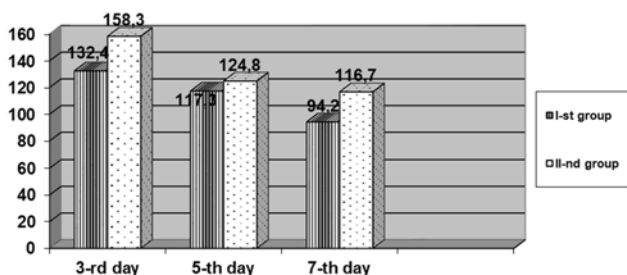


Figure 2. Dynamics of immunoglobulin content in cryoprecipitates of patients with ERBB2 amplification (3+) and its absence

These clinical indicators are reliable forecast markers to determine the development of relapses after the combined treatment after the processing of the results got in inflammatory breast cancer, diffuse-infiltrative stomach cancer, diffuse-infiltrative esophagus cancer, and diffuse-infiltrative colorectal cancer.

Discussion. The fact of the presence of chitinase-like proteins and increasing the index of their proliferation during cancer with amplification of ERBB2 as a marker indicates the aggressiveness of the process, suggested by Larionova [52]. In patients with breast, stomach, esophageal and colorectal cancer, increased amount of TAMs is a clear indicator for rapid tumor growth, aggressive metastatic process, and limited efficiency of therapy. In stomach and breast cancer, the major parameter associated with prognosis was not the total amount of CD68+ macrophages, but M1/M2 index. The prevalence of M1 macrophages was favorable for the patients, indicating that in colorectal tumor M1 TAMs have the ability to limit tumor progression.

However, in the future, and we are already carrying out such work, it may turn out that the presence and saturation of the tumor, microoperated tumor proteins will be a factor of higher sensitivity to special treatment with selected localizations. In addition, the expression of YKL-39 has negatively correlated with the number of lymph nodes with metastases (R = -0.89). Therefore, Kzhyshkowska [53] suggests, TAMs may contribute to resistance to therapy and facilitate tumor progression via macrophage-induced suppression of T-cell immunity, maintenance of tumor cell survival, and stimulation of tumor revascularization. Chemotherapeutic agents can edit macrophages in tumor-protective or antitumor directions, where three major mechanisms must be considered: changes in the macrophage phenotype; induced recruitment of monocytes or macrophages to the tumor site. Most likely, more pronounced activities in the hollow organ depend on the constant mechanical load, including enzymatic in the process of digestion.

Conclusion

1. In patients with the presence of ERBB2 amplification in inflammatory tumor infiltrate, the higher expression of the chitinase-like YKL-39 and M2 of the marker Stabilin-1 was revealed, compared with patient tumors without amplifying ERBB2.
2. Amplification of ERBB2 and macrophages surroundings Marker CD68, M2 subpopulation RS1 (Stabilin-1), chitinase-like YKL-39 proteins, SI-CLP are independent predictors of the detection of aggressiveness and develop recurrences in subgroups of patients with inflammatory breast cancer, diffuse stomach and diffuse cancer esophagus and have a bad forecast.
3. It is shown that patients with cryoglobulinemia with inflammatory breast cancer lead to secondary immunodeficiency. This is determined by anomalies in the cell and humoral immune system, and as a result of the development of postoperative inflammatory complications and relapses.
4. Any non-permitted chronic inflammation leads to cancer or cancer in the development of relapse and metastasis.

Perspectives of further research. The literature data on the prognostic factors of the cancer relapse process is quite contradictory. Therefore, it is advisable to estimate the factors of the prediction of relapse in the monocenter exam, for a relatively short time, when surgery and combined treatment regimen have not changed significantly. The data got on the factor of the forecast will improve the results of the treatment of cancerous diseases of selected localizations,

reduce the frequency of relapses and optimize the observation of patients after radical treatment.

Further, broadcast studies that bind laboratory data and clinical practice will help clarify the association between the cancer relapse and inflammation, as well as to create a more effective postoperative treatment under the aim of reducing the percentage of relapses.

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Competing interest. The authors declare that they have no competing interests.

Financial competing interests. In the past five years we have not received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future. We did not hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript. We did not hold applying for any patents relating to the content of the manuscript. We did not receive reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript.

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ВПЛИВ ЗАПАЛЬНОГО МІКРООТОЧЕННЯ НА РОЗВИТОК РЕЦИДИВУ РАКУ ПІСЛЯ КОМБІНОВАНОГО ЛІКУВАННЯ

Мовчан О. В., Багмут І. Ю.

Резюме. *Мета роботи* - вивчення впливу певних елементів запального мікрооточення пухлини в розвитку рецидиву раку основних локалізацій з ампліфікацією ERBB2 після комбінованого лікування.

Матеріали і методи. В дослідженні прийняли участь 80 пацієнтів, які проходили лікування з 2016 року по 2021 рік у Національному Інституті Раку, Київ, Україна. Вік 42-78 (в середньому 60) років, ECOG 0-2, всі жінки. У всіх пацієнток гістологічно доведена аденокарцинома GIII-GIV. У всіх був вивчений рівень хітиназоподібних білків, криоглобулінів, пухлинно-асоційованих макрофагів в передопераційний (вперше виявленим захворюванням, до початку хіміотерапії) і післяопераційний період.

1-й блок: з підтвердженою мутацією гена Her-2/Neu (ампліфікацією ERBB2 (3+)): а) запальний рак молочної залози (первинно-набрякова форма) - 10 осіб, б) дифузно-інфільтративний рак шлунка - 10 осіб; в) дифузно-інфільтративний рак стравоходу - 10 осіб; г) дифузно-інфільтративний колоректальний рак - 10 осіб. *2-й блок:* без підтвердженої мутації гена Her-2/Neu а) запальний рак молочної залози (первинно-набрякова форма) - 10 осіб, б) дифузно-інфільтративний рак шлунка - 10 осіб і в) дифузно-інфільтративний рак стравоходу - 10 людина і г) дифузно інфільтративний колоректальний рак - 10 осіб.

Результати – у пацієнтів з інфільтративним раком молочної залози, дифузно-інфільтративним раком шлунка і стравоходу, і дифузно-інфільтративним колоректальним раком була тенденція до збільшення експресії YKL-39 з ампліфікацією ERBB2 під час запальної інфільтрації пухлинної стромы. Висока експресія Стабіліна-1 ($2,1 \pm 0,70$, N = 22) була виявлена в порівнянні з пухлинами пацієнтів, у яких не виявили ампліфікації ERBB2 ($1,46 \pm 0,67$, N = 13, p = 0,015). У більшості пацієнтів з ампліфікацією ERBB2 вміст криоглобулінів був середнім ($298,6 \pm 2,5$ мг/л; $1,3 \pm 0,08\%$) - 20 (50%), що відповідає криоглобулінемії типу II; з незначною криоглобулінемією ($79,4 \pm 1,01$ мг/л) у 10 (25%); Високий вміст ($477,3 \pm 48$ мг/л; $3,4 \pm 0,2\%$) було виявлено у 10 (25%), що вказує на тип III криоглобулінемії (HR) = 0,71, 95%, (CI) : 0,22-0,83, p = 0,005]

Висновки - ампліфікація ERBB2 та насиченість макрофагами CD68, M2 підпопуляції RS1 (Стабіліну-1), хітиназоподібними білками YKL-39 і Si-CLP пухлини, визначені як незалежні фактори розвитку рецидивів у хворих із запальним раком молочної залози, дифузним раком шлунка і стравоходу, дифузного колоректального раку пов'язані з несприятливим прогнозом. Це дослідження показує важливу роль кількісних значень, пов'язаних з пухлинним фенотипом і макрофагами в процесі рецидивування пухлини, в залежності від наявності або відсутності ампліфікації ERBB2. У пацієнтів з присутністю криоглобулінемії із запальним раком розвивається вторинний імунodefіцит. Це визначається аномаліями в клітинній та гуморальній імунній системі, а також веде до розвитку післяопераційних запальних ускладнень і рецидивів.

Ключевые слова: рак, молочно залоза, шлунок, стравохід, колоректальний рак, рецидив.

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ВЛИЯНИЕ ВОСПАЛИТЕЛЬНОГО МИКРООКРУЖЕНИЯ НА РАЗВИТИЕ РЕЦИДИВА РАКА ПОСЛЕ КОМБИНИРОВАННОГО ЛЕЧЕНИЯ

Мовчан А. В., Багмут И. Ю.

Резюме. *Цель работы* – изучение влияния определенных элементов воспалительного микроокружения опухоли в развитии рецидива рака основных локализаций с амплификацией ERBB2 после комбинированного лечения.

Материалы и методы. В исследовании приняли участие 80 пациентов, которые проходили лечение с 2016 года по 2021 год в Национальном Институте Рака, Киев, Украина. Возраст 42-78 (в среднем 60) лет, ECOG 0-2, все женщины. У всех пациентов гистологически доказанная аденокарцинома GIII-GIV. У всех был изучен уровень хитиназоподобных белков, криоглобулинов, опухоль-ассоциированных макрофагов в предоперационном (впервые выявленным заболеванием, до начала химиотерапии) и в послеоперационный периоде.

1-й блок: с подтвержденной мутацией гена Her-2/Neu (амплификацией ERBB2 (3+)): а) воспалительный рак молочной железы (первично-отечная форма) - 10 человек, б) диффузно-инфильтративный рак желудка - 10 человек ; в) диффузно-инфильтративный рак пищевода - 10 человек; г) диффузно-инфильтративный колоректальный рак - 10 человек. *2-й блок:* без подтвержденной мутации гена Her-2/Neu а) воспалительный рак молочной железы (первично-отечная форма) - 10 человек, б) диффузно-инфильтративный рак желудка - 10 человек и в) диффузно-инфильтративный рак пищевода - 10 человек и г) диффузно-инфильтративный колоректальный рак - 10 человек.

Результаты - пациенты с инфильтративным раком молочной железы, диффузно-инфильтративным раком желудка и пищевода и диффузно-инфильтративным колоректальным раком была тенденция к увеличению экспрессии YKL-39 с амплификацией ERBB2 во время воспалительной инфильтрации опухолевой стромы. Высокая экспрессия Стабилина-1 ($2,1 \pm 0,70$, N = 22) была обнаружена в сравнении с опухолями пациентов, у которых не выявили амплификации ERBB2 ($1,46 \pm 0,67$, N = 13, $p = 0,015$). У большинства пациентов с амплификацией ERBB2 содержание криоглобулинов было среднее ($298,6 \pm 2,5$ мг/л; $1,3 \pm 0,08\%$) - 20 (50%), что соответствует криоглобулинемии типа II; с незначительной криоглобулинемией ($79,4 \pm 1,01$ мг/л) у 10 (25%); Высокое содержание ($477,3 \pm 48$ мг/л; $3,4 \pm 0,2\%$) было выявлен у 10 (25%), что указывает на тип III криоглобулинемии (HR) = 0,71, 95%, (CI): 0,22-0,83, $p = 0,005$]

Выводы - амплификация ERBB2 и насыщенность макрофагами CD68, M2 подпопуляции RS1 (Стабилина-1), хитиназоподобными белками YKL-39 и Si-CLP опухоли, определены как независимые факторы развития рецидивов у больных с воспалительным раком молочной железы, диффузным раком желудка и диффузного пищевода, диффузного колоректального рака и связаны с неблагоприятным прогнозом. Это исследование показывает важную роль количественных значений, связанных с опухолевым фенотипом и макрофагами в прогрессе рецидивирования опухоли, в зависимости от наличия или отсутствия амплификации ERBB2. У пациентов с присутствием криоглобулинемии с воспалительным раком развивается вторичный иммунодефицит. Это определяется аномалиями в клеточной и гуморальной иммунной системе, а также из-за развития послеоперационных воспалительных осложнений и рецидивов.

Ключевые слова: рак, грудная железа, желудок, пищевод, колоректальный рак, рецидив.

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The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of coauthors of the article.

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