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Morphological and Morphometric Parameters of the Small Intestine during Chemotherapy and Correction with an Immunomodulator

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Abstract: As the main method of treatment, chemotherapy does not show high results, so it is used in combination with other measures. So, drug treatment is prescribed in the pre- and postoperative period, when regional lymph nodes are involved in the tumor process. The use of immunomodulators in the treatment of cancer patients in combination with routine methods of exposure remains a little studied issue. The results of the analysis of literature data on the use of immunomodulators in the complex treatment of cancer patients with small intestine cancer during chemotherapy are presented.

Keywords: morphology, morphometry, cancer, small intestine, immunomodulator, chemotherapy.

Relevance. Tumors of the small intestine are extremely rare and account for up to 0.3% of all cancers and 2 to 6% of all tumors of the digestive system. In 75% of cases they are malignant. Of these, about 50% are adenocarcinomas of the small intestine [WHO, 2021]. The interaction of the body and a tumor that grows despite the existing immune response to it is one of the problems of modern tumor immunology. The significance of the immune response to tumor development is well known from the classical experimental immunology of tumors and studies on "immunological surveillance" (a term proposed by Burnet and now includes a much broader concept), as well as from modern studies on the mechanism of natural antitumor resistance [Kadagidze Z. G., 2022].

To improve the results of treatment, methods are being developed that include chemoradiotherapy, but their capabilities are limited by tumor resistance, low tolerance of surrounding tissues, and high toxicity of chemotherapy drugs. Therefore, an important approach in the treatment of patients with small bowel cancer is the methods of administration and delivery of chemotherapy drugs to the tumor. A promising direction is the use of various modulators that increase the effectiveness of chemotherapy drugs and positively affect the results of treatment [Kit O.I., 2013].

The experimental data presented in the review indicate the important role of lymphoid tissue under the influence of various extreme factors on the body, and it can be argued that all concomitant rearrangements occurred at the level of interaction of lymphocytes with the target tissue and are associated with the nature of intracellular changes in lymphocytes that determine the path to a controlled change. pathogenesis of diseases. (P.M. Maslyukov 2019). The multifunctionality of the small intestine determines its participation in many processes accompanied by immune responses that induce recovery. Given the migratory abilities of lymphoid cells, their ability to receive information and interact with other organs is expanding. They are able to provide a quick change of the program of the normal development of the organism to the reserve one and vice versa.

Any damage caused by a particular pathology leads to a violation of the protective barrier of the small intestine, the development of toxemia, a decrease in immunity and a violation of homeostasis. (P.K. Permyakov et al.; Yu.G. Parkhomenko 2015).

The concentration of lymphocytes in lymphoid tissue determines the speed and efficiency of the immune response, which is triggered by the interaction of several cell types, and therefore even a slight drop in concentration can lead to a significant weakening of the immune response. The mechanisms that regulate the volume of intact lymphoid tissue depend on many factors: the intensity of inflammatory and regenerative processes, the activity of connective tissue and the immune system. The role of cytokines and adhesive molecules in the process of lymphocyte settlement, the development of inflammation and the immune response is extremely important. Settlement, like classical migration, is a complex process with tissue specificity. Tissue-specific antigens that are involved in the distribution are widespread and give a signal determined by various chemokines [4, p.120-123; 26, p.52-55].

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The concept of the role of immune mechanisms in the development of malignant neoplasms was put forward in 1909 by Ehrlich and then expanded by many researchers. Back in 1929, A.A. Bogomolets suggested that the development of the malignant process proceeds against the background of immunosuppression that has developed for various reasons. Recent studies have confirmed the essential importance of the immunosuppression factor in the development of tumors.

To explain the possible mechanism of growth in the body of an antigenic tumor, several classifications of the causes of a violation of the immunological response to a developing tumor have been developed. In our opinion, the classification proposed by Klein (Klein, 1975) most fully reflected the possible deviations of immunological surveillance:

1) insufficient recognition of tumor-associated specific antigens;

2) immunological tolerance;

3) escape of the tumor from the immune response;

4) immunological deficiency of the host;

5) improper functioning of the effector mechanisms of the immune response.

In 1970-1980 much attention was paid to the study of the immunological reactivity of the organism and the study of the relationship between the level of the immune response and the clinical course and prognosis of the disease. The studies obtained during this period showed that the growth of most malignant neoplasms is accompanied by changes in the parameters of various parts of the immune response. To determine the nature and intensity of damage to the immune system, a panel of monoclonal antibodies (MCA) to differentiation antigens of immunocompetent cells and a number of tests that determine their functional activity are currently used. For quite a long time, the main changes that were given priority were violations in the ratio of immunoregulatory subpopulations of T-lymphocytes, a decrease in the number and decrease in the functional activity of natural killers.

Recently, in assessing the immune status of cancer patients, special attention has been paid to general leukocyte and activation antigens. Among general leukocyte antigens, of interest is the CD50 antigen (ICAM-3) of the immunoglobulin superfamily, which is expressed on resting hematopoietic cells, B-lymphocytes, and on T-lymphocytes its expression increases as they

mature and reaches a maximum on memory T-cells. The interaction of CD50 and LFA-1 is a strictly necessary secondary signal in the activation of T-lymphocytes and requires simultaneous activation of CD45 phosphotyrosine phosphatase and phosphotyrosine kinases. A decrease in CD50 expression leads to disruption of cell adhesion and migration of B-lymphocytes to the lymph nodes.

An analysis of 2-year survival in 80 patients with gastric cancer revealed a positive correlation between the level of CD50 expression and the prognosis of the disease: patients in whom CD50 expression remained at a high level had a more favorable course of the disease than those in whom the expression level was low or decreased in the process of treatment. The difference was statistically significant.

Another important prognostic indicator was the expression of the CD95 antigen (Fas/APO-1). This apoptosis-mediating antigen was independently discovered in two laboratories using mAbs anti-Fas and anti-APO-1, which induce apoptosis in some human cells. The CD95 antigen is a member of the tumor necrosis factor superfamily, which also includes nerve growth factor and CD27, CD40 antigens. The CD95 antigen itself is a receptor for the Fas ligand, which is part of the ligand superfamily. It is expressed on cortical thymocytes, various lymphoblastoid cell lines, activated T and B cells.

Analysis of the prognostic significance of the Fas antigen on bone marrow blast cells was carried out in children with ALL observed since 1987. It turned out that, depending on the expression of CD95, they are clearly divided into two subgroups: CD95+ and CD95-. It should be noted that the CD95 antigen is most often expressed in pre-pre-B ALL, which can be characterized as more favorable prognostically. In the CD95+ group, the median 10-year overall survival was 118.5 months, and in the CD95- group it was 24 months. Thus, expression of CD95 on the membrane of blast cells is a prognostically favorable sign that increases both relapse-free and overall survival, while the absence of CD95 antigen on the surface of blasts suggests a poor prognosis in the development of the disease. Similar data were obtained in patients with myelodysplastic syndrome and some solid tumors.

Despite all the data on changes in immunological parameters in cancer patients, one of the main issues discussed is the correct interpretation of the observed changes. It is known that "deviation from the average value may indicate a normal reaction of the immune system to a disturbing effect, i.e. a normal function" (Petrov R.V.). In this regard, special attention should be paid to the dynamics of the studied parameters of the immune system, taking into account both the number of immunocompetent cells and their functional activity. Preservation or strengthening of the negative dynamics of immunological indicators indicates the need to influence them in order to restore functional activity.

Modern immunotherapy includes several areas where they are used:

1) immunomodulators;

2) monoclonal antibodies and drugs based on them;

3) cancer vaccines.

The active use of immunomodulators began in the 70s. of the twentieth century, when it was shown that the use of a number of different drugs contributed to the restoration of immunological parameters. Clinical studies conducted over the past 5 years have revealed both positive and negative aspects of this type of treatment: along with data on the effectiveness of some immunomodulators, it was shown that inadequate use of drugs contributed to the acceleration of tumor growth and death of the patient. Currently, unlimited advertising campaigns have led to the use in clinics of drugs that do not have immunomodulatory properties, have not passed appropriate clinical trials and are approved for medical use, which is especially dangerous in the presence of a tumor process.

Currently, over 40 drugs with immunomodulatory properties are approved for use in Russia; these are mainly cytokines, thymus preparations and synthetic preparations. Most immunomodulators have a well-studied mechanism of action with a predominant effect on one or another part of the immune system, although, depending on various conditions, the drug may also affect its other components. All this indicates the need for a preliminary assessment of the parameters of the immune system in each case, followed by the appointment of the appropriate drug. In recent years, a large number of studies have been conducted on the use of immunomodulators for the correction of immunological parameters in patients receiving chemotherapy. It turned out that the use of these drugs helps to reduce the toxicity of chemotherapy drugs, reduce the recovery time of leukocytes, reduce the incidence of viral infections, and in some cases increase the duration of remission.

A special place among the studied drugs is occupied by cytokines; recent studies have shown the effectiveness of their use in some malignant neoplasms, in particular, in kidney cancer and malignant melanoma, as well as hairy cell and chronic myelocytic leukemia. Federal State Budgetary Institution National Medical Research Center of Oncology named after N.N. N.N. Blokhin" of the Ministry of Health of Russia, 119 patients with metastatic kidney cancer were treated with roferon A (HuIFNa-2b) both as monotherapy and in combination with 5-fluorouracil. Received 12 complete and 17 partial remissions; stabilization of the disease for a period of 6 months or more was achieved in 30 patients (25.2%). Immunological studies have shown that in order to assess the clinical effect of interferon, the initial state of the immunological status is more important than its dynamics during treatment. Current studies suggest that the mechanism of the antitumor effect of interferon is its effect on apoptosis. The data obtained will make it possible to develop more effective schemes for the sequential use of cytokines and their combinations with anticancer drugs.

Based on the foregoing, it is clear that the most difficult issue in the study of the effectiveness of the use of immunomodulators is the correct assessment of the appropriateness of prescribing immunocorrective treatment and its effectiveness. It is clear that a progressive tumor causes serious changes in the immune response, which the immune system cannot cope with on its own, and the inclusion of immunomodulators in the treatment of cancer patients is justified. At the same time, the expediency of immunorehabilitation measures, i.e. prevention of relapses and metastases in cancer patients requires clear justifications:

a) the patient must have persistent impairments in the functioning of various parts of the immune system;

b) correction of immune disorders should be carried out using drugs whose mechanism of action is well studied and aimed at stimulating the suppressed part of the immune system;

c) treatment must be carried out under strict immunological control.

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