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Comparative Characteristics of Morphological Changes and Morphometric Parameters of Gastromas during Chemotherapy and Correction with an Immunomodulator in Postnatal Ontogenesis

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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 gastric cancer during chemotherapy are presented.

Relevance. Cancer is one of the leading causes of death in the world, accounting for nearly 10 million lives in 2020 (1). stomach cancer (1.09 million cases). Gastric cancer ranks second in the structure of morbidity and mortality among malignant neoplasms in the Russian Federation [1]. In the world, gastric cancer ranks fourth in the incidence of malignant neoplasms, and in the structure of mortality - the second place in men and the fourth in women. The incidence ratio of men and women is 1.5:1 [2]. About 70% of new cases of gastric cancer are in developed countries [3]. However, in the last 50 years, there has been a steady decrease (up to 60%) in the incidence of gastric cancer [4]. In many countries, there is a decrease in mortality compared with morbidity [5]. In contrast to the current trend, in some populations an increase in the number of patients with a disease of the cardia of the stomach was found [6]. It has been shown that in countries with high incidence, longer survival is observed than in countries with low incidence [7, 8]. This can be explained by the success of screening programs, for example, in a country like Japan. In Japan, gastric cancer is diagnosed at stages I, II and III in 50.5%, 26.9% and 14.0% of patients, respectively, and their 5-year population survival rates are 95.2%, 39.8% and 2. 9%, respectively [9].

Chemotherapy for the treatment of stomach tumors.

This method of therapy is based on the use of cytostatics and is aimed at slowing down the progression of the malignant process. 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. Cytostatics slow down the growth of a cancerous tumor, so they are often used as

part of palliative therapy. This approach improves the patient's well-being.

In most cases, gastric cancer is diagnosed at an advanced stage [10]. In more than two-thirds of patients, the disease is detected only at stage IV, when the tumor is no longer resectable. In Russia in 2006, only 23.3% of patients were diagnosed with the disease at stages I–II, and the 5-year population survival rate does not exceed 13% [1]. The EUROCARE-4 study showed that the 5-year survival rate of patients with gastric cancer in Europe was only 24.1% [11]. Despite R0 resections in patients with local and locally advanced disease, the recurrence rate is high (up to 70%), and the 5-year survival rate does not exceed 30% [12].

Until recently, there were differing opinions about improving survival in metastatic gastric cancer (mGC) with chemotherapy. A meta-analysis by A. D. Wagner et al. [13], answered this question and demonstrated a significant increase in life expectancy when comparing chemotherapy with maintenance treatment, despite a small sample size. Three randomized trials [14-16] involving a total of 184 patients showed that chemotherapy, when compared with maintenance treatment, increases the life expectancy of patients with gastric cancer (9-11 months and 3-4 months, respectively, HR = 0.39). Another analysis comparing polychemotherapy and monochemotherapy demonstrated significant differences in favor of polychemotherapy (HR = 0.83, p = 0.001).

Thanks to new combinations, over the past 20 years, the life expectancy of patients receiving first-line chemotherapy has increased from 6 to 10-11 months. However, despite the emergence of new effective regimens, NRM remains less than a year with short objective responses [33]. The key to improving overall survival is the use of effective chemotherapy in the future, with progression after the first line of treatment. However, in daily practice, second-line chemotherapy is not given to all patients. With progression after the first line, only 20-30% of patients receive further chemotherapy [20, 34]. This is due to the fact that with progression after the first line of therapy, most patients have a severe clinical picture, for example, ECOG status ≥ 2, dysphagia, increasing ascites, pain, weight loss ≥ 10%. Chemotherapy in such patients results in serious complications due to both the toxicity of the antitumor drugs themselves and the course of the disease. In particular, in gastric cancer, weight loss, dysphagia due to stenosis or obstruction, and bleeding from an unremoved primary tumor are noted. In such patients, chemotherapy is a threat to life and is often complicated by the development of deep, often febrile, neutropenia, sepsis, stomatitis, enterocolitis, accompanied by severe diarrhea [35]. Administration of severely tolerated chemotherapy is not always possible, and the question of initiating second-line chemotherapy is a matter of debate.

Similar results have been obtained with paclitaxel alone or in combination [48–54]. Weekly administration of paclitaxel (60–80 mg/m2) had less toxicity (16–32% of grade 3–4 neutropenia) with the same number of objective effects (8–27%) compared with the standard three-week regimen in a series of Japanese studies [49, 50]. Paclitaxel in combination with cisplatin showed a high incidence of grade 3–4 neutropenia (up to 34%) and grade 2–3 peripheral neuropathy (up to 38%) [53, 54].

Combinations of irinotecan with cisplatin and fluoropyrimidines are highly effective (27–52%) in second-line chemotherapy. There are also new technologies - robot-assisted surgery, which is potentially even more accurate than laparoscopic surgery, radiation therapy, which is not yet used so often for stomach cancer, but nevertheless there are certain application points for new radiosurgical techniques. You can see a huge shift in the treatment of many tumors through the so-called immunotherapy: there is a way to give the cells of the immune system the ability to recognize tumor cells as foreign and fight them. For gastric cancer, this method works so far only in selected patients, but nevertheless, this method allows some patients to radically prolong life. The use of the main methods of special treatment of oncological patients: surgical, radiation

and chemotherapy does not raise any doubts among specialists. The allocation of immunotherapy as a separate type of complex cancer therapy remains debatable today. However, the effectiveness of this systemic method of influencing a tumor (especially in a number of localizations: kidney cancer, melanoma) has been absolutely proven and is widely used throughout the world. The use of immunomodulators in the treatment of cancer patients in combination with routine methods of exposure remains a little studied issue. In order to increase the effectiveness of antitumor therapy, more and more aggressive schemes of radiation and chemotherapy treatment are being developed and applied, which leads to the development of pronounced functional and quantitative disorders in the immune system, which are realized by autoimmune, allergic and infectious complications. The developed complications, in turn, hinder the implementation of the main treatment in the optimal mode, reducing its effectiveness and worsening the quality of life of patients [1-3]. Therefore, at the present stage, special attention is paid to the use of immunocorrective therapy in the process of complex treatment of patients [3, 4]. At the same time, the standards of immunocorrection are far from perfect. Questions remain open: which immunotropic drugs are most appropriate to use in combination with complex treatment of oncological diseases, and what are the criteria for prescribing these drugs [3]. In accordance with a number of existing classifications [1, 5, 6], the following groups of immunomodulators are distinguished: • preparations of microbial origin (ribomunil, imudon, sodium nucleinate, etc.); • peptide preparations (tactivin, thymalin, myelopid, etc.); • synthetic drugs (licopid, imunofan, polyoxidonium, levamisole, galavit, cycloferon, etc.); • preparations based on cytokines (interferons (IF), interleukins (IL), colony stimulating factors (CSF) • preparations based on natural factors (Biobran, Derinat, Erbisol, plant extracts). The main feature of preparations of microbial origin is activation, primarily natural resistance factors - systems of mononuclear phagocytes, neutrophilic granulocytes and natural killers (NK).The most important is the enhancement of the cytotoxic function of macrophages (MF), which is manifested by their ability to destroy syngeneic and allogeneic tumor cells in vitro.Activated monocytes and MF synthesize a number of cytokines: IL -1, IL-2, tumor necrosis factor (TNF), colony stimulating factors (CSF), etc., which leads to an increase in the antitumor resistance of the organism [5]. 16] This is a physiologically active high molecular weight compound with pronounced immunotropic activity. The immunomodulatory effect of polyoxidonium is associated with its predominant effect on neutrophils, monocytes/macrophages, natural killers, and indirectly on B- and T-lymphocytes. The consequence of this is the activation of the absorption and bactericidal abilities of phagocytes; enhancement of NK function; stimulation of the synthesis by monocytes and lymphocytes of a number of cytokines that increase the production of antibodies by B-lymphocytes and the functional activity of T-cells. In addition to the immunomodulatory effect, polyoxidonium has a pronounced detoxifying, antioxidant, and membrane stabilizing effect [17].

At the same time, the possibilities and goals of immunotherapy in cancer patients should be considered taking into account the stage of their treatment. In the early postoperative period, it is most advisable to use drugs that affect the cells of the mononuclear phagocyte system to prevent postoperative infectious complications. These drugs include: polyoxidonium, galavit, imunofan, biobran. The use of thymic drugs (tactivin, thymalin), which affect the proliferation and differentiation of T-cells, enhance the production of IL-2 and its reception by sensitive cells, is also justified. During radiation and PCT, preference should be given to drugs that can prevent the development of leukopenia and have an antitoxic effect - biobran, polyoxidonium, erbisol. To correct complications caused by radiation therapy, it is preferable to prescribe drugs with antioxidant and reparative effects: imunofan, polyoxidonium, derinat.

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