AJPMHS GLOBAL RESEARCH NETWORK

AMERICAN Journal of Pediatric Medicine and Health Sciences
Volume 01, Issue 02, 2023 ISSN (E): XXX-XXX

Morphological Features and Morphometric Parameters of the Colon after Correction with an Immunomodulator under the Conditions of Experimental Chemotherapy

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Abstract: Immunotherapy is an innovative method of cancer treatment. It is based on interference in the interaction of the patient's immune system and a malignant tumor. Immunotherapy goes well with classical methods of treatment [Ivanisova D.N., 2022]. The results of the analysis of literature data on the use of immunomodulators in the complex treatment of cancer patients with colon cancer during chemotherapy are presented.

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

Relevance. Colon cancer (colorectal cancer) is a group of oncological diseases in which a malignant tumor is formed from the mucous membrane of the distal intestine (caecum, colon, sigmoid and rectum). In terms of the frequency of diagnosis, colorectal cancer ranks first among malignant tumors of gastrointestinal cancer and second or third in the overall structure of oncological diseases. Every year, more than 600 thousand people are diagnosed with malignant tumors of the large intestine. Moreover, in 60-70% of patients, late stages of the disease are detected. Colorectal cancer is more commonly found in patients older than 50 years of age. The gender ratio is 1:1.5 (men get sick more often). Colorectal cancer is formed as a result of malignant transformation of intestinal epithelial cells. Most often, the tumor occurs in the descending colon. The mechanism of neoplasia has not been studied. Presumably, the development of the disease is promoted by chronic inflammatory processes, contacts with carcinogens, and the presence of polyps in the intestine [Makarov O.G., 2022].

Immunotherapy is an innovative method of cancer treatment. It is based on interference in the interaction of the patient's immune system and a malignant tumor. Immunotherapy goes well with classical methods of treatment [Ivanisova D.N., 2022].

"The goal of cancer immunotherapy is to get the patient's immune system to work in such a way that it can counteract the growth of a malignant tumor on its own." With regard to chemotherapy, in most cases, its combination with immunotherapeutic drugs is most effective. For example, vaccination with dendritic cells may occur between cycles of chemotherapy, or chemotherapy may precede CAR T cell therapy. Certain chemotherapy regimens can enhance the immune response against tumors, which allows patients to achieve cancer remission faster [Zhilyuk D.V., 2022]. Chemoradiation therapy can be used in a number of nosologies not for the purpose of actively influencing the tumor, but as a conditioning regimen to create favorable conditions for the activity of administered specific autologous CTLs, with which immunotherapy should be started in these cases [6]. In this case, various methods of CTL administration should be envisaged, depending on the location of the tumor and the expected degree of its accessibility to

CTL (intravenously, intrathecally). The transition to dendritic cell vaccines seems appropriate only after the restoration of the ability of the immune system to generate a response to antigenic stimulation - 1.5–2 months after the end of chemotherapy. An example of the consistent use of chemoradiotherapy and immunotherapy is the work of S. Rosenberg et al. [6], where 3- and 5-year survival in 93 patients with metastatic melanoma who received immunotherapy with autologous tumor-infiltrating lymphocytes was 36 and 29%, which is at least comparable to those achieved with chemotherapy programs. In 20 patients who achieved a complete response, the survival rates in the above terms were 100%. The toxicity was not due to the cellular immunotherapy itself, but to an interleukin 2 preparation that was administered to patients at high doses. According to other studies, chemoradiation preparation of patients is not mandatory for effective CTL immunotherapy. In a study by J. Wolchok et al. [7], which included patients with stage III–IV melanoma who received antibodies to CTLA-4 and PD-1 receptors, in more than 50% of cases a long-term positive clinical response was achieved with a significant reduction in visible tumor. However, only in 9% of cases, therapy was interrupted due to the development of acute toxicity. There were no deaths due to treatment. Encouraging results in the absence of toxicity were shown by the tactics of immunotherapy using dendritic cell vaccines and in the treatment of patients with recurrent and chemotherapy-resistant glioblastoma multiforme. Patients showed not only stabilization and shrinkage of the tumor, but also a significant (3-fold) increase in the non-progressive interval compared with the control group, and in some cases of chemoradiotherapy-resistant gliomas, and a complete long-term (more than 5–7 years) remission [8 -10].

These results are encouraging not only in the context of long-term disease-free survival in patients with MSI, but also in the possibility of neoadjuvant therapy in early-stage colon cancer and the MSS phenotype. However, the question arises as to whether the addition of neoadjuvant immunotherapy is necessary for operable colon cancer, since we know that the presence of disorders in the mismatch system determines a favorable prognosis in stage II disease with risk factors and often does not even require adjuvant therapy. But in this regard, we can recall the results of a joint analysis of individual data from 12 randomized trials on the study of adjuvant chemotherapy in colon cancer, in which the favorable prognostic effect of MSI was already lost at the N2 index in stage III of the disease [8]. In addition, abstracts from authors from the USA were presented at ASCO 2022, in which 9634 patients with stage II colon cancer and MSI were collected, clinical risk factors for progression were identified in 2538 patients (26%), among them 505 patients had 2 or more risk factors. Multivariate analysis confirmed the absence of a negative impact on the prognosis in MSI with lymphovascular invasion and a low degree of differentiation. However, perineural invasion, study of less than 12 lymph nodes, R1 resection, and stage T4N0M0 retained independent negative effects. Moreover, 5-year overall survival was 77% with no risk factors, 66% with 1 risk factor, and 54% with 2 risk factors. At the same time, in the entire patient population, chemotherapy increased OS (HR 0.76; $p<0.0001$), although in patients younger than 60 years, adjuvant chemotherapy worsened OS (HR 1.4; $p=0.0156$) [9].

All this suggests that in the case of T4N0M0, perineural invasion, the study of less than 12 lymph nodes, R1 resection or the presence of 2 or more risk factors, adjuvant chemotherapy should be considered for stage II disease and a microsatellite unstable tumor phenotype in the amount of 4 courses of the XELOX regimen, but, on the other hand, shows an indicative population of patients, even with colon cancer, in which the effectiveness of neoadjuvant immunotherapy can be studied. But what to do when a full clinical effect is achieved, the criteria for which have not been developed, for colon cancer on the background of immunotherapy - to leave it under observation or to operate - is unknown [Fedyanin Mikhail Yuryevich, 2022].

At the moment, it is time to think about changing the paradigm of the treatment of certain types of cancer from chemotherapeutic to immunotherapeutic as relatively low toxicity, which allows for a personalized approach to the patient, has a broad base for development, provides a good quality of life for patients and has shown its effectiveness in a number of studies. This requires the formation of treatment protocols based precisely on the principles of immunotherapy and

excluding chemoradiotherapy where it has not demonstrated its effectiveness. Undoubtedly, the implementation of immunotherapeutic programs requires a clinical base with modern laboratories and specialists in the field of cell cultivation, immunology, molecular genetics and can only be implemented in specialized centers with high scientific potential [I.S. Dolgopolov, G.Z. Chkadua, 2018].

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