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Immunohistochemical Markers in the Assessment of Tumor Response

Mozerov S.A.[1], Komin Yu.A.[2], Yuzhakov V.V.[1], Pashkin S.B.[3], Larkin A.A.[4], and Mozerova E.S.[1]

[1]National Research Nuclear University MEPhI (Moscow Engineering Physics Institute), Kashirskoe shosse 31, Moscow, 115409, Russia
[2]Military medical facility, Moscow, Russia
[3]Herzen State Pedagogical University of Russia, Saint-Petersburg, Russia
[4]Biosintez PJSC, Sun Pharmaceutical subsidiary, Penza, Russia

Abstract

The examination of the possibility of using immunohistochemical and molecular genetic markers as predictors of effectiveness of neoadjuvant chemoradiotherapy (NCRT) and prognostic factors of the disease state. The study included 21 patients with locally advanced gastric cancer. All patients underwent the NCRT followed by gastrectomy D2. We analyzed the expression of HER2 / neu marker, Ki-67, p53, Cyklin D1, E-cadherin in biopsy (before therapy) and the operating material (after chemoradiotherapy and the treatment gap). We have found statistically significant decrease in the expression of Ki-67 markers and Cyklin D1, a trend towards to a decrease of p53 expression after the NCRT. The dynamics of expression of immunohistochemical markers examination is a promising approach in search for predictors of NCRT effectiveness for patients with locally advanced gastric cancer.

Keywords: neoadjuvant chemoradiotherapy, immunohistochemical markers, molecular genetic markers, therapeutic pathomorphism, gastric cancer.

Corresponding Author:
Komin Yu.A.
yura.komin@yandex.ru

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1. Introduction

According to a WHO report in 2014, the oncological diseases are one of the leading causes of death worldwide. In 2012, about 14 million new cases of cancer and about 8.2 million deaths from malignant neoplasms were detected [1].

Today, treatment of a malignant tumor often involves neoadjuvant radiotherapy and/or chemotherapy. The tactics of managing the patient and the prognosis of the course of the disease after neoadjuvant therapy largely depends on the degree of therapeutic pathomorphism of the tumor-the tumor response. With an incomplete (partial) response of the tumor to treatment, the choice of further tactics becomes ambiguous. This circumstance dictates the need to search for new methods for studying therapeutic pathomorphosis, in particular, to the study of the possibility of using IHC

for it. It is expected that a change in the content of different markers in resected tissues after treatment may allow more accurate assessment of the degree of pathomorphosis and determine the prognosis, as well as adjust the patient management tactics.

The use of an immunohistochemical method of staining the slices to evaluate the pathomorphism of neoplasia after neoadjuvant therapy primarily concerns the proteins of cell proliferation (Ki-67, PCNA, EGFR, CyclinD1, COX-2, $p57^{kip2}$, AURKA, HER2), apoptosis (BAX, bcl-2, p53), cell adhesion (E-cadherin), and also angiogenesis (VEGF).

The high efficacy of antitumor therapy was indicated by a decrease in proliferative activity, which was accompanied by a decrease in expression of Ki-67 and PCNA markers in neoplastic cells [2].

CyclinD1 and E-cadherin are among the least studied markers in the evaluation of pathomorphosis.

One of the main problems of managing patients receiving neoadjuvant therapy for cancer is evaluation of the results of therapy and predicting the course of the disease. There are many classifications and systems for assessing therapeutic pathomorphosis, but none of them takes into account the results of immune staining of tumor tissue. At the same time, contradictory data, which were obtained by different researchers, indicate the possible importance of immunohistochemical staining for the evaluation of pathomorphosis. In addition, for this purpose it is necessary to develop a system of complex analysis, including the inclusion of clinical, pathomorphological and molecular-genetic parameters [3].

2. Materials and methods

The study included 21 patients with morphologically verified diagnosis of stomach cancer. The average age of the patients was 61 years; 10 men and 11 women. All patients were NCRT with further D2 gastrectomy. Preparation of material for histological and immunohistochemical studies were performed according to standard protocols.

3. Results

When evaluating changes in the expression of markers Ki-67, p53, Cyklin D1 we have identified that the majority of patients following NCRT a decrease in expression of these markers by tumor cells. 19 (90,4%) patients showed a reduction of expression of Ki-67, 12 (57%) - the decrease in the expression of p53, and 16(76.2 %) - a decrease in the expression Cyklin D1. The increase in the expression of p53 was observed in

3(14.5%) and Cyklin D1 – 2(9.5%) patients. The increase in the expression of Ki-67 were detected only in one patient (4.8 per cent). Expression of the marker HER2/neu in the majority of patients 12(57,1%) remained unchanged, 9 (42,9%) patients noted a decrease in the expression of this marker. In 18 (85,7%) did not change the expression of E-cadherin. The data obtained are presented in table 1.

Table 1: Dynamics of changes in expression of immunohistochemical markers in patients with gastric cancer after neoadjuvant chemoradiotherapy.

	The decrease in the expression	The increase in the expression	Expression unchanged
p53	12(57%)	3(14,5%)	6(28,5%)
Cyklin D1	16(76,2%)	2(9,5%)	3(14,3%)
Ki-67	19(90,4%)	1(4,8%)	1(4,8%)
E- cadherin	3(14,3%)	-	18(85,7%)
HER2/neu	9(42,9%)	-	12(57,1%)

4. Discussion

In the present study an attempt was made to assess changes in the expression of the immunohistochemical markers. It is shown that in operating the material in comparison with biopsy revealed a statistically significant decrease in the number of cells that express Cyklin D1 and Ki-67, the downward trend of the expression of marker p53, indicating a decrease in the malignant potential of the tumor.

5. Conclusion

The search for new markers of tumor response in the combination therapy of gastric cancer is an important issue. Therefore, further research is needed to study the prognostic and predictive value of a wide panel of immunohistochemical markers, as well as confirmation of the results obtained in randomized trials.

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