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Molecular-genetic markers of the oral mucositis development in squamous cell cancer patients

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Abstract

The aim of the study is to investigate molecular-genetic markers of oral mucositis development in squamous cell cancer patients. Combined and complex treatment of patients with oral mucous layer cancer was performed according to the standards of treatment of malignant neoplasms as a method. The results of the hybridization were registered with a universal hardware and software complex (UAPC) for the analysis of the images obtained from the diagnostic microarrays. In conclusion, oral mucositis remains one of the most serious and often registered complications after antitumor therapy that significantly decreases the quality of life of oncologic patients.

Keywords: Mucositis, Polymorphism, Genes of Xenobiotic Detoxication.

Marcadores moleculares y genéticos del desarrollo de la mucositis oral en pacientes con cáncer de células escamosas

Resumen

El objetivo del estudio es investigar los marcadores moleculares y genéticos del desarrollo de la mucositis oral en pacientes con cáncer de células escamosas. El tratamiento combinado y complejo de

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pacientes con cáncer de la capa mucosa oral se realizó de acuerdo con los estándares del tratamiento de neoplasias malignas como método. Los resultados de la hibridación se registraron con un complejo universal de hardware y software (UAPC) para el análisis de las imágenes obtenidas a partir de los microarrays de diagnóstico. En conclusión, la mucositis oral sigue siendo una de las complicaciones más graves y con frecuencia registradas después de la terapia antitumoral que disminuye significativamente la calidad de vida de los pacientes oncológicos.

Palabras clave: mucositis, polimorfismo, genes de la desintoxicación xenobiótica.

1. INTRODUCTION

The rate of oncologic diseases in Russia is constantly increasing. By the end of 2015, its increase for the period 2005-2015 was roughly 20.4% per every 100,000 people. According to the data of International cancer association, in the structure of world oncologic morbidity, malignant tumors of the head and neck and hemoblastosis represent a significant group of neoplasms characterized by progressive growth. An evident tendency towards the increase in the morbidity, high mortality rates in patients with the head and neck tumors and hemoblastosis, high rate of disabilities in patients contribute to a significant social-economic damage that is caused by these diseases and lead to the necessity in searching for new methods of the increase in the quality of medical care for patients with these pathologies.

The enhancement of the aggressiveness of antitumor treatment, in particular, simultaneous chemo radiotherapy, is accompanied by the

alteration of the surrounding healthy tissues. The rate of the associated complications, including those that are located in the oral cavity, remains quite high and reaches 100% of cases.

Oral mucositis remains one of the most severe and widespread complications after antitumor therapy, which significantly reduces the quality of life of cancer patients. The development of mucositis leads to the interruption of antitumor therapy and the decrease in its effectiveness, which unfavorably influences the disease prognosis. Besides, mucositis significantly increases the cost of the cancer patient's treatment and the period of hospitalization. Presently, the existing methods of prevention and treatment of oral mucositis are often complicated and multicomponent, require expensive equipment and long-term preparation of the specialists. Often, the recommended groups of drugs are produced abroad, which contributes to their high cost. Thus, there is a necessity in the search for and development of highly effective and available means of prevention and treatment of different forms of oral mucositis for the enhancement of the effectiveness of antitumor therapy and increase in the quality of life of cancer patients.

Mucosit of the Multinational Association of supportive care in cancer (MASCC) and International society of oral oncology (ISOO) developed practical clinical recommendations on the treatment of oral mucositis based on the systematic literature review. Treatment of oral mucositis is divided into the following sections: provision of nutrition, pain control, oral antiseptics, and palliative treatment of xerostomia

and prevention of oral bleeding. Presently, the authors study several types of the means of prevention of mucositis and treatment of oral mucositis: anti-inflammatory drugs, antimicrobial drugs, modifications of the immune response, antioxidants and non-pharmacologic methods. Thus, a search for new approaches to the prevention and treatment of oral mucositis remains an acute research task. But any approach to the prevention and treatment must be based on the etiopathogenetic mechanisms of the development of oral mucositis. In the present work, the molecular-genetic aspects will be explored as the risk factors (Galloway, 2014).

2. METHODOLOGY

The aim of the present study was to perform a pilot study on the identification of the prognostic significance of the incidence rate of the alleles in the genes that encode the enzymes of biotransformation and xenobiotics detoxication and the genes of the immune response in oncologic patients with oral mucositis. From January 2016 to January 2018, the authors performed a genetic study that included 23 patients that were diagnosed with squamous cancer of the oropharyngeal region in the department of radiotherapy in the Russian scientific center of radiology and nuclear medicine. The average age of the patients with morphologically verified diagnosis squamous cancer of the oropharyngeal region was 54 years old.

The study included 60.9% (n=14) of men and 39.4% (n=9) of women. The cancer was localized in tongue (30.4%), oropharynx (26.1%) and oral cavity (17.4%). The majority of the patients had cancer stage T2N0M0 (39.1 %), T3N0M0 (17.4 %) and T3N1M0 (21.7%). The aggravated somatic anamnesis was observed in the majority of patients older than 50 years old. More than half of the patients (65.2%, 15 patients) had associated chronic diseases, among them, patients with several pathologies prevailed (78.3%): cardiovascular diseases, chronic non-specific lung diseases, pathologies of the gastrointestinal tract, diabetes mellitus (Farrokhi, 2017).

Combined and complex treatment of patients with oral mucous layer cancer was performed according to the standards of treatment of malignant neoplasms. All the patients were given recommendations on the means of individual hygiene of the oral cavity and the technique of teeth cleaning. Since the patients' examination was performed 1-2 days before the start of radio or chemotherapy, the authors were limited in the invasive means of treatment and prevention of stomatological diseases because of the potential risk of the development of complications. Those patients that had sharp teeth edges received partial teeth polish and treatment of caries and its complications with conservative methods (Ivanova, 2016; Nebert, 2013).

The diagnostics of mucositis and identification of its grade in patients was performed by the scale proposed by the American Radiation Therapy Oncology Group (RTOG) for the evaluation of

changes in the mucus (Table 1, note: the mentioned criteria is used only for the evaluation of acute reactions to the radiotherapy (from the 1st to the 30th day of the radiotherapy)) (Ulrich, 2001). The symptoms of the disease were not considered during the evaluation of the acute response to the radiotherapy. Any reaction to the radiotherapy that caused lethality was estimated as Grade 5. In all the patients, the grade of mucositis was identified and registered every 2nd-3rd day at the fraction dose 0Gy (before the radiotherapy), 6Gy, 10Gy, 16Gy, 20Gy, 26Gy, 30Gy, 36Gy, 40Gy, 46Gy, 50Gy.

Table 1: Evaluation of the severity of oral mucositis by the RTOG scale

Grade				
0	1	2	3	4
No changes in comparison with the initial status	Hyperemia, weak pains (no need in analgesic)	Focal mucositis with possible production of serosanguineous discharge, edema, mild pains can be observed (analgesics are required).	Expressed fibrinous mucositis, severe pains can be observed (narcotic analgesics are required)	Ulcerm necrosis, bleeding

All the patients were indicated herbal drugs for the prevention and treatment of oral mucositis. The treatment plan included their application in combination with everyday sanitation by a dentist, i.e. irrigation of mucus under pressure, application of herbal drugs of prolonged effect.

3. RESULTS

The results of the study are presented in Table 2 and 3:

Table 2: The results of the microarray assay by the genes of metabolism and biotransformation of xenobiotics in the studied groups

Gene, variant, genotype		Group I	Group II	P (additive model) OR 95% CI
		N (%)	N (%)	
CYP1A1 4887 C>A rs1799814		n = 14	n = 9	0.19 17.69 1.20 – 259.80
	C/C	14 (100)	7 (77.8)	
	C/A	0(0)	0 (0)	
	A/A	0(0)	2 (22.2)	
CYP1A1 4889 A>G rs1048943		n = 14	n = 9	0.19 17.69 1.20 – 259.80
	A/A	14 (100)	7 (77.8)	
	A/G	0 (0)	0 (0)	
	G/G	0 (0)	2 (22.2)	
CYP1A1 6235 T>C rs4649903		n = 14	n = 9	0.494 1.84 0.50 – 6.76
	T/T	9 (64.2)	6 (66.6)	
	T/C	5 (35.8)	3 (33.3)	
	C\C	0 (0)	0 (0)	
CYP2D6 1934 G>A rs3892097		n = 14	n = 9	0.728 1.41 0.38 – 5.27
	G/G	10 (71)	6 (66.7)	
	G/A	2 (14.5)	1 (11.1)	
	A/A	2 (14.5)	2 (22.2)	
MDR 3435 C>T rs1045642		n = 14	n = 9	0.761 0.77 0.23 – 2.59
	T/T	5 (35.7)	4 (44.4)	
	C/T	7 (50.0)	4 (44.4)	
	C/C	2 (14.3)	1 (11.1)	
NAT2 341 T>C rs1801280		n = 14	n = 9	0.378 0.55 0.17 – 1.79
	T/T	3 (21.4)	4 (44.4)	
	T/C	7 (50.0)	3 (33.3)	
	C/C	4 (28.6)	2 (22.2)	
NAT2 590 G>A		n = 14	n = 9	0.666

rs1799930	G/G	11 (78.5)	6 (66.7)	1.67 0.34 – 8.19
	G/A	3 (21.5)	3 (33.3)	
	A/A	0 (0)	0 (0)	
MTHFR 677 C>T rs1801133		n = 14	n = 9	0.739 0.71 0.19 – 2.71
	C/C	6 (42.9)	5 (55.5)	
	C/T	8 (57.1)	4 (44.5)	
	T/T	0 (0)	0(0)	
CYP2C9 430C>T rs1799853		n = 14	n = 9	0.144 0.15 0.01 – 2.15
	C/C	10 (71.4)	9 (100)	
	C/T	4 (29.6)	0 (0)	
	T/T	0 (0)	0 (0)	

Table 3: Results of the microarray assay by the genes of the immune response in the studied groups

Gene, variant, genotype		Group I	Group II	P (additive model) OR 95% CI
		N (%)	N (%)	
PTPN22 1693C>T Arg620Trp rs2476601		n = 14	n = 9	1.00 0.75 0.14 – 3.99
	G/G	10 (71.4)	7 (77.8)	
	A/G	4 (28.6)	2 (22.2)	
	A/A	0 (0)	0 (0)	
TLR2 2258G>A Arg753Gln (rs5743708)		n = 14	n = 9	0.513 –
	G/G	12 (85.7)	9 (100)	
	G/A	2 (14.3)	0 (0)	
	A/A	0 (0)	0 (0)	
TLR4 896A>G Asp299Gly rs498679)		n = 14	n = 9	0.513 –
	A/A	12 (85.7)	9 (100)	
	A/G	2 (14.3)	0 (0)	
	G/G	0 (0)	0 (0)	
TLR4 1196C>T Thr399Ile rs4986791		n = 14	n = 9	0.513 –
	C/C	12 (85.7)	9	

			(100)	
	C/T	2 (14.3)	0 (0)	
	T/T	0 (0)	0 (0)	
IL4 589C>T rs2243250		n = 14	n = 9	–
	C/C	14 (100)	9 (100)	
	C/T	0 (0)	0 (0)	
	T/T	0 (0)	0 (0)	
IL4 33C>T rs2070874		n = 14	n = 9	0.008 10.40 2.02 – 53.42
	C/C	12 (85.7)	4 (44.4)	
	C/T	2 (14.3)	2 (22.2)	
	T/T	0 (0)	3 (33.3)	
IL10 1117A>G rs1800896		n = 14	n = 9	0.072 0.29 0.08 – 1.00
	A/A	2 (14.3)	4 (44.4)	
	A/G	8 (57.1)	5 (55.6)	
	G/G	4 (28.6)	0 (0.0)	

«–» the obtained distribution of the genotypes incidence rates did not allow the authors to perform statistical analysis. Table 2 shows that there were no statistically significant results obtained in all the studied alleles of the genes of metabolism and detoxication of xenobiotics. Table 3 shows a polymorphic variant of the gene IL4 (rs2070874) associated with the risk of the development of severe oral mucositis. Patients with squamous cancer in the oropharyngeal region that received antitumor therapy and local treatment of oral mucositis with herbal drugs of the prolonged effect had oral mucositis of different grade. That was the criterion for their distribution into two groups: group I included the patients with a 0-2 grade of mucositis by

the RTOG scale, group II included the patients with a 3-4 grade of mucositis by the RTOG scale.

Both groups were not statistically different by other risk factors for the development of complications after antitumor treatment (age, sex, cancer stage, process localization, a method of treatment stomatological risk group). The allele rs2070874-T of the gene IL4 appeared to be associated with the development of severe oral mucositis. This variant is located on the promoter part of the gene that encodes anti-inflammatory cytokine IL4 and can influence its expression.

4. DISCUSSION

Chemo and radiotherapy are one of the main methods of treatment of cancer patients. Combination of these two antitumor therapies increases the rate and severity of the side effects that can lead to severe mucositis and involve into this process all the components of the oral cavity: the mucosa, minor and major salivary glands, bone structures with obligatory alterations in teeth. Identification of prognostic factors for the development of oral mucositis can determine the methods of prevention and treatment of oral mucositis because only etiopathogenetic treatment can have maximum effect. Presently, there are some scientific publications that describe different risk factors or etiological factors that contribute to the development of oral mucositis.

According to some data, the most important factors of the development of complications in the oral cavity are total radiation dose and antitumor drugs, ways and dosing schedule. The prevention of oral mucositis development can only be based on the controlled doses of the radiation, i.e. the only interruption of the radiotherapy can be really effective for patients with oral mucositis. Certainly, such an approach exists, but its implementation into the clinical practice would mean the planned interruption of the course of antitumor therapy, which will negatively influence the prognosis of the main disease.

According to Gevorkov (2016), the effectiveness of antitumor therapy primarily depends on the initial status of the patient. Different authors specify several groups of factors that contribute to the development of complications after antitumor therapy (Keefe, 2007). The first group of the risk factors of the early development of severe side effects includes atrophy and grave psychological status of a patient, senior age, associated diseases, injuries of the oral cavity and pharynx mucosa, caries, expressed pain syndrome, smoking, and alcohol drinking. Another group of risk factors for the development of side effects includes the characteristics of the neoplastic process. The localization in the oral cavity and pharynx and significant local spread of the malignant neoplasm indicate a high possibility of the development of side effects after the chemotherapy. The third group of risk factors combines the parameters of antitumor therapy.

Expressed side effects are expected to appear in patients who receive high total radiation doses (total boost dose 50Gy), non-

traditional mode of fractioning with intensive dosing, combined radio, and chemotherapy, preliminary induction chemotherapy, vast areas of exposed tissues. According to Semin et al (2011), there are three groups of factors in the etiology of the development of alterations in the oral cavity: a) Condition and the products of metabolism in the dental deposit and plaque; b) factors of the oral cavity that can strengthen or weaken the pathogenetic potential of microorganisms and their metabolism; c) general factors that regulate metabolism in the tissues of the oral cavity that initiate the response reaction to the pathogenic influence (Mortensen, 2013).

The risk factors can also include genetic peculiarities (polymorphism) that can change as a response to the radio or chemotherapy. For example, the metabolism of methotrexate is associated with the gene MTHFR which has three variants of polymorphism (CC, CT and TT). Ulrich et al. in their study showed that during the preventive treatment with methotrexate after the GVHD allogenic transplantation of bone marrow, 220 patients with chronic myeloleukemia had a higher risk of mucositis development if they had a TT variant of the gene MTHFR. It is known that the development of carcinomas of the head and neck are primarily associated with the increase in the oncogenic load in smokers and alcohol abusers. Enzymes of the cytochrome P450 play an important role in the realization of oncogenic risks because they metabolize and inactivate carcinogens. However, due to individual peculiarities of the system of detoxication, these enzymes can increase the carcinogenic potential of some chemical substances. Hence, the study of the genetic variants of

the enzymes of cytochrome P450 is relevant in the aspect of the development of different types of cancer.

Besides, the spread of smokers among the population in the Russian Federation varies around 40%, however, not all of the smokers develop oncologic diseases of the head and neck and some non-smokers do. Thus, it can be suggested that there are other factors that influence the neoplastic transformation of epithelial tissue in the upper respiratory tracts. So, the mechanisms that underlie the development of carcinomas and include complicated interactions with the immune system, different suppressors of the neoplasm process, growth factors, and detoxication systems require detailed studies.

The authors did not find any published data on the possible association between genetic factors and the severity of oral mucositis. The role and significance of genetic factors in the development of radio and chemotherapy-induced mucositis is understudied, which makes it an acute research issue. Some authors highlight that genetic factors are often involved in the development of respiratory infectious diseases, but their study results are controversial in replications. The authors found 386 studies (out of the total 24 823) in four bibliographic databases, conducted a meta-analysis of the studies on TB, influenza, respiratory syncytial virus, ARVI coronaviruses, and pneumonia. One single nucleotide polymorphism from the gene IL4 was significant for these respiratory infections (rs2070874; 1.66). IL4- TLR2 – the core CCL2 can be an interesting marker used in clinical practice. Still, this

conclusion is based on insufficient evidence, 95% of the identified studies were biased or confusing.

Other authors also evaluated the role of genetic variations in the sensitivity to several respiratory infectious diseases (TB, influenza, respiratory syncytial virus, SARS coronavirus, and pneumonia). It was established that the allele of the gene IL4 2070874-T was the only variant associated with the respiratory infections in the united group (TB and respiratory syncytial virus). IL4 rs2243250 T-allele, that is in full imbalance by the binding with rs2070874-allele T ($r2 = 1.0$), is an NP sensitive allele in the present study. Thus, it can be suggested that the obtained data on IL4 are not accidental. This gene can be associated with the development of oral mucositis of the moderate and severe grade.

5. CONCLUSION

The growth of the median of survival rate in oncologic and oncohematologic patients confirms the decrease in the incidence rate of relapse and increase in the average length of life, which is explained by the implementation of new approaches and methods of treatment, optimization of chemotherapy plans, and application of conformal radiotherapy. However, despite the successful results obtained in the early diagnostics and treatment of oncologic diseases, the observed tendency to the increase in the aggressiveness of antitumor therapy, in particular, combined radio and chemotherapy, is inevitably associated

with temporary or permanent alterations in the surrounding tissues. Oral mucositis remains one of the most serious and often registered complications after antitumor therapy that significantly decreases the quality of life of oncologic patients.

Presently, the existing methods of prevention and treatment of oral mucositis appear to be ineffective. The methods described in the literature are complicated, multicomponent, require expensive equipment and long-term training of the specialists. The recommended drugs are often produced abroad, which contributes to their cost. Thus, despite the variety of existing methods of prevention and treatment of mucositis, the search for new effective and available methods remains relevant. The method of prevention and treatment of oral mucositis can be effective only when it has etiopathogenetic grounds. The patients with different grade of oral mucositis, who were included in one group of stomatological risk and who followed similar recommendations of the dentist, had a different incidence rate of polymorphism in the genes of the immune response. Allele rs2070874-T of the gene IL4 is associated with the development of severe oral mucositis. This variant is located in the promoter part of the anti-inflammatory cytokine IL4 and can influence its expression.

The obtained results confirm the possibility that there could be genetic grounds for the development of oral mucositis in oncologic patients that receive antitumor therapy. The present pilot study determined the perspectives of this scientific and research direction of the studies on the evaluation of the prognostic significance of genetic

factors in the development of oral mucositis and creation of effective methods of its prevention and treatment based on the genetic screening. Such studies require a bigger sampling of patients.

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