UDC: 616.34-006.6
DOI: 10.52532/2663-4864-2022-3-65-47-51

THE ROLE OF MICROSATELLITE INSTABILITY IN COLORECTAL CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *According to Globocan 2020, colorectal cancer (CRC) incidence in Kazakhstan is lower than in all OECD countries except Mexico. However, the CRC incidence in Kazakhstan is steadily growing. In the structure of cancer incidence, CRC went up from 5th place in 2006 to 3rd place in 2021. More than 80% of tumors associated with Lynch syndrome were found to have microsatellite instability (MSI). Thus, MSI is detected in 12% of sporadic colon tumors., MSI in cancer is caused by a decreased activity of DNA repair genes due to hereditary and somatic causes.*

The study aimed to *systematize the current literature data to consider the need and adequacy of prescribing preventive chemotherapy, personalizing the treatment of patients, and predicting the course of the disease in CRC.*

Methods: *A review was made of the published results of scientific and clinical studies for 2006-2021 from the PubMed, MedLine, and Cancer Observe databases for the keywords "colon cancer," "microsatellite resistance," "adjuvant chemotherapy," "PCR study," "IGH-study."*

Results: *The value and adequacy of determining the IHC characteristics of the MSI status. The prognostic and predictive value of MSI in CRC has been proven. The optimal treatment options were selected depending on the status of MSI.*

Conclusion: *Tumors with certain MSI status should be classified as a separate group of malignancies. Instability status determination is preferred in case of suspected Lynch syndrome in patients with stage II CRC, as well as in clinical and histological features characteristic of MSI (proximal localization of the primary tumor, mucinous histotype, poorly differentiated tumors, lymphocytic infiltration of the tumor). Further determination of these tumors' molecular characteristics will help stratify patients who may respond differently to chemotherapy. Also, the MSI status determination can be an important prognostic marker in patients whose tumors have a somatic mutation in the BRAF gene.*

Keywords: *colorectal cancer (CRC), microsatellite instability (MSN).*

Introduction: According to Globocan 2020, colorectal cancer (CRC) incidence in Kazakhstan is lower than in all OECD countries except Mexico. However, the CRC incidence in Kazakhstan is steadily growing. In the structure of cancer incidence, CRC went up from 5th place in 2006 to 3rd place in 2021. Microsatellite instability (MSI) is found in more than 95% of tumors caused by Lynch syndrome and in more than 80% of tumors associated with Lynch syndrome. In particular, MSI is detected in 12% of sporadic colon cancer cases. At that, MSI in the tumor is caused by a decrease in the DNA repair activity that can be due to hereditary and somatic reasons.

To date, the identification of MSI in CRC is becoming increasingly popular. This study creates the prerequisites for more effective screening of patients with Lynch syndrome and allows for to resolution of the need for and adequacy of prescribing prophylactic chemotherapy. In addition, MSI analysis helps to detail the prognosis of the disease in patients whose tumors have a somatic mutation in the BRAF gene. Patients with CRC are divided into three groups depending on the nature of the modifications: high microsatellite instability (MSI-H), low microsatellite instability (MSI-L), and microsatellite stability (MSS).

The study aimed to systematize the current literature data to consider the need and adequacy of prescribing preventive chemotherapy, personalizing the treatment of patients, and predicting the course of the disease in CRC.

Materials and methods: A review involved published results of scientific and clinical studies for 2006-2021 from the PubMed, MedLine, and Cancer Observe databases for the keywords "colon cancer," "microsatellite resistance," "adjuvant chemotherapy," "PCR study," "IGH-study."

Results: Microsatellites are stretches of DNA that consist of tandem repeats of a simple sequence of 1-6 nucleotides. In 1993, 3 independent groups of researchers showed in the study of DNA in CRC that a significant part of tumors demonstrates the phenomenon of MSI, i.e., change in the number of repeated nucleotides compared to their number in DNA from normal tissue [1]. DNA repair system proteins include MSH2,

MSH6, MLH1, and PMS2. The first two proteins are responsible for finding mismatched bases in this system. These errors occur during the synthesis of the DNA strand by the polymerase. When the MSH2-MSH6 protein complex finds a mistake, a heterodimer, including MLH1 and PMS2, is added. Then, an exonuclease consisting of 4 proteins "approaches" the complex and ferments the DNA section containing the error. Next, the polymerase completes the DNA chain with correctly paired nucleotides [2].

Today, MSI is detected using two different approaches: immunohistochemistry (IHC) and methods based on the polymerase chain reaction (PCR). IHC examines MLH1, MSH2, MSH6, and PMS2 staining in tumor samples to determine the loss of protein expression that characterizes MMR-D as a surrogate of MSI. Molecular DNA testing using a PCR-based approach evaluates a specific panel of microsatellite markers, i.e., a panel of 5 features including two mononucleotides (BAT25/26) and three dinucleotides (D2S123, D5S346, and D17S250) markers to detect instability at these selected loci. Tumors are classified as MSI-H if 30% or more of the loci show instability, MSS if none of the microsatellite markers show instability, and MSI-low (MSI-L) if less than 30% of the features are unstable. If MSI (PCR-based method) or MMR-D (IHC-based method) is detected, further testing is recommended to identify carriers of germline mutations in the MMR gene.

PCR-based test and IHC are sensitive and specific for detecting MSI and have a high degree of agreement (>92%). Either test can be performed separately, or two tests can be used as a complementary approach to increase detection rates in cases that may be missed by one test (false negative results are approximately 5% to 10% for each) [3].

Colorectal tumors with MSI are associated with a higher life expectancy than those without MSI. A study of 175 patients with Lynch syndrome (120 patients with MLH1 type Lynch syndrome) compared with more than 14,000 patients with CRC showed that the 5-year cumulative relative survival of patients with Lynch syndrome was 65% compared with 44% of patients with sporadic CRC older than 65 years. The pooled analysis of MSI, which included 32 studies and 7642 cases of CRC, showed an overall hazard ratio of 0.65 for patients with MSI tumors. Patients with Lynch syndrome have a lower stage of the disease at screening compared to patients with other types of CRC, and patients with Lynch syndrome are less likely to develop metastases. Patients with MSI tumors have lower mortality rates when stratifying patients by tumor stage, including patients with stage IV cancer [3]. Approximately 3% of all cases of CRC are due to Lynch syndrome. At the same time, the first tumor in Europeans and North Americans develops mainly in the correct colon sections (60-80% of cases) [4].

The incidence of Lynch syndrome in Europeans is approximately 1:1000. Thus, up to 1,000,000 people in Europe have a pathogenic mutation in one of the DNA repair genes, which can lead to colon cancer with a probability of 70-75% [4, 5]. Moreover, tumors of the endometrium, urinary system organs, breast, small intestine, stomach, etc., may occur in such patients. The genetic diagnosis of Lynch syndrome is determined by the need for individual clinical monitoring of the patient, an extended set of surgical interventions in case of colon cancer, and the possibility of effective use of pembrolizumab as a targeted drug.

Discussion: To date, FDA had approved five PD-1 inhibitor drugs to treat various types of cancer. The first FDA-approved PD-1 inhibitor drug was pembrolizumab, a humanized IgG4 monoclonal antibody used for melanoma. In a phase I study, this drug was tested in patients with solid tumors and hemoblastoses, and patients with multiple solid tumors tolerated pembrolizumab well. Patients with advanced non-small cell lung cancer (NSCLC) with high PDL1 expression showed a significantly higher survival rate with minimal side effects than those receiving platinum-based chemotherapy. Among patients with CRC, pembrolizumab is highly beneficial for patients with mismatch repair deficiency or high CRC microsatellite instability (dMMR/MSI-H). Their progression-free survival reaches 78% compared to 11% in patients with good mismatch repair and microsatellite stability (pMMR/MSS). Nivolumab is another successful PD-1 inhibitor that has demonstrated a consistent response in patients with metastatic dMMR CRC (mCRC). Approximately 69% of these patients survive over 12 months. Interestingly, the combination of nivolumab with habiliment (CTLA4-targeted drug) shows a higher response rate of up to 94% in these patients. This suggests that the combination of immune checkpoint therapy can significantly increase the effectiveness of treating patients with dMMR/MSI-H mCRC [6].

Our immune system provides a natural defense against infection and disease. A new cancer treatment called immunotherapy is based on increasing the immune system activity, thus improving its ability to detect and destroy tumor cells. Immune drugs from the group of checkpoint inhibitors are used to treat colon cancer.

T-cells, a specific type of lymphocytes, are an essential element of the immune system. Their primary function is to destroy micro-objects harmful to the body, such as bacteria, viruses, and tumor cells. For that purpose, T-cells possess specific proteins on their surface.

When T-cell proteins meet specific proteins on the surface of tumor cells, a so-called immune checkpoint occurs. Instead of attacking the tumor cell, the T-cell is instructed to leave it alone. Drugs from the group of checkpoint inhibitors (nivolumab, pembrolizumab, ipilimumab) interfere with the interaction between the tumor cells and T-cell proteins. Here, nothing prevents T-cells from performing their function and destroying tumor cells [8].

Pembrolizumab is the most promising for patients with Lynch syndrome. Its efficiency was proved by high relapse-free and overall survival rates in such patients [6].

After initial successes in the treatment of melanoma, immunotherapy quickly established itself as the mainstream treatment for several types of solid cancers. Pembrolizumab and nivolumab, two antibodies that block programmed cell death 1 (PD1), have shown efficacy in patients with mCRC, characterized by mismatch repair deficiency and high microsatellite instability (dMMR-MSI-H). Unlike most other treatments for metastatic cancer, immunotherapy can achieve long-term stable remission in some patients, highlighting the great promise of immunotherapy in treating dMMR/MSI-H mCRC [7].

Thus, the determination of MSI in CRC is essential in patients under 45 years of age or patients with a burdened family history for further genetic diagnosis of Lynch syndrome since this syndrome is established only based on a hereditary mutation in one of the DNA repair genes. Moreover, the MSI status determination is indicated for patients with stage II CRC to decide on adjuvant chemotherapy and those with a BRAF gene somatic mutation to clarify the prognosis.

MSI is a crucial biomarker of CRC, with a significant diagnostic and prognostic value. Thus, testing for MSI status is critical in CRC and should be recommended for all patients with newly diagnosed CRC. MSI-H mCRC immunotherapy has changed the therapeutic scenario for patients with these tumors. It is one of the most significant changes in mCRC treatment practice, although its availability is limited to a small subset of patients. Due to the low prevalence of MSI-H mCRC, research in this area has been limited. Future efforts should be aimed at better characterizing these tumors to guide new treatment strategies and analyze the mechanisms of immunotherapy resistance, potentially extending relevant results to improve the treatment of MSS tumors [10].

Conclusion: To date, the detection of MSI in GI cancers is becoming a more reasonable and relevant issue in an individual approach to treating patients and predicting the course of the disease. This study contributes to the early diagnosis of patients with Lynch syndrome (by determining the MSI status) and answers the need for and adequacy of prescribing prophylactic chemotherapy.

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ТҰЖЫРЫМ

КОЛОРЕКТАЛЬДЫ ҚАТЕРЛІ ІСІК КЕЗІНДЕГІ МИКРОСАТЕЛЛИТТІК ТҰРАҚСЫЗДЫҚТЫҢ РӨЛІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Globocan 2020 деректері бойынша Қазақстанда колоректальды обырдың (КРК) жиілігі Мексикадан басқа ЭЫДҰ-ның барлық елдерінен төмен. Дегенмен, Қазақстанда КҚК сырқаттанушылық тұрақты түрде өсуде – 2006 жылғы онкологиялық аурулар құрылымында 5-ші орыннан 2021 жылы 3-ші орынға дейін. Линч синдромымен байланысты ісіктердің 80%-дан астамында микросателлиттік тұрақсыздық бар екені анықталды (MSI) анықталады. Көп жағдайда MSI спорадикалық тоқ ішек қатерлі ісігінің 12% жағдайда анықталады. Сонымен қатар, ісіктегі MSI пайда болу себебі ДНҚ жөндеу жүйесінің гендерінің белсенділігінің төмендеуі болып табылады, ол тұқым қуалайтын және соматикалық себептерге байланысты болуы мүмкін.*

Зерттеудің мақсаты: *профилактикалық химиотерапияны тағайындаудың қажеттілігі мен сәйкестігін, пациенттерді емдеуді жекелендіруді және КҚК кезінде аурудың ағымын болжауды қарастыру үшін қазіргі әдебиет деректерін жүйелеу.*

Әдістері: *PubMed, MedLine, Cancer Observe деректер базасынан 2006-2021 жылдарға арналған ғылыми-клиникалық зерттеулердің жарияланған нәтижелеріне шолу жасалды, «тоқ ішектің қатерлі ісігі», «микроспутниктік төзімділік», «адъювантты химиотерапия», «ПТР зерттеу» кілт сөздері үшін. , «IGH-study».*

Нәтижелер: *MSI мәртебесінің IHC-сипаттамасын қолданудың мәні мен сәйкестігі анықталды. CRC кезінде MSI болжамдық және болжамдық мәні дәлелденді. Оңтайлы емдеу нұсқалары MSI күйіне байланысты анықталды.*

Қорытынды: *Белгілі бір MSI статусы бар ісіктерді жеке МН тобына қою керек. Тұрақсыздық жағдайын анықтау Линч синдромына күдіктенген жағдайда, КҚК II сатысы бар емделушілерде, сондай-ақ МСИ-ге тән клиникалық және гистологиялық белгілерде (бастапқы ісіктің проксимальды локализациясы, муцинозды гистотип, нашар дифференциацияланған ісіктер, ісіктің лимфоцитарлы инфильтрациясы) қолайлы. Бұл ісіктердің кейінгі молекулалық сипаттамаларын анықтау химиотерапияға басқаша жауап беретін пациенттердің кіші тобын анықтауға көмектеседі. Сондай-ақ, MSI мәртебесін анықтау ісіктері BRAF генінде соматикалық мутацияға ұшыраған науқастарда аурудың болжамын анықтауға көмектеседі.*

Түйінді сөздер: *колоректальды қатерлі ісік, микросателлиттік тұрақсыздық.*

АННОТАЦИЯ

ЗНАЧЕНИЕ МИКРОСАТЕЛЛИТНОЙ НЕСТАБИЛЬНОСТИ ПРИ РАКЕ ТОЛСТОЙ КИШКИ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Согласно данным Globocan 2020, заболеваемость колоректальным раком (КРР) в Казахстане ниже всех стран ОЭСР, за исключением Мексики. Однако заболеваемость КРР в Казахстане неуклонно растет – с 5-го места в структуре онкозаболеваемости в 2006 г. до 3-го места в 2021 г. Выявлено, что в более чем 80% опухолей, ассоциированных с синдромом Линча, определяется микросателлитная нестабильность (МСН). В частности, МСН выявляется в 12% случаев спорадического рака толстой кишки. При этом причиной возникновения МСН в опухоли является снижение активности генов системы репарации ДНК, которая может быть обусловлена как наследственной, так и соматической причиной.*

Цель исследования *– систематизировать актуальные литературные данные для рассмотрения вопроса необходимости и адекватности назначения профилактической химиотерапии, персонификации лечения пациентов и прогнозирования течения заболевания при КРР.*

Методы: *Был проведен обзор опубликованных результатов научных и клинических исследований за 2006-2021 годы из базы данных PubMed, MedLine, Cancer Observe по ключевым словам «рак толстой кишки», «микросателлитная нестабильность», «адъювантная химиотерапия», «ПЦР-исследование», «ИГХ-исследование».*

Результаты: *Установлена ценность и адекватность применения ИГХ-характеристики статуса МСН. Доказано прогностическое и предиктивное значение МСН при КРР. Определены оптимальные варианты лечения в зависимости от статуса МСН.*

Заключение: *Опухоли с определенным статусом МСН следует выделить в отдельную группу ЗНО. Определение статуса нестабильности предпочтительно проводить при подозрении на синдром Линча, у пациентов со II стадией КРР, а также при свойственных для МСН клинико-гистологических особенностях (проксимальная локализация первичной опухоли, муцинозный гистотип, низкодифференцированные опухоли, лимфоцитарная инфильтрация опухоли). Дальнейшее выявление молекулярных характеристик данных опухолей будет способствовать выделению подгрупп пациентов, которые могут по-разному отвечать на химиотерапию. Также, определение статуса МСН может являться одних из важных прогностических маркеров у пациентов, в чьих опухолях выявляется соматическая мутация в гене BRAF.*

Ключевые слова: *колоректальный рак (КРР), микросателлитная нестабильность (МСН).*

Transparency of the study: *Authors take full responsibility for the content of this manuscript.*
Conflict of interest: *Authors declare no conflict of interest.*
Financing: *This study was financed under the STP no. BR11065390 (Targeted Financing of the Ministry of Healthcare of the Republic of Kazakhstan).*
Authors' input: *contribution to the study concept – Turkpenova I.T., Smagulova K.K.; study design – Shayakhmetova D.U., Dzhumanov A.I.; execution of the study– Smagulova K.K.; interpretation of the study – Yesenkulova S.A.; preparation of the manuscript – Turkpenova I.T.*
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