UDC: 616.33-006.6:615.37 DOI: 10.52532/2663-4864-2022-4-66-64-68

THE USE OF IMMUNE CHECKPOINT INHIBITORS IN TREATING LOCALLY ADVANCED AND METASTATIC GASTRIC CANCER: A LITERATURE REVIEW

M.S. Dmitrenko[1], K.K. Smagulova[1,2], R.Z. Abdrahmanov[1,2], R.K. Raskaliev[1], I.T. Turkpenova[1], E.P. Medetbekova[1], S.N. Kaldarbekov[1], A.O. Kuanysh[1], Zh.S. Kenzhebayeva[1], D.U. Shayakhmetova[2], A.Zh. Zhiyenbayeva[1], A.K. Dzhakipbaeva[2]

[1]«Kazakh Institute of Oncology and Radiology» JSC, Almaty, the Republic of Kazakhstan;
[2]«Asfendiyarov Kazakh National Medical University» NCJSC, Almaty, the Republic of Kazakhstan

ABSTRACT

Relevance: *Gastric cancer is one of the most common malignant neoplasms and ranks fifth in cancer incidence worldwide. The only curative approach to localized gastric cancer is radical surgery with or without prior chemotherapy. But chemotherapy is the main treatment method for metastatic or locally advanced gastric cancer. Later stages of gastric cancer are highly resistant to chemotherapy; therefore, there is a need for modern treatment approaches. Particular attention is paid to therapy for metastatic/locally advanced gastric cancer.*

The study aimed to *describe the possibilities of using immune checkpoint inhibitors (ICIs) to treat metastatic or locally advanced gastric cancer.*

Methods: *The data from modern literary sources of recent years were studied using specialized sci-entific search engines: Scopus, PubMed, Google Scholar, and Web of Science for the possibility of promising application of various immunotherapeutic approaches in treating metastatic or locally advanced gastric cancer.*

Results: *The article describes modern methods of treatment of metastatic or locally advanced SC using ICIs, including PD-1, PD-L1, and CTLA-4, demonstrates the mechanisms of immunological surveillance, characteristics of PD-1, PD-L1, CTLA-4, and their significance in suppressing the T-cell response. The effectiveness of using ICIs, particularly PD-1, PD-L1, and CTLA-4, has been es-tablished in the first and subsequent lines of therapy.*

Conclusion: *ICIs are a recent finding in antitumor therapy. Frequent resistance of gastric cancer to chemotherapy urges the use of ICIs to treat advanced gastric cancer.*

Keywords: *Immunotherapy of metastatic or locally advanced gastric cancer, immune checkpoint in-hibitors (ICIs), PD-1, PD-L1, CTLA-4, immune response mechanisms.*

Introduction: Gastric cancer (GC) is one of the most common malignant neoplasms and ranks fifth in the structure of cancer incidence in the world [1]. The only curative approach to localized gastric cancer is radical surgery with or without prior chemotherapy. However, with metastatic or In locally advanced gastric cancer, chemotherapy is the primary treatment [2]. According to modern sources and clinical guidelines, the use of combined chemotherapy regimens increases the objective response rate (ORR) and overall survival (OS) compared with monotherapy. At the same time, the use of combined chemotherapy regimens does not give significant practical results due to their high toxicity. In the later stages of gastric cancer, there is high resistance to chemotherapy, so there is a need to search for modern treatment approaches. This article studies the use of immune checkpoint inhibitors (ICIs) in therapy, in particular, PD-1 (Programmed cell death-1), PD-L1 (Programmed death-ligand 1), CTLA-4 (Cytotoxic T – lymphocyte-associated protein 4). Monoclonal antibodies that block PD-1, PD-L1, and CTLA-4 are currently the most studied [3]. ICIs can be used as monotherapy or as part of combination therapy. This drug therapy has become a breakthrough in treating solid tumors, including gastric and colorectal cancer [4]. This review explores the prospects and emerging pathways for using immunotherapy to treat gastric cancer, especially in its metastatic/locally advanced forms.

The study aimed to describe the possibilities of using immune checkpoint inhibitors (ICI) to treat metastatic or locally advanced SC.

Materials and methods: The data from peer-reviewed sources published over the past ten years and indexed in the scientific search engines Scopus, PubMed, Scholar, Web of Science, and Google were studied. A total of 89 sources, including research articles and NCCN Clinical Guidelines in Oncology (NCCN Guidelines®), were analyzed for study keywords. Of these, 18 sources were included in the analysis, which considered the mechanisms

of avoidance of protective immune responses by the tumor cell and the use of immunotherapy in treating metastatic or locally advanced gastric cancer.

Results:

Immunosurveillance

Every day in the human body, cells are formed with signs of tumor cells, which are destroyed by the human immune system due to the body's immunological control over tumor cells [5]. Without exception, all tumor cells are potentially immunogenic and trigger the mechanisms of the immune system to recognize and destroy cancer cells [6]. One of these well-known subpopulations is T-killers, which can destroy defective body cells. They are also called cytotoxic lymphocytes (CD8+T lymphocytes).

Immunoscape

However, the immune system does not always have sufficient influence because the tumor has properties that prevent the immune system from recognizing and destroying cancer cells. The mechanism for avoiding immunological surveillance may be the production of several co-inhibitory receptors by the cancer cell [4, 7]. For example, PD-1 and CTLA-4 receptors bind to tumor cell ligands (PD-L1 ligand) and inhibit T cell activation. Figure 1 shows the presence of the PD-1 protein on the surface of T-lymphocytes.

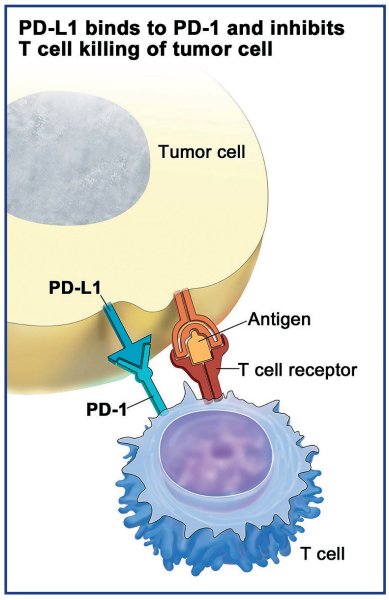

Figure 1 – Expression of a transmembrane protein, PD-L1 ligand, on tumor cells [8]

Antitumor effect of ICI immunity in the treatment of solid tumors, including gastric cancer

Monoclonal antibodies that block ligands or receptors of immune checkpoint inhibitors were developed to overcome this phenomenon. ICIs inhibit negative T-cell co-stimulation, resulting in a T-cell response. Thus, the antitumor effect is achieved due to the activation of one's immune system and not through the effect on tumor cells (Figure 2).

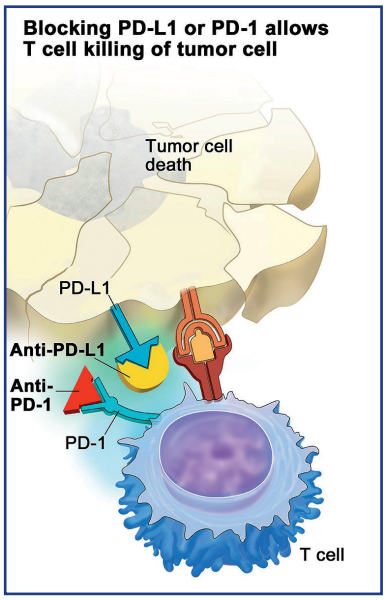

Figure 2 – ICIs' mechanisms of action [9]

Currently, ICIs provide reliable clinical results in treating metastatic or locally advanced gastric cancer [10].

Immunotherapy in anti-PD-1/PD-L monotherapy

In the ATTRACTION-2 phase III trial, anti-PD-1 ICIS (nivolumab) was used as monotherapy in patients with locally advanced or metastatic gastric cancer after two or more lines of chemotherapy. Improved OS compared to placebo (median OS 5.26 vs. 4.14 months). The median time to progression (TTP) was 1.61 months vs. 1.45 months. The ORR was 11.2% vs. 0%; p<0.0001. These results led to the approval of nivolumab in Asian countries. The analysis showed that the expression status of PD-L1 on tumor cells did not affect the OS of patients with locally advanced or metastatic gastric cancer in the phase III ATTRACTION-2 study. Of the undesirable effects, there was a decrease in appetite, diarrhea, and general fatigue [11].

In the KEYNOTE-059 phase II study, three cohorts of patients with advanced gastric cancer/CEC were identified who received three or more lines of chemotherapy. We want to focus on the first largest cohort of patients (n=259) who received anti-PD-1 ICI therapy in mono mode (pembrolizumab) as the third and subsequent lines of therapy. The ORR was 15.5% for patients with PD-L1-positive tumors (CPS≥1) and 6.4% for patients with CPS<1. The median OS was 5.6 months [12].

In the JAVELIN 300 phase III study, an anti-PD-L1 antibody (avelumab) showed no improvement in OS compared with third-line chemotherapy in patients with locally advanced or metastatic gastric cancer [13].

The KEYNOTE-061 phase III randomized trial studied the efficacy of an ICI drug (pembrolizumab) compared with chemotherapy in patients with metastatic PD-L1 CPS≥1 with locally advanced or metastatic gastric cancer after 1st line chemotherapy. The median OS was 9.1 months when using ICI vs. 8.3 months during chemotherapy [14].

In the ATTRACTION-02 Asian phase III study, the role of nivolumab in the treatment of advanced gastric cancer after two lines of therapy was evaluated in 493 patients, regardless of PD-L1 status. In patients treated with nivolumab compared with placebo, the ORR was 11.4%, with an improvement in OS (median OS, 5.3 vs. 4.1 months). After one year, 26.2% of patients treated with nivolumab were alive compared to 10.9% in the placebo group [11]. Based on these results, nivolumab was approved as a monotherapy in Japan in 2017. In Europe, the approval was rejected since the population included only patients from Asian countries.

In the KEYNOTE-012 study (the first trial of an anti-PD-1 antibody for the treatment of gastric cancer), pembrolizumab was used in the second and subsequent lines to treat metastatic gastric cancer, with an objective response rate of 22%, a median OS of 11.4 months was obtained. [15].

Anti-PD-1/PD-L1 antibodies plus chemotherapy

In the KEYNOTE-062 study, chemotherapy in combination with anti-PD-L1 (pembrolizumab) showed no benefit in terms of OS and TTP in both populations (CPS≥1 and CPS≥10). However, the ORR was higher in the pembrolizumab plus chemotherapy group (49% vs. 37% for CPS≥1).

ESMO 2020, ASCO 2021, and ASCO – GI 2022 presented significant results from CHECKMATE-649, a global phase III trial of first-line combination immunotherapy of PD-1 co-inhibitors (nivolumab) and CTLA-4 (ipilimumab) without chemotherapy and CTLA-4 (ipilimumab) in combination with chemotherapy vs. chemotherapy alone. The large population of 1581 patients with locally advanced gastric cancer (histological type adenocarcinoma) included 24% Asians and 76% non-Asians. 60% of patients treated with chemotherapy (n=955) had a PD-L1 CPS ≥ 5. Combination treatment with CTLA-4 (ipilimumab) plus chemotherapy for PD-L1 CPS≥5 provided a significant improvement in median OS (14, 4 months vs. 11.1 months in patients receiving chemotherapy alone). The median TTP was 7.7 months vs. 6.0 months. Survival rates at 12 months with PD-L1 CPS≥5 were significantly higher in the nivolumab plus chemotherapy combination group compared to chemotherapy alone (57% vs. 46%). All CPS≥5 subgroups improved ORR in response to nivolumab plus chemotherapy. The combination of nivolumab plus ipilimumab without chemotherapy showed no clear benefit in terms of OS compared with chemotherapy alone.

Based on these results, the Food and Drug Administration (FDA) and Taiwan food and drug Administration (TFDA) have approved nivolumab in combination with chemotherapy in patients with advanced/metastatic gastric cancer regardless of PD-L1 CPS status in the US and Taiwan, respectively. In Europe, the European Medicines Agency (EMA) has approved nivolumab in combination with chemotherapy in patients with PD-L1 CPS≥5. These results allow patients with advanced or metastatic gastric cancer to access promising, effective ICI immune response therapy in a first-line setting.

The ORIENT-16 Asian phase III trial studied a placebo-controlled PD-1 inhibitor (sintilimab) in combination with chemotherapy (XELOX) in 650 patients with advanced gastric adenocarcinoma (61% with PD-L1 CPS≥5). As presented at ESMO 2021, early results show a survival benefit of combination therapy in all randomized patients compared to chemotherapy plus placebo (median OS 15.2 vs. 12.3 months), with longer TTP and higher ORR [16]. This effect was even more evident in the group of patients with PD-L1 CPS≥5 tumors (median OS 18.4 vs. 12.9 months) [16].

The JAVELIN Gastric 300 trial compared avelumab with chemotherapy as a third-line treatment in patients with advanced gastric cancer. In 371 randomized patients, the primary endpoint (improvement in OS: median OS 4.6 vs. 5.0 months) and the secondary endpoints of OS and ORR were not met. However, avelumab was safer than chemotherapy [15].

Anti-PD-1 antibody plus anti-CTLA4 antibody

The CheckMate-032 study compared the ORR of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (ORR – 24%) with nivolumab 3 mg/kg plus 3 mg/kg . kg of ipilimumab (ORR – 12%) [17].

The CheckMate-649 phase III study included a cohort treated with nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) vs. chemotherapy. The combination of nivolumab plus ipilimumab did not improve OS compared with chemotherapy in patients with PD-L1 CPS≥5 (median 11.2 months vs. 11.6 months). Regardless of PD-L1 expression, a combination of nivolumab plus ipilimumab produced a median OS of 2.8 months compared with 6.3 months after chemotherapy. ORR was lower in the nivolumab plus ipilimumab group (27%) compared with chemotherapy (47%) for CPS≥5 in all randomized populations.

The ATTRACTION-6 phase III trial is currently underway. Study of the combination of nivolumab (1 mg/kg) with ipilimumab and chemotherapy vs. chemotherapy. The study is being conducted in Asian countries.

The negative side of immunotherapy is immune-mediated adverse events, including nephrotoxicity, cardiotoxicity, gastric toxicity, and damage to lung tissues, skin, and endocrine glands [18].

Discussion: Gastric cancer treatment is a complex task that requires a multidisciplinary approach for optimal treatment. In particular, special attention is paid to the treatment of metastatic/ locally advanced gastric cancer. Immunotherapy is a new anticancer treatment that uses antitumor antibodies (our article presents the most studied ICIs, such as PD-L1 and CTLA-4). Immunotherapy is a rapidly growing area of research in treating gastric cancer. The approval of ICIs in patients with progressive gastric cancer expands the existing treatment options and represents a viable option for personalized therapy. Many studies continue to assess the possibility of using ICIs to treat locally advanced or metastatic gastric cancer. Ongoing phase II and III trials give

patients access to immunotherapy in every line of therapy. Combination therapy with nivolumab and chemotherapy provided a clinically significant improvement in OS as first-line therapy in all patients with advanced gastric adenocarcinoma (CPS≥5). It was approved for use in Europe, the USA, Taiwan, and other countries. As a third-line drug, Nivolumab prolonged OS compared to a placebo and was approved in Japan. In addition, pembrolizumab significantly prolonged the duration of a positive response to immunotherapy, leading to its approval for patients with PD-L1 CPS≥1 tumor in the United States. Today, the efficacy of different biomarkers (such as MSI and TMB) is studied in the personalized treatment of locally advanced or metastatic gastric cancer.

Conclusion: ICIs are the main valuable recent success in anticancer therapy. Their use has led to significant results in treating tumor diseases and improved patient prognosis. ICIs are the preferred option for gastric cancer, which is often resistant to chemotherapy. ICIs are included in various gastric cancer treatment regimens currently studied in many clinical trials. Other promising biomarkers, such as MSI and tumor mutation load, have been isolated in addition to PD-L1 expression. Searching for different biomarkers of ICI efficacy is required to achieve better treatment outcomes.

References:

1. Malignant neoplasms in Russia in 2017 (incidence and mortality) / eds. A.D. Kaprin, V.V. Starinsky, G.V. Petrova. – M.: MNIOI im. P.A. Herzen - branch of the Federal State Budgetary Institution «NMIC of Radiology» of the Ministry of Health of Russia, 2018. - 250 p. [Zlokachestvennye novoobrazovaniya v Rossii v 2017 godu (zabolevaemost' i smertnost') / pod red. A.D. Kaprina, V.V. Starinskogo, G.V. Petrovoj. – M.: MNIOI im. P.A. Gercena – filial FGBU «NMIC radiologii» Minzdrava Rossii, 2018. – 250 s.] https://glavonco.ru/upload/pages/cancer-register/statistika_zabol_2017.pdf

2. Charalampakis N., P. Economopoulou, Kotsantis I., Tolia M., Schizas D., Liakakos T., Elimova E., Ajani J.A., Psyrri A. Medical management of gastric cancer: a 2017 update // Cancer Med. – 2018. – Vol. 7(1). – P.123-133. https://onlinelibrary.wiley.com/doi/10.1002/cam4.1274

3. Massari F., Santoni M., Ciccarese C. PD-1 blockade therapy in renal cell carcinoma: current studies and future promises // Cancer Treat Rev. – 2015. – Vol.41(2). – P.114-121. https://doi.org/10.1016/j.ctrv.2014.12.013

4. Bonotto M., Garattini S.K., Basile D., Ongaro E., Fanotto V., Cattaneo M., Cortiula F., Iacono D., Cardellino G.G., Pella N., Fasola G., Antonuzzo L., Silvestris N., Aprile G. Immunotherapy for gastric cancers:emerging role and future perspectives // Expert Rev. Clin. Pharmacol. – 2017. – Vol.10 (6). – P.609-619. https://doi.org/10.1080/17512433.2017.1313113

5. Alsina M., Moehler M., Hierro C., Guardeno R., Tabernero J. Immunotherapy for gastric Cancer: a focus on immune checkpoints // Target. Oncol. – 2016. – Vol.11. – P.469-477. https://doi.org/10.1007/s11523-016-0421-1

6. Yang H., Wang L., Zhang J. Leukocyte modulation by natural products from herbal medicines and potential as cancer immunotherapy // J. Leukoc. Biol. – 2022. – Vol. 112. – P.185-200. https://doi.org/10.1002/JLB.3RU02 22-087

7. Motallebnezhad M., Younesi V., Aghebati-Maleki L., Nickho H., Safarzadeh E., Ahmadi M., Movassaghpour A.A., Hosseini A., Yousefi M. Antiproliferative and apoptotic effects of a specific anti-insulin-like growth factor I receptor single chain antibody on breast cancer cells // Tumour Biol. – 2016. – Vol. 37. – P.14841-14850. https://doi.org/10.1007/s13277-016-5323-4

8. Gellrich F.F., Schmitz M., Beissert S., Meier F. Anti-PD-1 and Novel Combinations in the Treatment of Melanoma – An Update // J. Clin. Med. –2020. – Vol. 9 (1). – P. 223. https://doi.org/10.3390/jcm9010223

9. Ratner D., Lennerz J.K. Implementing Keytruda/Pembrolizumab Testing in Clinical Practice // Oncologist. – 2018. – Vol. 23 (6). – P. 647-649. https://doi.org/10.1634/theoncologist.2017-0591

10. Riley R.S., June C.H., Langer R., Mitchell M.J. Delivery technologies for cancer immunotherapy // Nat. Rev. Drug Discov. – 2019. – Vol. 18(3). – P. 175-196. https://doi.org/10.1038/s41573-018-0006-z

11. Kang Y.K., Boku N., Satoh T., Ryu M.H., Chao Y., Kato K., Chung H.C., Chen J.S., Muro K., Kang W.K. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): A randomised, double-blind, placebo-controlled, phase 3 trial// Lancet – 2017. – Vol. (390). – P. 2461–2471. https://doi.org/.10.1016/S0140-6736(17)31827-5

12. Gellrich F.F., Schmitz M., Beissert S., Meier F. Anti-PD-1 and Novel Combinations in the Treatment of Melanoma – An Update // J. Clin. Med. –2020. – Vol. 9 (1). – P. 223. https://doi.org/10.3390/jcm9010223

13. Bang Y.J., Ruiz E.Y., Van Cutsem E., Lee K.W., Wyrwicz L., Schenker M., Alsina M., Ryu M. H., Chung H.C., Evesque L. Phase III, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: Primary analysis of JAVELIN gastric 300 // Ann. Oncol. 2018. Vol. 29. – P. 2052–2060. https://doi.org/.10.1093/annonc/mdy264

14. Shitara K., Özgüroğlu M., Bang Y.J. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, openlabel, controlled, phase 3 trial // Lancet. – 2018. – Vol. 392 (10142). – P.123-133. https://doi.org/.10.1016/S0140-6736(18)31257-1

15. Muro K., Chung H.C., Shankaran V. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial // Lancet Oncol. – 2016. – Vol.17 (6). – P. 717-726. https://doi.org/.1016/S1470-2045(16)00175-3

16. Xu J.,Jiang H., Pan Y., Gu K., Cang S., Han, L., Shu Y., Li J., Zhao J., Pan H.. LBA53 - Sintilimab plus chemotherapy (chemo) versus chemo as first-line treatment for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma (ORIENT-16): First results of a randomized, double-blind, phase III study//Oncology pro.Educational Portalfor Oncologists. – 2021. – Vol. 32. – P. 1331. https://doi.org/10.1016/j.annonc.2021.08.2134 .

17. Janjigian Y.Y., Bendell, J.C., Calvo E., Kim J.W., Ascierto P.A., Sharma P., Ott P.A., Bono P., Jaeger D., Evans T.J. CheckMate-032: Phase I/II, open-label study of safety and activity of nivolumab (nivo) alone or with ipilimumab (ipi) in advanced and metastatic (A/M) gastric cancer (GC). J. //Clin. Oncol. – 2016. – Vol. 34 – P. 4010. https://doi.org/10.1200/JCO.2017.76.6212

18. Taieb J., Moehler M., Boku N. Evolution of checkpoint inhibitors for the treatment of metastatic gastric cancers: current status and future perspectives // Cancer Treat Rev. – 2018. – Vol. 66. – P. 104-113. https://doi.org/.10.1016/j.ctrv.2018.04.004

АҢДАТПА

ЖЕРГІЛІКТІ ТАРАЛҒАН ЖӘНЕ МЕТАСТАЗДЫҚ АСҚАЗАН ОБЫРЫН ЕМДЕУДЕ БАҚЫЛАУ НҮКТЕСІ ИНГИБИТОРЛАРЫН ҚОЛДАНУ: ӘДЕБИЕТТЕРГЕ ШОЛУ

М.С. Дмитренко[1], К.К. Смагулова[1,2], Р.З. Абдрахманов[1,2], Р.К. Раскалиев[1], И.Т. Туркпенова[1], Э.П. Медетбекова[1], С.Н. Калдарбеков[1], А.О. Куаныш[1], Ж.С. Кенжебаева[1], Д.У. Шаяхметова[2], А.Ж. Жиенбаева[1], А.К. Джакипбаева[2]

[1]«Қазақ онкология және радиология ғылыми-зерттеу институты» АҚ, Алматы, Қазақстан Республикасы;
[2]«С.Ж. Асфендияров атындағы Қазақ Ұлттық Медицина Университеті» КЕАҚ, Алматы, Қазақстан Республикасы

Өзектілігі: *Асқазанның қатерлі ісігі (ҚІ) ең көп таралған қатерлі ісіктердің бірі болып табылады және әлемде қатерлі ісік ауруларының арасында бесінші орында. Асқазанның оқшауланған қатерлі ісігін емдеудің жалғыз әдісі – алдын ала химиотерапиямен немесе радикалды хирургия. Бірақ, метастаздық немесе жергілікті дамыған асқазан обырында химиотерапия негізгі ем болып табылады. Асқазан қатерлі ісігінің соңғы сатыларында химиотерапияға төзімділігі жоғары, сондықтан заманауи емдеу тәсілдерін іздеу қажет. Асқазанның метастаздық/жергілікті асқынған обырын емдеуге ерекше көңіл бөлінеді.*

Зерттеудің мақсаты *метастаздық немесе жергілікті асқынған асқазан обырын емдеу үшін иммундық бақылау нүктелерінің ингибиторларын (БНИ) пайдалану мүмкіндіктерін сипаттау болып табылады.*

Әдіс-тәсілдері: *арнайы ғылыми іздеу жүйелері арқылы, соңғы жылдардағы заманауи әдебиет дереккөздері бойынша зерттелді: Scopus, PubMed, Google Scholar, Web of science, метастаздық немесе жергілікті асқынған асқазан обырын емдеуде иммунотерапияның әртүрлі тәсілдерін ұтымды қолдану мүмкіндігі үшін.*

Нәтижелер: *Мақалада метастаздық немесе жергілікті асқынған асқазан обырын АКТ көмегімен емдеудің заманауи әдістері сипатталған, соның ішінде PD-1, PD-L1, CTLA-4, иммунологиялық қадағалау механизмдері, PD-1, PD-L1, CTLA- 4 сипаттамалары көрсетілген және олардың Т-жасушасының супрессиясына жауабының маңыздылығы. БНИ-ды қолданудың тиімділігі, атап айтқанда, PD-1, PD-L1, CTLA-4, терапияның бірінші және кейінгі бағыттарында да белгіленді.*

Қорытынды: *БНИ ісікке қарсы терапиядағы соңғы жылдары ашылған жаңалық. Асқазан қатерлі ісігінің химиотерапияға жиі төзімділігі нәтижесінде, БНИ-ды асқазанның кеш сатысындағы қатерлі ісігін емдеуде қолданған жөн.*

Түйінді сөздер: *Метастатикалық немесе жергілікті асқынған асқазан қатерлі ісігінің иммунотерапиясы, бақылау нүктесі ингибиторлары (СРТ), PD-1, PD-L1, CTLA-4, иммундық жауап механизмдері.*

АННОТАЦИЯ

ПРИМЕНЕНИЕ ИНГИБИТОРОВ КОНТРОЛЬНЫХ ТОЧЕК В ЛЕЧЕНИИ МЕСТНОРАСПРОСТРАНЕННОГО И МЕТАСТАТИЧЕСКОГО РАКА ЖЕЛУДКА: ОБЗОР ЛИТЕРАТУРЫ

М.С. Дмитренко[1], К.К. Смагулова[1,2], Р.З. Абдрахманов[1,2], Р.К. Раскалиев[1], И.Т. Туркпенова[1], Э.П. Медетбекова[1], С.Н. Калдарбеков[1], А.О. Куаныш[1], Ж.С.Кенжебаева[1], Д.У. Шаяхметова[2], А.Ж. Жиенбаева[1], А.К. Джакипбаева[2]

[1]АО «Казахский научно-исследовательский институт онкологии и радиологии», Алматы, Республика Казахстан;
[2]НАО «Казахский Национальный медицинский университет им. С.Д. Асфендиярова», Алматы, Республика Казахстан

Актуальность: *Рак желудка (РЖ) является одним из самых распространенных злокачественных новообразований и занимает пятое место в структуре онкозаболеваемости в мире. Единственным лечебным подходом к локализованному РЖ является радикальная операция с предшествующей химиотерапией или без нее. Но при метастатическом или местнораспространенном РЖ химиотерапия является основным методом лечения. На поздних стадиях РЖ наблюдается высокая резистентность к химиотерапии, в связи с чем существует необходимость поиска современных подходов лечения. Особое внимание уделяется терапии при метастатическом/местнораспространенном РЖ.*

Цель исследования *– описать возможности применения ингибиторов контрольных точек иммунитета (ИКТ) для лечения метастатического или местнораспространенного РЖ.*

Методы: *Были изучены данные современных литературных источников последних лет с использованием специализированных научных поисковых систем: Scopus, PubMed, Google Scholar, Web of science, для возможности перспективного применения различных подходов иммунотерапии в лечении метастатического или местнораспространенного РЖ.*

Результаты: *В статье описаны современные методы лечения метастатического или местнораспространенного РЖ с использованием ИКТ, включая PD-1, PD-L1, CTLA-4, продемонстрированы механизмы иммунологического надзора, характеристики PD-1, PD-L1, CTLA-4 и их значение в супрессии Т-клеточного ответа. Установлена эффективность применения ИКТ, в частности PD-1, PD-L1, CTLA-4, как в первой, так и последующих линиях терапии.*

Заключение: *ИКТ являются находкой последних лет в противоопухолевой терапии. В результате частой резистентности РЖ к химиотерапии, целесообразно использовать ИКТ в терапии РЖ поздних стадий.*

Ключевые слова: *Иммунотерапия метастатического или местнораспространенного РЖ, ингибиторы контрольных точек (ИКТ), PD-1, PD-L1, CTLA-4, механизмы иммунного ответа.*

Transparency of the study: *Authors take full responsibility for the content of this manuscript.*
Conflict of Interest: *The authors declare no conflict of interest.*
Financing: *This study was financed under the Scientific-Technical Program BR11065390 "Elaboration and development of innovative technologies for early diagnosis and treatment of malignant diseases taking into account modern genomics approaches" (Program-targeted financing of the Ministry of Healthcare of the Republic of Kazakhstan).*
Authors' input: *contribution to the study concept – Dmitrenko M.S., Smagulova K.K., Raskaliyev R.K.; study design – Dmitrenko M.S., Smagulova K.K., Abdrahmanov R.Z., Turkpenova I.T. , Kenzhebayeva Zh.S., Kuanysh A.O.; execution of the study – Dmitrenko M.S., Abdrahmanov R.Z., Kaldarbekov S.N., Medetbekova E.P., Turkpenova I.T., Kenzhebayeva Zh.S., Kuanysh A.O.; interpretation of the study – Dmitrenko M.S., Abdrahmanov R.Z., Dzhakipbayeva A.K., Kuanysh A.O., Kenzhebayeva Zh.S., Shayahmetova D.U., Zhiyenbayeva A.Zh.; preparation of the manuscript – Dmitrenko M.S., Smagulova K.K., Abdrahmanov R.Z., Turkpenova I.T., Kenzhebayeva Zh.S., Kuanysh A.O.*
Authors' data:
Dmitrenko M.S. (corresponding author) – Oncologist-chemotherapist, «KazIOR» JSC, **Almaty, 050000, Abay ave. 91, the Republic of Kazakhstan**, tel. +77011009649, e-mail: masha_0206@inbox.ru, ORCID ID: https://orcid.org/0000-0003-0731-6019;
Smagulova K.K. – Candidate of Medical Sciences, Head of the Day Patient Chemotherapy Department, «KazIOR» JSC, Almaty, the Republic of Kazakhstan, tel. +77017615973, e-mail: akaldygul@mail.ru, ORCID ID: https://orcid.org/0000-0002-1647-8581;
Abdrahmanov R.Z. – Candidate of Medical Sciences, Head of Chemical Therapy Center, «KazIOR» JSC, Almaty, the Republic of Kazakhstan, tel. +77023211031, e-mail: ramil_78@inbox.ru, ORCID ID: https://orcid.org/0000-0002-8870-8091;
Raskaliyev R.K. – Oncologist-Surgeon of the Abdominal Surgery Center, «KazIOR» JSC, Almaty, the Republic of Kazakhstan, tel. +77015562688, e-mail: Raskalievrk@mail.ru, ORCID ID: https://orcid.org/0000-0001-7956-640X;
Turkpenova I.T. – Oncologist-chemotherapist, «KazIOR» JSC, Almaty, the Republic of Kazakhstan, tel. +77023618918, e-mail: innara92@mail.ru, ORCID ID: https://orcid.org/0000-0002-8603-6674;
Medetbekova E.P. – Oncologist-chemotherapist-transfusiologist, «KazIOR» JSC, Almaty, the Republic of Kazakhstan, tel. +77075062950, e-mail: medet-bekova.elmi@mail.ru, ORCID ID: https://orcid.org/0000-0001-7157-1562;
Kaldarbekov S.N. – Oncologist-chemotherapist, «KazIOR» JSC, Almaty, the Republic of Kazakhstan, tel. +77759043412, e-mail: samat_261294@mail.ru, ORCID ID: https://orcid.org/0000-0002-4950-9794;
Kuanysh A.O. – Oncologist, Resident at «KazIOR» JSC, Almaty, the Republic of Kazakhstan, tel. +77784781318, e-mail: aknietkuanys92@gmail.com, ORCID ID: https://orcid.org/0000-0002-8741-4112;
Kenzhebayeva Zh.S. – Oncologist, Resident of «KazIOR» JSC, Almaty, the Republic of Kazakhstan, tel. +77072583127, e-mail: ojluminary@mail.ru, ORCID ID: https://orcid.org/0000-0003-0628-8730;
Shayahmetova D.U. – Oncologist, Resident at «KazIOR» JSC, Almaty, the Republic of Kazakhstan, tel. +77058751990, e-mail: di-nara.shkhmt@gmail.com, ORCID ID: https://orcid.org/0000-0001-6283-5431;
Zhiyenbayeva A.Zh. – Oncologist, Resident at«KazIOR» JSC, Almaty, the Republic of Kazakhstan, tel. +77476301737, e-mail: zaripov.o-a@mail.ru, ORCID ID: https://orcid.org/0000-0002-5542-1609;
Dzhakipbayeva A.K. – Candidate of Medical Sciences, Ass. Prof., Nugmanov Oncology Department, «Asfendiyarov Kazakh National Medical University» NCJSC, Almaty, the Republic of Kazakhstan, tel. +77013672078, e-mail: atkan1@mail.ru, ORCID ID: https://orcid.org/0000-0002-3221-9758.