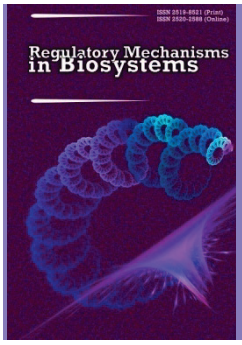

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Biological mechanisms of resistance to immune checkpoint inhibitors and overcoming this resistance: Challenges in medical oncology

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Immune checkpoint inhibitors have opened up new possibilities in clinical oncology. Monoclonal antibodies have shown their high clinical efficiency. They block CTLA-4, PD-1, and PD-L1 receptors and activate the immune response. Many patients have stable and even complete responses. However, some patients have primary or acquired resistance. Therefore, the treatment results in this category of patients are not predictable. Mechanisms of resistance to immune checkpoint inhibitors have not been definitively studied. Many theories try to explain the mechanisms of this phenomenon. Our study aimed to structure and combine the data into groups depending on the etiological factor that reduces the immune response. In addition, based on understanding the mechanisms of resistance and the results of recent clinical studies, we aimed to identify the main ways to overcome it. Therefore, mechanisms that lead to resistance may be associated with tumor properties, tumor microenvironment, or patient characteristics. Tumor properties that reduce the immune response include a) low tumor mutation burden and loss of tumor neoantigens, b) changes in the processing or presentation of neoantigens, and c) changes in signaling pathways of tumor development and epigenetic modifications in genes. The tumor microenvironment is represented by stromal and immune cells, extracellular matrix, cytokines, and blood vessels. Each structure can enhance or reduce the immune response and contribute to the acquired resistance to immune checkpoint inhibitors. The effectiveness of the treatment depends not only on the cells in the tumor microenvironment but also on the metabolic background. In addition, the basic characteristics of the patient (gender, gut microbiota, HLA-I genotype) can modify the immune response. Based on knowledge about the mechanisms of resistance to immune checkpoint inhibitors, several therapeutic strategies aimed at activating antitumor activity have been evaluated. All of them are based on combining immune checkpoint inhibitors with other drugs. One of the most common options is a combination of PD-1/PD-L1 and CTLA-4 inhibitors. Alternative immune checkpoints are TIM-3, LAG-3, TIGIT and VISTA. Combining immunotherapy with chemotherapy, targeted therapy, neoangiogenesis inhibitors, epigenetic modifiers, PARP or TGF-β inhibitors enhances antitumor response by preventing depletion of effector T cells, enhancing T cell infiltration in the tumor, changes on the tumor microenvironment, and decreasing the accumulation of immunosuppressive cells. This review explores the biological mechanisms of resistance and potential ways of solving this problem.

Keywords: immunotherapy; cancer; tumor microenvironment; mechanisms; cytotoxic T-lymphocyte antigen-4; programmed cell death protein 1.

Introduction

Immune checkpoint inhibitors are a modern and promising direction in oncology (Dagher et al., 2023; Rui et al., 2023; Schaft et al., 2023). The role of monoclonal antibodies is to block CTLA-4, PD-1, and PD-L1 receptors and activate the immune response. Despite the significant clinical effectiveness, resistance to this type of drug is observed in some patients (Liu et al., 2023; Zhang et al., 2023). As a result, the response to treatment can be unpredictable and unsatisfactory.

Mechanisms of resistance to immune checkpoint inhibitors have not been definitively studied. Insensitivity to this type of immunotherapy can be primary (innate) or acquired. The reasons for developing resistance can be considered in terms of the mechanism of action of immune checkpoint inhibitors. First, the effectiveness of immunotherapy is reduced by the insufficient generation and infiltration by T cells. Secondly, inadequate synthesis of T-cell memory causes the absence of a long-term therapeutic effect. Thirdly, the so-called dysfunction of tumor-specific T cells and insufficient presentation of antigens can lead to resistance (Ziogas et al., 2023). However, the concept of resistance is much deeper and requires a detailed approach. Different theories try to explain the mechanisms of resistance to immune checkpoint inhibitors. Many scientific works are devoted to the investigation of the impact of the tumor microenvironment (TME) (Baghy et al., 2023), lymphoid depletion and signaling pathways (Lu et al., 2023), tumor mutational burden (TMB) (Moeckel et al., 2023; Moskalenko et al., 2023), expression of inhibitory receptors (TIM-3, VISTA, LAG-3, and TIGIT (Tian & Li, 2021; Abi-Aad et al., 2023; Chu et al., 2023), metabolites (Chaudagar et al., 2023; Chen et al., 2023; Yang et al., 2023) and other factors. Our study aimed to structure and combine the data into groups depending on the etiological factor that reduces the immune response. In addition, based on understanding the mechanisms of resistance and the results of recent clinical studies, we attempted to identify the main ways to overcome it.

So, all mechanisms can be divided into three groups associated with 1) properties of the tumor, 2) the tumor microenvironment, and 3) patient characteristics.

Mechanisms of resistance associated with tumor properties

The reasons for resistance to therapy with immune checkpoint inhibitors can be a) low TMB and loss of tumor neoantigens, b) changes in the processing or presentation of neoantigens, and c) changes in signaling pathways of tumor development and epigenetic modifications in genes.

Patients whose tumors have high TMB show a significantly better sensitivity to immunotherapy. The primary resistance or weak effect of

this group of drugs is due to low TMB, which is associated with insufficient formation or loss of neoantigens (Vryza et al., 2023). Accounting for small mutational insertions and deletions in TMB calculation algorithms is essential. Many tumors, one of which is renal cell carcinoma, have a low number of single nucleotide variants (low TMB) but a high frequency of deletions. These deletions lead to an increase in the number of neoantigens and a good response to immunotherapy. The emergence of resistance in treating tumors of this type may be associated with immunoediting, in which subclones that cannot express neoantigens remain in the tumor tissue (Turajlic et al., 2017).

Another cause of resistance directly related to the properties of the tumor is changes in the processing or presentation of neoantigens. Tumor cells become invisible to tumor-specific CD8+ T cells if there is a decrease in the expression of MHC-I (major histocompatibility complex-1) and β_2-microglobulin (one of its components) (Luo et al., 2024).

Epigenetic modification of components involved in antigen presentation and processing is another reason for resistance to immunotherapy. Looi et al. (2023) investigated the relationship between immune escape in patients with nasopharyngeal carcinoma and crosstalk between epigenetic mechanisms. The role of DNA methyltransferase and histone deacetylase inhibitors in reverse suppression of immunity and improving antitumor activity has been established. The scientists concluded that immune checkpoint inhibitors should be used with epigenetic therapy to overcome immune resistance.

Other epigenetic modifications of components include chromatin remodeling, DNA methylation of immune-dependent genes, DNA methylation in the differentiation process of myeloid cells and CD8+ T cells, and regulation of PD-1 due to changes in chromatin accessibility (Topper et al., 2020).

A consequence of epigenetic modifications can be a deterioration of cytokine synthesis. For example, suppression of the synthesis of chemokines promotes the spreading of cytotoxic T-lymphocytes into the tumor microenvironment. Epigenetic modifications contribute to developing resistance to immune checkpoint inhibitors by DNA methyltransferase-1 and modifying histones by the protein EZH2 (enhancer of the polycomb subunit of the zeste repressive complex 2). Studies confirm that EZH2 methyltransferase inhibitors increase the sensitivity to immunotherapy in patients with squamous cell carcinomas of the lung. During the experiment, scientists used two-dimensional lines of human cancer cells and three-dimensional organoids of mice and patients. The samples were treated with two EZH2 inhibitors and interferon-γ. As a result, the expression of the major histocompatibility complex class I and II (MHCI/II) increased (DuCote et al., 2023).

Response to immune checkpoint inhibitor therapy may depend on genes responsible for DNA damage repair (FANCA, MSH, POLE, ERCC2, ATM, and BRCA). In the case of renal cell carcinomas and colorectal cancers, mutations in the SWI/SNF genes provide high microsatellite instability and high expression levels of PD-L1 and TMB. As a result, such tumors are susceptible to therapy with immune checkpoint inhibitors (McKean et al., 2020).

Lebedev et al. (2023) investigated the mechanisms underlying the immunomodulatory role of AT-rich interaction domain 1A (ARID1A). ARID1A is the most frequently mutated epigenetic regulator among all human malignancies. It is possible to stimulate the immune response and improve treatment results by influencing this factor.

Alterations in the oncogenic PTEN, IFN-γ, MAPK, STK11, CDK4/6, and Wnt/β-catenin signaling pathways can also lead to resistance to immune checkpoint inhibitor therapy. The main factor that can suppress the immune response is loss of function mutations and decreased expression in the interferon-γ (IFN-γ) signaling pathway. Xie et al. (2023) found that resistance to immune checkpoint inhibitors is associated with the effects of IFN-γ on NSDHL (NAD(P)-dependent steroid dehydrogenase-like) and SREBP1 (sterol regulatory element-binding protein 1). Due to these processes, the production of TGF-β1 (transforming growth factor beta-1) increases, the cytotoxicity of T cells decreases, and the infiltration of Tregs increases. All together, these factors lead to a decrease in the immune response. Regulation of the pathological NSDHL/SREBP1/ TGF-β1 pathway using tyrosine kinase inhibitors leads to better outcomes in patients treated using immune checkpoint inhibitors. Mutations in IFN-γ signaling components can also lead to resistance, as T lymphocytes use this abnormal signaling pathway to induce PD-L1 expression.

Manolakos & Ward (2023) concluded that STK11 (serine/threonine kinase 11) is a single mutation that shows mixed results and cannot be considered a prognostic biomarker for immune checkpoint inhibitor therapy. However, the combination of KRAS (Kirsten rat sarcoma viral oncogene homolog) and STK11 mutations are predictors of primary resistance. The study was conducted in patients with metastatic non-small cell lung cancer. There is a direct correlation between the low PD-L1 expression on tumor cells and the inactivation of STK11. In this case, there is no dependence on the degree of TMB and the immune response since innate resistance to PD-1 blockade is observed in individuals with KRAS-mutant non-small cell lung cancer.

Disturbance in the PTEN signaling pathway leads to increased expression of VEGF (vascular endothelial growth factor) and activation of the PI3K (phosphatidylinositol-3-kinase) pathway. It leads to the emergence of resistance to immune checkpoint inhibitors by reducing the level of PD-L1 expression (Peng et al., 2016).

The MAPK (mitogen-activated protein kinase) signaling pathway activates VEGF and immunoregulatory cytokines (IL-6, IL-8, IL-10). As a result, tumor-infiltrating lymphocyte (TIL) function deteriorates, and there is a decrease in the immune response (Persa & Mauch, 2021). Activation of the Wnt/β-catenin pathway leads to impaired infiltration and activation of CD103+ dendritic cells. CD103+ dendritic cells are involved in the preparation and activation of CD8+ T cells, so the result is inhibition of the immune response and a decrease in the effectiveness of immune checkpoint inhibitors (Morita et al., 2023).

The CDK4/6 (cyclin-dependent kinase 4/6) signaling pathway can directly alter T-cell function and influence the immune response. The effect of CDK4/6 receptor blockers is based on increased TILs and decreased M2 macrophages. At the same time, the degree of exhausted T cells and Tregs decreases (Salewski et al., 2022).

Another factor of resistance to immune checkpoint inhibitors is hormone-dependent tumors. For example, prostate cancer and the luminal type of breast cancer are considered insensitive to immunotherapy. Such tumors have low levels of TIL and TMB, and a hormonal factor mediates oncogenesis (O'Leary et al., 2023).

Mechanisms of resistance associated with the tumor microenvironment

All tumors, depending on the type of immune infiltrates, belong to certain immunophenotypes. Based on the results of the immunohistochemical examination, "hot" (inflammatory) and "cold" tumor phenotypes are distinguished. "Hot" tumors are characterized by infiltration around the tumor. As a result, a pattern of pronounced immune protection is observed. "Cold" immunophenotype means the absence of infiltration. Depending on this factor, the response to therapy with immune checkpoint inhibitors will be different. Inflammatory tumors are susceptible to immunotherapy, while the effectiveness of "cold" treatment is limited. The tumor microenvironment (TME) is represented by various structures: stromal and immune cells, extracellular matrix, cytokines, and blood vessels. Each can either enhance or reduce the immune response and contribute to the emergence of acquired (secondary) resistance to immune checkpoint inhibitors (Galon & Bruni, 2019).

Immune cells that consist of the TME and impair the effect of immunotherapy include Tregs (regulatory T cells), MDSCs (myeloid suppressor cells), and TAMs (tumor-associated macrophages). The action of Tregs is associated with the production of inhibitory cytokines (TGF-β, IL-10, IL-35). As a result, suppression of B and T cells is observed. In addition, Tregs can directly contact and block effector lymphocytes. Determining the ratio of Tregs and effector T cells allows one to predict the effect of therapy with immune checkpoint inhibitors. MDSCs also play an essential role in tumor pathogenesis. These cells suppress the immune response by influencing tumor-specific CD8+ T cells. That is why a high concentration of MDSCs in the tumor microenvironment indicates resistance to immune checkpoint inhibitors (Heller et al., 2023).

In addition to Tregs and MDSCs, TAMs have been associated with treatment resistance and poor prognosis. All tumor-associated macro-

phages are divided into classical proinflammatory (M1) and alternative anti-inflammatory (M2). Proinflammatory macrophages secrete proinflammatory cytokines (for example, TNF, IL-1, IL-6). Alternative anti-inflammatory macrophages are associated with the synthesis of inhibitory cytokines (IL-10, IL-13, and TGF-β) (Li et al., 2023).

Fibroblasts and endothelial cells belong to the stromal cells of the TME and play a supporting role in the growth of a malignant tumor. They can also alter the immune response and promote the development of resistance. In addition, tumor endothelial cells contribute to neoangiogenesis. They produce platelet-derived growth factors, VEGF, IL, and TGF-β. As a result, vascularization and tumor growth are stimulated, and a violation of the process of effector extravasation of T cells is observed. Tumor endothelial cells contribute to the accumulation of Tregs and enhance negative regulators of T cell activation (PD-L1, PD-L2, and IL) (Fischer & Alsina-Sanchis, 2024).

As a part of the TME, fibroblasts participate in matrix remodeling, synthesis of factors that stimulate tumor progression (chemokines and cytokines), and tumor invasion. Alteration of the immune response is mediated by chemokines and cytokines that enhance the immunosuppressive properties of TAMs, T cells, MDSCs, and dendritic cells. Many Tregs and myeloid cells are involved in the pathological process. Because chemokines and cytokines affect the proliferation and activation of immune cells, they can influence the outcome of patients receiving immune checkpoint inhibitor therapy. CXCL8/12 and CCL5/7/17/22 are the most common chemokines associated with oncogenesis. Their role is to stimulate the migration of MDSCs and Tregs to the TME. Therefore, increased chemokine activity results in resistance to immune checkpoint inhibitors (Salehi-Rad et al., 2023).

The effect of cytokines (VEGF and TGF-β) is related to the effect on Tregs and T-cells. However, the mechanisms of action are somewhat different. The cytokine VEGF suppresses the level of effector CD8+ T-cells and promotes the recruitment of Tregs. It leads to a deterioration of T-lymphocyte synthesis, difficulties with their movement, and general exhausttion. As a result, the immune response and the effect of immunotherapy are reduced. Elevation of the cytokine TGF-β leads to tumor progression by suppressing cytotoxic T-lymphocytes and activating Tregs. After that, the tumor can escape the immune response (Chhabra & Weeraratna, 2023).

The most common biomarker to predict response to immune checkpoint inhibitor therapy is PD-L1 expression. Krieger et al. (2020) discovered that the response to immunotherapy in patients with non-small cell lung cancer or melanoma directly depends on the level of PD-L1 expression. However, in the case of Merkel cell carcinoma, breast cancer, gastric cancer, and clear-cell renal carcinoma, the response is not always predictable.

Zhang et al. (2023) concluded that it is essential to determine the expression of PD-L1 in tumor tissue and tumor-infiltrating immune cells. Scientists believe PD-L1 and CD8 of TME cells are novel prognostic biomarkers in patients with esophageal squamous cell carcinomas. They can be used to select the type of therapy and predict response to therapy with immune checkpoint inhibitors.

Molecules of TME, such as TIGIT, LAG-3, TIM-3, and VISTA, can accelerate T-cell exhaustion and reduce the immune response. Disrupting adenosinergic signaling increases the level of cyclic adenosine monophosphate. This process results in decreased T-cell function and the effectiveness of immune checkpoint inhibitors (Vigano et al., 2019).

The response to therapy with immune checkpoint inhibitors depends on the cells located in the TME and the metabolic background. Adequate maintenance of the aerobic glycolysis process is necessary for the activation and functioning of CD8+ T cells. An increase in lactate dehydrogenase levels in the blood leads to a deterioration of this process. As a result, the immune response decreases. Arginase, glutaminase, and tryptophan-metabolizing enzymes can affect immune cell function. They inhibit the proliferation and function of effector T cells by producing toxic metabolites. In addition, amino acids affect tissue homeostasis and the immune response. Dysregulation of amino acid metabolism in immune cells leads to metabolic reprogramming of the TME, tumor growth, and metastasis. The differentiation and functioning of immune cells depend on the concentration of free amino acids, the number of membrane receptors, and the functioning of the main metabolic pathways (mTOR and GCN2) (Yang et al., 2023). Hypoxia in the TME may be another mechanism for developing resistance to immune checkpoint inhibitors. This condition can result from the active proliferation of tumor cells and increased oxygen consumption. As a result, there is increased regulation of PD-L1 and activation of the immunosuppressive microenvironment (Chen et al., 2023).

Mechanisms of resistance associated with patient characteristics

Gut microbiota can cause both oncogenic and antitumor effects. It is considered an essential modulator of the immune response. The consequence of dysbacteriosis can potentially be not only colorectal cancer but also hepatocellular carcinoma and breast cancer. A healthy gut microbiota is thought to increase the levels of effector T cells, upregulate MHC-II, and activate dendritic cells (Kiousi et al., 2023).

The patient's gender can influence the effectiveness of therapy with immune checkpoint inhibitors. Wu et al. (2018) found that men's recurrence-free survival and overall survival rates are significantly higher. Hormonal and genetic factors can play a major role in this process. Estrogen can alter immune and stromal cells of TME and regulate PD-1 and PD-L1 expression and cytokine secretion. However, there are differences in women depending on the population, smoking status, mutational profile, histological subtype, and hormonal status. Nevertheless, hormonal therapy is considered a potentially promising treatment, increasing the effectiveness of immune checkpoint inhibitors and overcoming acquired resistance (Rodriguez-Lara et al., 2023).

The effectiveness of immunotherapy depends on the HLA-I (human leukocyte antigen class I) genotype, which can impair the recognition of neoantigens by CD8+ T cells and the immune response. Exposure to specific HLA-I mutations could increase the efficacy of immune checkpoint inhibitors (Chowell et al., 2018).

Ways of overcoming resistance to immune checkpoint inhibitors

Based on understanding the biological mechanisms of resistance to immune checkpoint inhibitors, choosing the right strategy for treating patients is necessary. Based on the results of studies, combining an immune checkpoint inhibitor with other drugs, such as another immune checkpoint inhibitor, chemotherapy, targeted therapy, neoangiogenesis inhibitors, PARP inhibitors, TGF-β inhibitors, or epigenetic modifiers, maybe the right choice.

Combination of two immune checkpoint inhibitors

In the Phase 3 CheckMate 067 study, researchers concluded that among patients with advanced melanoma, the best five-year survival rates were for those receiving the combination of nivolumab and ipilimumab. The median overall survival in this cohort of patients was 60 months, while in the nivolumab and ipilimumab monotherapy groups, it was 36.9 and 19.9, respectively. 52% of people overcame the five-year barrier after combined therapy. The rates were significantly lower in the nivolumab and ipilimumab monotherapy groups (44% and 26%, respectively). The combination of immune checkpoint inhibitors did not lead to the appearance of late toxic effects and did not worsen the quality of life of the patients (Larkin et al., 2019). Similar results were obtained in the phase III study CheckMate 214. Patients with clear cell renal carcinoma receiving the combination of nivolumab and ipilimumab had better five-year survival results than the cohort using sunitinib alone (Motzer et al., 2022).

The CheckMate 227 study summarized the effectiveness of treatment in patients with metastatic non-small cell lung cancer. Patients were treated regardless of PD-L1 expression level. The cohort receiving the combination of nivolumab and ipilimumab showed the best results. Five-year survival rates were higher in the immunotherapy group than in the chemotherapy group (24% vs. 14%). The scientists concluded that nivolumab plus ipilimumab can be used as the first line of therapy (Brahmer et al., 2023).

The combination of nivolumab and ipilimumab has been approved as the new standard of care for patients with esophageal squamous cell carcinoma. In the global phase III study CheckMate 648, the median overall survival was 17.6 months in the nivolumab and ipilimumab group,

15.5 months in the nivolumab and chemotherapy group, and 11 months in the chemotherapy group. Treatment tolerability with a combination of immune checkpoint inhibitors was acceptable. Scientists recommend this scheme for the first-line treatment (Kato et al., 2023).

Another study evaluated the efficacy of nivolumab and ipilimumab in patients with metastatic hepatocellular carcinoma. One of the main inclusion criteria was prior therapy with PD-1 or PD-L1 inhibitors. Previous CTLA-4 inhibitor therapy was considered an exclusion criterion. The computed tomography results showed that the objective response rate was 22%. 3% of patients showed a complete response, 19% – partial response, 25% – stable disease, 50% – progressive disease, and 3% could not be assessed. The scientists concluded that the combination of ipilimumab and nivolumab has sufficient clinical efficacy. This strategy is indicated for treating advanced hepatocellular carcinoma in patients previously treated with monoclonal antibodies against PD-1 or PD-L1 (Alden et al., 2013).

Recently, a regimen of nivolumab plus ipilimumab was approved for the treatment of metastatic colorectal cancer with high microsatellite instability (Touati et al., 2022). About 95% of colorectal carcinomas are microsatellite stable. Therefore, they are not sensitive to immune checkpoint inhibitors. However, temozolomide can sensitize colorectal carcinomas and improve the effectiveness of nivolumab and ipilimumab (Gonzalez et al., 2023). According to the phase III study CheckMate 743 results with a median follow-up period of 43.1 months, nivolumab and ipilimumab showed significantly better efficacy in patients with unresectable pleural mesothelioma than chemotherapy. The median overall survival was longer in the immunotherapy group (18.1 versus 14.1 months). Three-year survival rates were 23% for immune checkpoint inhibitors and 15% for chemotherapy (Peters et al., 2022).

In the NEONIPIGA phase II study, scientists studied the frequency of histopathological complete response and the toxicity of the combination of nivolumab with ipilimumab in patients with resectable gastric cancer. The inclusion criterion was a high level of microsatellite instability in the tumor tissue. All 32 patients received neoadjuvant therapy with immune checkpoint inhibitors. After that, surgery was done for 29 of them. Three patients had a complete response by computed tomography, endoscopic examination, and biopsy and did not undergo surgery. All patients had negative resection margins according to histopathological examination. The toxicity of combined therapy with immune checkpoint inhibitors was significant. Immune-related adverse events of the third and fourth-grade severity were registered in 19% of patients (André et al., 2023).

Antitumor activity is demonstrated by another combination of immune checkpoint inhibitors – durvalumab and tremilimumab. Specifically, in the Phase III POSEIDON study, patients with metastatic non-small cell lung cancer were divided into three groups. The first group was treated with tremelimumab, durvalumab and chemotherapy, the second – with durvalumab and chemotherapy, and the third – with chemotherapy. As a result, the best overall and recurrence-free survival rates were for patients whose treatment with durvalumab and chemotherapy was supplemented with tremilimumab (Johnson et al., 2023).

Essential conclusions were made in the MYSTIC Phase III study. For optimal efficacy of the combination of durvalumab and tremilimumab, the TMB threshold should be more significant than 20 mutations per megabase. Otherwise, overall survival rates are similar to the durvalumab monotherapy or chemotherapy group (Rizvi et al., 2020).

The efficacy of the combination of durvalumab and tremilimumab in patients with unresectable hepatocellular carcinoma was evaluated in the HIMALAYA study. This scheme demonstrated better treatment results than monotherapy with durvalumab or sorafenib (Abou-Alfa et al., 2023).

The effectiveness of treatment with immune checkpoint inhibitors may depend on the presence of metastases in the liver of patients with colorectal cancer. Such patients have lower overall and relapse-free survival. In the group of patients without liver metastases treated with the combination of durvalumab and tremilimumab, the disease control rate was 49%, while in the group with metastases it was only 14%. This feature must be considered when choosing a therapeutic strategy (Chen et al., 2023). Patients with advanced colorectal cancer treated with durvalumab and tremilimumab have better overall survival compared to those treated with other available medications (chemotherapy, neoangiogenesis inhibitors, targeted therapy). The best results were observed in TMB patients with more than 28 mutations per megabase and microsatellite-stable tumors (Chen et al., 2020).

Combined blockade of PD-1/PD-L1 and CTLA-4 receptors causes a complementary effect. As a result, effector T cells are activated, T cell exhaustion decreases, and Tregs are suppressed. Monoclonal antibodies against PD-1/PD-L1 and CTLA-4 have different mechanisms of action but one common goal (strengthening the immune response). Therefore, if resistance develops to one of the drugs, the other provides a stimulating effect in an alternative way (Zhang et al., 2021).

An important mechanism of immune response escape is the expression of other immune checkpoints (LAG-3, TIM-3, VISTA, TIGIT) (Ziogas et al., 2023). The effect of monoclonal antibodies against PD-1/PD-L1 and CTLA-4 can be enhanced by using inhibitors of these molecules. For example, inhibition of LAG-3 blocks negative regulation and promotes the antitumor response of T cells. The process is based on reducing LAG-3 expression in TILs, exhausted T cells, and other types of immune cells. In addition, blocking LAG-3 disrupts interactions with dendritic cells and MHC-II molecules on Tregs. The synergistic interaction between LAG-3 and PD-1 in the tumor microenvironment can increase treatment efficacy and overcome resistance (Abi-Aad et al., 2023).

Another promising target on the way to overcome resistance is TIGIT. A high level of expression of these receptors is associated with exhaustion of T cells. The effect of TIGIT consists of inhibiting the effector function of natural killer cells, stimulating the transformation of macrophages to the M2 phenotype. These inhibitory molecules contribute to the differentiation of T cells into Tregs and inhibit the maturation of dendritic cells. In addition, there is a direct relationship between the expression level of TIGIT and PD-L1. Preclinical studies have demonstrated that co-inhibition of TIGIT and PD-1/PD-L1 results in an enhanced immune response and improved survival in patients with various tumor types. Overall, the combined inhibition of TIGIT and PD-1/PD-L1 is a promising new therapeutic strategy capable of overcoming resistance to classical immune checkpoint inhibitors (Chu et al., 2023).

Enhancing the antitumor response and eliminating the immunosuppressive effects by inhibiting TIM-3 is possible. TIM-3 is expressed on exhausted or dysfunctional T cells and promotes the development of suppressor cells of myeloid origin. High expression of PD-1 and TIM-3 in CD4+ and CD8+ T-cells is associated with poor prognosis. Combined therapy with monoclonal antibodies against PD-1 and TIM-3 has a more pronounced clinical effect than monotherapy with PD-1 inhibitors. Scientists proved that the antitumor response is provided by the infiltration of T cells into the tumor tissue and the downregulation of the expression of TIM-3 and PD-1 on CD8+ T cells. Combining immune checkpoint inhibitors ensures the production of effector cytokines IFN-γ and TNF-α. In addition, the production of immunosuppressive cytokines IL-10 and IL-6 decreases in the tumor tissue. Together, these effects make it possible to increase antitumor activity and overcome resistance (Zhang et al., 2023).

A promising new therapeutic target is VISTA. This immunosuppressive molecule belongs to the B7 family. VISTA is expressed by myeloid lineage cells in the immunosuppressive tumor microenvironment. Scientists have developed a potential monoclonal antibody against VISTA. Clinical candidate KVA12123 shows no cross-activity against other B7 family members but is highly specific against VISTA. The potential VISTA inhibitor activates T cells and monocytes. In an open-label phase 1/2 clinical trial in patients with advanced solid tumors, KVA12123, in combination with pembrolizumab, demonstrated better antitumor activity and increased efficacy compared to monotherapy (Iadonato et al., 2023).

Combining immune checkpoint inhibitors with neoangiogenesis inhibitors

Inhibition of vascular endothelial growth factor (VEGF) receptors can alter the tumor microenvironment and increase the effectiveness of immunotherapy. Humanized biospecific antibody AK112 targets PD-1 and VEGF receptors. The efficacy and safety of AK112 in combination with chemotherapy were studied in patients with metastatic non-small cell lung cancer. Platinum-based chemotherapy in combination with AK112 has demonstrated satisfactory antitumor activity in various patient cohorts.

This combination was used for first-line therapy in patients without an EGFR driver mutation and for second-line therapy after ineffective treatment with tyrosine kinase inhibitors, immune checkpoint inhibitors, or chemotherapy. Combining PD-1 and VEGF inhibitors is a potential way to overcome resistance (Zhao et al., 2023).

Combination therapy with avelumab and axitinib demonstrated its benefits in the phase III study JAVELIN Renal 101. Objective response rates and progression-free survival in patients with metastatic renal cell carcinoma were better than those in the sunitinib cohort. The scientists concluded that avelumab and axitinib are appropriate for first-line therapy in patients of all age groups. Data on overall patient survival are unavailable as the study is ongoing (Tomita et al., 2022).

The combined PD-1 and VEGF receptor inhibitors pembrolizumab and axitinib have proven effective as first-line therapy in patients with metastatic renal cell carcinoma. Overall survival and progression-free survival were significantly higher than those in the sunitinib group. In addition, this trend was maintained when using this scheme for the second and third lines of therapy. Median progression-free survival with pembrolizumab and axitinib was 11.1 months, and the objective response rate was 31.4% (Dizman et al., 2023).

Combination therapy with atezolizumab and bevacizumab compared with lenvatinib increases overall survival in patients with hepatocellular carcinoma. This effect is observed only in the viral etiology of the tumor. If hepatocellular carcinoma developed due to fatty liver disease, overall survival would be better in the lenvatinib group (Casadei-Gardini et al., 2023). The phase II TELMA study examined the effect of atezolizumab and bevacizumab therapy on 12-month recurrence-free survival in patients with stage IIIB or IV lung adenocarcinoma. The inclusion criterion was a TMB of more than ten mutations per megabase. As a result, the recurrence-free survival rate for 12 months was 51.3%, and the overall survival rate was 72.0% (Provencio et al., 2023).

Combination therapy with pembrolizumab and lenvatinib has shown better rates of recurrence-free and overall survival in patients with advanced hepatocellular carcinomas. The researchers concluded that combination therapy had a more significant survival advantage than pembrolizumab monotherapy. The combination of PD-1/PD-L1 inhibitors increases the infiltration of tumor tissue by T cells and helps overcome resistance. At the same time, the number of Tregs and MDSCs, which have an immunosuppressive effect, decreases. In addition, VEGF inhibition stimulates dendritic cell maturation (Liu et al., 2023).

Combining immune checkpoint inhibitors with chemotherapy

The benefits of combining immune checkpoint inhibitors with chemotherapy have been observed in many clinical trials. For example, the phase III study KEYNOTE-407 compared the treatment results of patients with metastatic non-small cell lung cancer. Pembrolizumab and chemotherapy were used to treat patients in the first group, and placebo and chemotherapy in the second group. Five-year progression-free survival and overall survival were significantly higher with pembrolizumab than placebo (18.4% vs. 9.7%, respectively) (Novello et al., 2023).

Combining pembrolizumab with chemotherapy showed its advantages in the phase III study KEYNOTE-859. Compared to participants in the chemotherapy and placebo groups, the researchers observed better overall survival rates and manageable toxicity. As a result, the combination of pembrolizumab and chemotherapy is recommended for first-line therapy in patients with metastatic or locally advanced HER2-negative adenocarcinoma of the gastroesophageal junction or stomach (Rha et al., 2023).

Improved patient survival due to the combination of immune checkpoint inhibitors with chemotherapy has been observed in patients with cervical cancer (Monk et al., 2023), pleural mesothelioma (Chu et al., 2023), biliary tract carcinoma (Kelley et al., 2023), triple-negative breast cancer (Hattori et al., 2023), and other malignancies.

It is believed that the basis of increased sensitivity to immune checkpoint inhibitors is the immunostimulating effect of chemotherapy. The accumulation of tumor-specific effector T-cells, stimulation of immunogenic cell death, and downregulation of MDSCs and Tregs in the TME manifests this. In addition, chemotherapy avoids lymphoid depletion and improves the immune response (Marshall et al., 2018).

Combining immune checkpoint inhibitors with targeted therapy

Combining immune checkpoint inhibitors with targeted therapy is a promising direction. The combination of dabrafenib (a BRAF inhibitor) with trametinib (a MEK inhibitor) is used to treat patients with anaplastic thyroid cancer with the BRAFV600E mutation (Kononenko et al., 2023). However, resistance occurs after a certain period, and the disease progresses. To overcome this problem, scientists used monotherapy with an immune checkpoint inhibitor, demonstrating a median overall survival of 5.9 months. However, the best results were obtained with a regimen that included dabrafenib, trametinib, and pembrolizumab. In this cohort of patients, the median overall survival was 9.0 months (Hamidi et al., 2024).

A similar combination of drugs was used to treat patients with advanced BRAF-mutant non-small cell lung cancer. Relapse-free survival in patients receiving a combination of an immune checkpoint inhibitor and targeted therapy was better than in those receiving targeted therapy alone (18.5 vs. 4.1 months, respectively) (Wang et al., 2023).

Unfortunately, in the phase III study of IMspire150, scientists previously found that in patients with metastatic melanoma with a positive BRAFV600 mutation, overall survival in the atezolizumab, vemurafenib, and cobimetinib group did not differ from the placebo, vemurafenib, and cobimetinib group. The final analysis results are awaited (Ascierto et al., 2023). The prospect of combining immune checkpoint inhibitors with BRAF/MEK inhibitors results from their clinical effects. As is known, patients who respond well to immunotherapy receive a long-term therapeutic effect. Targeted therapy allows a therapeutic effect to be quickly achieved, but the duration of the response is limited. That is why a good clinical response (short and long-term) is expected from the combination of drugs from different groups. BRAF inhibitors have a positive effect on the TME and increase immune response. This occurs by activating CD8+ T cells, improving their function, increasing antigen and PD-L1 expression, and reducing immunosuppressive cytokines. MEK inhibitors also enhance T-cell infiltration and stimulate antigen expression (Ragusa et al., 2022).

Active studies are devoted to the effectiveness of combining immune checkpoint inhibitors with PI3K (Yan et al., 2021; Lin et al., 2022) or CDK4/6 (Egelston et al., 2021; Rebecca et al., 2023) inhibitors. The effect of PI3K inhibitors is to increase the expression of PD-1 and CTLA-4 receptors on T cells, increase the infiltration of effector T cells, and transform tumor-associated myeloid cells. The consequence of these changes in the TME is the activation of the immune response (Zhang et al., 2022).

CDK4/6 inhibitors also improve antitumor activity. Their effect is to enhance tumor antigen presentation and inhibit the function and proliferation of Tregs (Jang et al., 2021).

Combining immune checkpoint inhibitors with epigenetic modifiers

Epigenetic modifiers make the TME more favorable for a good immune response. The combination of pembrolizumab with 5-azacytidine and romidepsin was used in patients with advanced colorectal cancer that was resistant to blocking only PD1 receptors. The scientists concluded that combined inhibition of DNA methyltransferase and histone deacetylase increases sensitivity to therapy with immune checkpoint inhibitors (Baretti et al., 2023).

In another study, scientists investigated the efficacy and effect on the TME of a combination of decitabine and ipilimumab (a DNA methyltransferase and CTLA-4 inhibitor, respectively) in patients with myeloma. Decitabine caused a predominantly cytoreductive effect. Ipilimumab provided activation of the immune response. It altered CD4+ T cell gene expression by ongoing T cell differentiation (Penter et al., 2023).

Combining ipilimumab with guadecitabine also demonstrated immunomodulatory activity and good clinical response. The findings were made after a five-year follow-up for melanoma patients participating in the NIBIT-M4 Phase Ib trial. The combined effect of ipilimumab and guadecitabine provides increased expression of HLA-I and regulation of genes of the IFN-γ pathway. In this way, the transmission of antitumor signals is facilitated (Noviello et al., 2023).

Pembrolizumab and vorinostat are promising ways to overcome immune checkpoint inhibitor therapy resistance. This combination of drugs was used in patients with classic Hodgkin's lymphoma, resistant to pre-

vious PD-1 blockade. The complete response rate in this cohort was 11%, and the overall response rate was 56% (Mei et al., 2023).

Two phase II studies, PEMDAC (Ny et al., 2021) and ENCORE 601 (Hellmann et al., 2021), showed a good antitumor effect of the combination of pembrolizumab and entinostat. Synergistic effects were observed in patients with uveal melanoma and advanced non-small cell lung cancer resistant to prior immune checkpoint inhibitor therapy. They were manifested in the inhibition of Tregs and MDSCs and an increase in the immune response. Unfortunately, this combination of drugs did not help to improve the results of treatment of patients with myelodysplastic syndrome and acute myeloid leukemia (Bewersdorf et al., 2024).

Combining immune checkpoint inhibitors with DNA damage repair inhibitors

Olaparib is the most common cytotoxic agent inhibiting poly(ADP-ribose) polymerase (PARP). The efficacy of olaparib and durvalumab has been evaluated in several studies. This combination of drugs has proven to be effective in patients with operable tumors of the head and neck. The scientists concluded that durvalumab and olaparib reduce Ki67 expression, induce the synthesis of pro-inflammatory cytokines by macrophages, and stimulate the regulation of PD-L1 (Moutafi et al., 2023). The combination of pembrolizumab and niraparib has shown good results in patients with recurrent ovarian cancer (Maiorano et al., 2022), advanced non-small cell lung cancer (Ramalingam et al., 2022), triple-negative breast cancer (Vinayak et al., 2019), and other tumors.

The synergistic effect of immune checkpoint inhibitors and PARP inhibitors is due to an activating effect on the immune system. As a result of damage to the micronuclei, DNA is released into the cytoplasm, which activates the innate immune system. An increase in TMB, increased neoantigen expression, activation of effector T cells, stimulation of dendritic cell maturation, and upregulation of PD-L1 were observed (Fernandes et al., 2023).

Combining immune checkpoint inhibitors with TGF-β inhibitors

TGF-β is an immunosuppressive cytokine. Its effect consists of stimulating the activity of Tregs, inhibiting the differentiation and infiltration of effector T cells. In some preclinical studies, scientists have concluded that blocking TGF-β signaling sensitizes tumor cells and makes them sensitive to immune checkpoint inhibitors (Matsuda et al., 2023). The combination of durvalumab and galunisertib, which was used to treat patients with recurrent pancreatic cancer, was expected to have high antitumor activity and a good clinical outcome. However, the effect of such treatment was limited (Melisi et al., 2021).

Conclusions

Although immune checkpoint inhibitors are a modern and advanced method in oncology, the treatment results are not always satisfactory. The weak immune response is associated with the different resistance mechanisms related to the tumor, the tumor microenvironment, or the patient's characteristics. Resistance to immune checkpoint inhibitors can be primary or acquired. The phenomenon is based on one or more pathological mechanisms. Understanding these mechanisms allows one to choose the correct treatment strategy to overcome resistance. The key to overcoming resistance to immune checkpoint inhibitors is testing for a wide range of biomarkers and investigating the molecular and genomic profile of the tumor. These methods of diagnosis allow physicians to choose the appropriate drug or combination of drugs to achieve the best treatment results and increase patients' overall survival. Such an approach could be helpful when selecting patients for participation in clinical trials.

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