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Research Progress of the Combating Drug Resistance in Cancer Immunotherapy

Siyuan Qian *

Admiral Farragut Academy Tianjin, Tianjin, 300074, China

* Corresponding Author: 2120190848@mail.nankai.edu.cn

Abstract. Cancer drug resistance is one of the reasons why cancer remains one of the deadliest diseases. Many drugs show initial efficacy in treatment but fail to exert their effects due to various mechanisms, which is particularly evident in immunotherapy. Currently, research is ongoing on anti-resistance drugs that target immune suppression, mutations, and the tumor microenvironment (TME). However, the current immunotherapy approaches have not yielded satisfactory results, with most patients developing long-term resistance or the drugs themselves not being ideal for clinical use. This article reviews the causes of resistance and common immunotherapies along with their associated anti-resistance strategies. It is found that the clinical efficacy of anti-resistance drugs and long-term survival rates for patients are not ideal. Future research should focus on improving individual and cooperative effects of cytokine therapy, CAR-T cell therapy, ICI, and combination therapies to avoid the development of secondary resistance. The role of cytotoxicity, as one of the most significant treatment barriers, should also be investigated. Many anti-resistance drugs are limited in their use due to the damage they cause to normal cell survival and metabolism.

Keywords: Immunotherapy; drug resistance; cancer.

1. Introduction

With the gradual rise of the clinical application of cancer immunotherapy, a significant problem was soon discovered in the treatment: A variety of immunotherapies that have been used in clinical trials will develop varying degrees of drug resistance during the treatment of patients due to the influence of various factors. In cancers that respond to the use of immunotherapy before patients develop resistant (there are certain cancer types that are not active to immunotherapy, such as pancreatic cancer and some subtypes of breast cancer), relapse due to therapeutic failure leads to reduced survival and duration.

For most cancers, high recurrence rates lead to poor prognosis and low survival rates, which have prompted researchers to propose several strategies in the study of anti-drug resistance. This article will focus on treatments that are more intensively used and proven to be effective. Combined immunotherapy, the simultaneous application of multiple immunotherapies, can effectively reduce drug resistance and enhance therapeutic efficacy. For instance, in the treatment of hepatocellular carcinoma, a combination of immune checkpoint inhibitors (ICIs), various monoclonal antibodies, and tyrosine kinase inhibitors has been utilized, resulting in an approximate response rate of 20%. Targeted signaling pathway regulation was also applicated in clinical practice. Targeted inhibition of the PI3K signaling pathway has been shown to suppress immune evasion and enhance immunogenicity of tumor cells, thereby improving responsiveness to immunotherapy. Modulating the TME is also a viable strategy, as damage to the TME can diminish the efficacy of drugs. In the treatment of hepatocellular carcinoma, regulating the abundance of peripheral immune cells has proven to be an effective method to reduce drug resistance. Other clinical methods to mitigate the occurrence of acquired drug resistance include immunomodulators, pharmacological modulators, precision medicine, and gut microbiota modulation. However, despite the current increase in mitigation rates, there is no significant change in overall survival rate (OS). Currently, research on combating drug resistance is still ongoing [1].

Analyzing the resistance to immunotherapy can provide valuable insights into extending patients' OS. Understanding the relationship between drug mechanisms and resistance can help prevent or delay relapse. Moreover, studying resistance mechanisms and relevant data can guide the development of new drugs, fostering innovative treatments and providing new therapeutic options.

This article will compare and analyze the relapse rates and related clinical data of various immunotherapies to explore common resistance mechanisms. Distinctive pharmacological characteristics of medications exert an influence on drug resistance will be investigated, thereby potentially impacting the drugs used to reduce relapse rates and death rates. As the effectiveness of immunotherapy is correlated with the type of cancer, this study will conduct an analysis specific to each therapy, which will cover various types of cancer and conclude with trend analysis. Comparisons of mortality rates and survival durations will be conducted to draw conclusions based on different variables and patient populations.

2. Drug resistance Mechanisms of Cancer Cells

The causative factors of the development of acquired drug resistance in cancer cells are highly diverse; a common feature among these factors is their negative impact on the therapeutic efficacy of various immunotherapeutic agents. The effects of drug molecules in inducing immune attack or slowing down cancer growth are weakened.

2.1. Immune Escape

One of the reasons for the failure of immunotherapy is immune escape. Immune escape is a phenomenon in which the immune system is unable to effectively recognize and attack cancer cells due to various spontaneous adaptations of cancer cells. These mechanisms include altering their own surface antigens, reducing antigen presentation or recognition capabilities, activating immune suppression pathways, or directly affecting immune cells. Immune escape can lead to targeted and multi-drug resistance, and the resulting resistance can occur in any treatment regimen based on the principle that drug molecules affect the immune response. Furthermore, other comprehensive factors can indirectly or directly lead to the failure of immunotherapy agents. Due to the instability of cancer tissue, these causing factors of drug resistance do not occur in a single occurrence, they can occur simultaneously or in a relationship with each other (For example, components in the adverse TME provide prerequisites for the occurrence of drug non-absorption, immune escape due to mutation, etc. 1]).

One common cause of immune escape is the increased expression of immune inhibitory factors. PD-1 is a transmembrane protein expressed on tumor cells, inflammatory cells and some normal cells. Interaction with PD-L1 can inhibit the activation, proliferation and immune response of cells in human body, which is an adaptive immune mechanism [2]. However, when PD-L1 is influenced by different signaling pathways in tumors, this pathway is exploited by tumor cells to evade immune surveillance, leading to non-immune cell growth effects. Elevated levels of PD-L1 expression have been found in lung cancer, gastric cancer, and bladder cancer [2]. It has been observed that higher levels of PD-L1 have a negative impact on prognosis, recurrence rates, and OS [3]. This characteristic provides a research direction for studying immune evasion caused by strong expression of immune inhibitory factors.

2.1.1. PD-1/PD-L1 inhibitors

A few inhibitors are now in application. For example, monoclonal antibody (mAbs) inhibition is widely utilized for PD-1/PD-L1 inhibitors (Nivolumab, Pembrolizumab, Atezolizumab, etc.) [4]. However, its safety and dose control features are still being studied. For instance, one drawback is that it can simultaneously lead to a low or absent expression of tumor-associated antigens (TAA), which can allow cancer cells to escape immune system attacks due to a weaker immune recognition response [5].

2.1.2. CTLA-4

For other immune escapes caused by similar mechanisms, such as CTLA-4 (cytokine T lymphocyte-associated antigen 4, an inhibitory receptor), the activity of T cells can be inhibited by binding to the B7 molecule to weaken the immune system's ability to attack. Inhibitors of CTLA-4 have made clinical progress [2]. The U.S. Food and Drug Administration (FDA) has approved an immunotherapy drug against CTLA-4, Ipilimumab (Yervoy), for the treatment of advanced melanoma and has shown efficacy, with significant increases in T cell activity and immune response [3].

2.2. Cancer Cell Mutation

Cancer cell mutation is one of the reasons for drug resistance, which cannot be prevented because of its underlying principle. There are two leading causes of drug resistance caused by mutations, one is that the mutation causes the cancer cells to increase neoantigens, and the other is that the mutation is generated during DNA rerepair and division. These can make the immune system recognition dysfunction and immune escape can occur. Multiple, targeted, drug efflux and metabolic resistance, and even resistance to chemotherapy caused by partial variation may occur in the mutation.

PIK3CA mutations could be an example of this in colon cancer. Due to the mutation of special gene segments, abnormal activation of PI3K causes cancer proliferation, down-regulation of apoptosis and increased expression of some drug-resistant proteins [6]. Ability of the cell to repair DNA and tolerance to specific chemicals can potentially increase. Mutations leading to drug resistance have also been observed in other types of cancers, such as acute myeloid leukemia with mutated FLT3-ITD [7], non-small cell lung cancer with EGFR mutation, etc [8]. For organs with rapid cell renewal metabolism, variants are more likely to emerge. Such as cutaneous cell malignant melanoma.

These mutations have similar underlying principles, sometimes increasing cell signaling activity or causing differences in cancer cell antigens. They all contribute to drug resistance in cancer and reduce overall survival within a given time period.

2.3. TME

The TME can also affect drug efficacy, with adverse effects leading to drug resistance and its effect on drug resistance is not significantly improved by changing the composition of other immune drugs. The composition of the TME will greatly affect the phenomenon of drug resistance. Not only limited to immune escape caused by immune cells, cytokines, etc., but the influence of microenvironment is more comprehensive. The activation of cell survival signaling pathway can activate growth factors, extracellular matrix, etc. to accelerate tumor growth and resist drug killing [9]. Angiogenic factors provide nutrients that increase the ability of tumor cells to resist drugs. Fibroblasts and stromal molecules can promote the fibrosis of tumor tissue and form barriers to the structure of tumor tissue, thus preventing the penetration of drugs [4]. These can negatively influence the efficacy of the drug.

2.4. Tumor Heterogeneity

Tumor heterogeneity also plays a role in cancer drug resistance. Malignant tumor tissues exhibit highly diverse characteristics. Heterogeneity is mainly divided into two types. Intratumor heterogeneity refers to the presence of different subpopulations of cells within a tumor tissue due to various factors, while intertumor heterogeneity refers to the variability of tumor cells in different tissues after metastasis [10]. These subpopulations exhibit significant differences in genetic, phenotypic, and functional attributes. These differences can lead to the evolution of diverse cancer cell populations, resulting in varying responses to the best immune therapies. In comparison to the previously mentioned functional resistance factors, tumor heterogeneity resembles a promoting factor [11]. Once subclones with a survival advantage emerge within the body, the traits of tumor heterogeneity increase the risks of tumor recurrence, metastasis, and rapid growth.

Many other adverse symptoms related to cancer and the main causes of drug resistance are a result of these phenomena and their associated cascading reactions. Overall, acquired resistance that arises

from these reasons often lacks reversibility, which results in reduced patient OS, relapse, and prognosis. The current technology for achieving universal clinical application seems to require more time, but some have already been approved by the FDA.

3. Current approaches to tackling drug resistance

Currently, there are diverse therapeutic strategies to combat immunotherapy drug resistance in cancer based on different principles. A large part of them has produced research results and been put into clinical application. Anti-drug resistance explores strategies including the improvement of drug molecules, combination with other treatments, use of special therapies, etc. to enhance the effect of immunotherapy.

3.1. Treatments

3.1.1. ICIs

ICIs have high clinical activity, mainly by disrupting inhibitory T cell signaling to prevent immune escape. Some typical ICIs have been approved by the FDA are relatively mature. Ipilimumab, Nivolumab, Pembrolizumab and other monoclonal drugs (most of which target CTLA-4/PD-1 antibodies) are already used to treat a variety of cancers. At present, this method has been widely used in anti-drug resistance because of its significant initial treatment effect, but its subsequent effect is still not optimistic. According to clinical data, late relapse occurred after the use of ICI, which is unexpected and indicates that the human body has developed resistance to ICI [12]. For example, several targeted inhibitors described above (PD-A, CTLA-4, etc., which have significant effects on the initial immune escape resistance of a variety of tumors), patients initially exhibit significant clinical remission but relapse in the long run 5-10 years, which also proves that drug resistance against such ICI is also acquired). For example, melanoma patients using ipilimumab (anti-CTLA-4) have a recurrence rate of about one-fifth in the time range of 5-10 years after use, which is speculated to be due to several problems with the immune response to T cells [12]. It can be speculated that the emergence of this "re-resistance" is still a clinical problem. Furthermore, the re-adjustment of T cells at present, such as the principle and regulation methods of T cell formation, expansion, memory, efficiency and other problems have not been studied and perfected. ICI resistance brought negative effects on the long-term survival rate of patients.

3.1.2. Cytokines therapy

Cytokines therapy stimulates the immune system through different chemical components or directly affects tumor growth. Various cytokines are important components of TME. The FDA has already approved the individual use of specific cytokines, but research is still looking into how to use combined therapy for most other cytokines to make them effective. The disadvantage of cytokine therapy is that it appears as a monotherapy with unsatisfactory results. The half-life of most cytokines is short, as a result, the duration of drug action cannot play a significant anti-tumor effect. Although there are molecules that prolong the half-life of some cytokines (such as PEGylated IFN-α, which is used in adjuvant therapy), the overall view is not ideal [13]. In addition, most of the cytokines are toxic, and the control of concentration and dosage is very strict and needs to be combined with anti-side effects of drugs.

There are many cytokines that can play a role, and the therapeutic effects have been shown in a variety of cancers. Due to the very different regulatory principles of different cell molecules for TME or tumor cells themselves, the use of cytokine therapy in the clinic is very diverse. For example, IFN-α can directly change the proliferative activity of tumor cells, and Interleukin-2 (IL-2) can promote the increase of the number of immune cells such as NK cells and T cells. These and a variety of other cytokines (such as other pro-inflammatory factors) can enhance the immune response (but most need to be treated with other monoclonal antibodies) [13]. Inhibiting the immunosuppressive activity can also be completed by some cytokines (such as TNF-α, TGF-β, etc.), which have substantial effect on the remission rate. It can also be applied to a variety of cancers such as renal cell carcinoma (RCC),

metastatic melanoma and hairy cell leukaemia [13]. However, because the use of cytokines for TME components is strict and toxic of cytokines, it is still being improved.

3.1.3. Chimeric antigen receptor (CAR)-T cell therapy

CAR-T (generally lymphocyte) cell therapy redirects cells through cell engineering (synthetic receptors) to make T cells more active to improve anti-tumor response. It has shown good efficacy in the treatment of B-cell leukemia, lymphoma and other non-solid cancers, and some drugs have been approved by FDA for clinical application [14]. However, CAR-T cell therapy still has a number of limitations.

Antigen escape is one of the problems. The single-antigen property of CAR structure improves the response rate while losing the targeting ability to cancer cells. This resistance mechanism has led to relapse rates as high as 30%-70% in patients with ALL treated with CD19-targeted CAR-T cell therapy [14]. The disappearance of targeted down-regulation also occurred in BCM and IL13Ra2 (solid tumors). The current strategy is to use dual CAR or tandem CAR constructs to increase the quantity and quality of target antigens [14]. This strategy has been proved to be effective in clinical practice, significantly increasing anti-tumor activity and reducing antigen escape [14].

Another major limitation is that the effect of CAR-T cell therapy in solid tumors (non-hematological malignancies) will show a targeted dememorization effect, that is, the antigen expression level is different on the cancer tissue [14]. This implies a reduction in the antitumor effect. Screening for target antigens can alleviate this problem while reducing toxicity. Another limitation shown against solid tumors is the ability to infiltrate and transport [14]. The physical barriers of TME and cells limit the flow therapeutic effect of CAR-T. This problem has not been significantly improved by local injection. The depletion of CAR-T cells and the side effects (some of which can be fatal, such as cytokine-release syndrome (CRS) and macrophage activation syndrome (MAS)) of CAR-T cells are in improvement at present.

3.1.4. Combined therapy

Combination therapy is the most widely used. In fact, the various types of immunotherapies mentioned above are rarely used alone due to their own characteristics. However, the properties of many drugs complement or even promote each other, making combination therapy more effective for patients and providing higher OS and short-term relief rates.

Combined therapy between immunotherapies is diverse. Collaboration with ICIs is common, and the combination of therapies can help them work better. For example, PD-1, which faces a deficiency in targeted T cells against mutated tumor cells, requires cancer vaccines (such as TLR) to provide stimulation and trigger immune infiltration [15]. Cancer vaccines can serve as adjuvant therapy to enhance the effectiveness of ICI. CAR-T cell therapy is also used in combination with ICI, as it improves the inflamed TME caused by CAR-T cell therapy, making the treatment more effective with rapid and durable responses [15]. Cytokines are often used in combination with monoclonal antibody drugs to modulate their toxicity and negative effects on the TME. The side effects of many immunotherapies can be alleviated through other therapies, and the diversity of medications and inhibition of resistance mechanisms improve treatment outcomes. Immune response and activity (i.e., the effectiveness of immunotherapy) are significantly enhanced after the application of combination therapy and have proven effective in various types of cancer.

Furthermore, more comprehensive combined therapies are widely used. For example, the downregulation of immune response expression levels caused by immune cell destruction from radiotherapy and chemotherapy can be improved by using immunotherapies in combination. Certain drugs that directly affect tumors, such as angiogenesis inhibitors, can modulate tumor immunity. Specific radiation doses in radiotherapy have been effective in activating or inducing immune responses, and chemotherapy-induced cancer cell death and promotion of antigen presentation can activate T cells, among other effects [15]. Most of the aforementioned combined therapies have been approved by the FDA and are used in clinical settings. In practice, there are rarely treatment regimens

that consist of only a single type of therapy, as combination therapy can effectively alleviate drug resistance issues.

3.2. Current clinical efficacy

Overall, the use of the aforementioned anti-resistance therapies has shown significant effectiveness in alleviating symptoms in the early stages, and many drugs have entered clinical applications. However, due to the occurrence of secondary drug resistance or other drawbacks that reduce treatment effectiveness, long-term overall survival (OS) remains challenging. After a second relapse or the emergence of side effects, the lack of comprehensive treatment strategies significantly reduces patient survival rates. Comparatively individualized treatments are also being applied, but their maturity and cost requirements need improvement. The standalone use of immunotherapy is rare, as there are still challenges in terms of side effects and efficacy. The use of combination therapy is relatively more widespread in clinical applications for most types of cancer.

4. Conclusion

In conclusion, acquired drug resistance in cancer cells is a major obstacle to the success of immunotherapeutic agents. Immune escape, cancer cell mutation, TME, and tumor heterogeneity, contribute to the development of drug resistance as the main mechanisms. Different therapeutic strategies such as ICI therapy, cytokines therapy, CAR-T cell therapy, and combination therapy were developed as current approaches to tackling drug resistance. However, emergence of secondary drug resistance and potential side effects, limit their long-term effectiveness.

The summary of this article can provide a comprehensive reference for the common principles and treatment methods of immunotherapy and related drug resistance. With a more detailed understanding of these, future drug development can be more attentive to the treatment strategies that still need to be improved. Other common treatments other than immunotherapy, such as chemotherapy and radiotherapy, are not described in this review and are only briefly mentioned in the combination therapy. Due to the diversity of different tissue structures and properties and other combined factors, the comparison of data specific to one type of cancer was not mentioned. However, the data presented here provide an overview of the trends in response rates, mortality, and other data with respect to treatment and resistance. It is believed that in the future research, the problem that is still vacant can be solved, so that the OS of cancer patients can increase.

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