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Review

Current Advances and Future Prospects in Cancer Immunotherapeutics

Kanser İmmünoterapilerinde Güncel Durum ve Gelecek Öngörüsü

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ABSTRACT

Cancer is a disease that results from the uncontrolled proliferation and growth of cells. Due to early detection methods, there is a decrease in death rates in many types of cancer. However, among the causes of death worldwide, cancer still ranks second after cardiovascular diseases. Therefore, cancer research has focused mainly on developing more effective treatments to reduce deaths from cancer. With a better understanding of the molecular mechanisms in cancer cells, advances in cancer treatment have evolved and changed. The main priority of research is to develop treatment modalities with the highest response rate and less side effects. In this context, immunotherapies have started a new era in cancer treatments. In this review, an overview of the future of next-generation treatment methods is presented by including the most preferred immunotherapy methods.

Keywords: Cancer, immunotherapy, CAR-T-cell therapy, monoclonal antibody, mRNA vaccine

ÖZ

Kanser, hücrelerin kontrolsüz şekilde çoğalması ve büyümesi sonucu oluşan bir hastalıktır. Erken teşhis yöntemleri sayesinde birçok kanser türünde ölüm oranlarında düşüş yaşanmaktadır. Ancak tüm dünyada ölüm nedenleri arasında kanser, kardiyovasküler hastalıklardan sonra halen ikinci sıradadır. Bu nedenle, kanser araştırmalarının çoğu kanserden ölümleri azaltmak için daha etkin tedaviler geliştirmeye odaklanmıştır. Kanser hücresindeki moleküler mekanizmaların daha da iyi anlaşılmasıyla kanser tedavisindeki gelişmeler, zaman içinde gelişmiş ve değişmiştir. Araştırmaların temel önceliği en yüksek yanıt oranına ve en düşük yan etkiye sahip tedavi yöntemleri geliştirmektir. İmmünoterapiler bu bağlamda kanser tedavilerinde yeni bir dönemi başlatmıştır. Bu derlemede en çok tercih edilen immünoterapi yöntemlerine yer verilerek yeni nesil tedavi yöntemlerinin geleceğine dair genel bir bakış açısı sunulmuştur.

Anahtar kelimeler: Kanser, immünoterapi, CAR-T-hücre tedavisi, monoklonal antikor, mRNA aşısı

INTRODUCTION

Cancer is a disease of cells that proliferate uncontrolled. Some features distinguish cancer cells from healthy cells: maintaining proliferative signaling, being insensitive to growth suppressive signals, resistance to cell death, providing unlimited replication capability, promoting angiogenesis, stimulating invasion and metastasis, reprogramming environmental and cellular metabolism, and evading immune destruction[1]. Because to their genetic mutations, cancer cells are not caught in cell cycle control mechanisms and they escape from apoptosis[2]. The role of environmental factors in carcinogenesis is critical and genetic alterations. These factors include physical carcinogens such as ionizing and ultraviolet radiation; chemical carcinogens such as smoking, alcohol consumption and asbestos exposure, and dietary consumption of arsenic and aflatoxin. Biological carcinogens, including infections from certain bacteria, viruses or parasites are also among the causes of cancer deaths; approximately one-third of those are related to smoking, alcohol consumption, high body mass index, unhealthy diet, and insufficient physical activity[3,4].

Today, despite early detection methods and advanced therapies, cancer still is a global health problem with a high incidence and mortality rate. According to the World Health Organization, it is estimated that approximately 10 million deaths and one in 6 deaths in 2020 are caused

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by cancer. Breast, colorectal, lung, cervical, and thyroid cancers are most common among women while lung, prostate, colorectal, stomach, and liver cancer are most common among men. While the most common cancer types in terms of new cases diagnosed in 2020 breast, lung, colon and rectum, prostate, skin and stomach, lung, colon and rectum, liver, stomach, and breast cancers are the most common causes of cancer deaths in 2020[5].

Although there is a decline in death rates in many cancer types due to effective treatment methods, most of the cancer research is focused on developing better therapies to reduce the deaths. Cancer treatment has evolved and changed with a better understanding of the molecular mechanisms underlying cancer. With an increasing number of cancer patients, significant challenges arise worldwide. However, the search for treatment with the highest response rate and fewer side effects continues apace[6]. There are different types of cancer treatments used in the clinic: surgery, radio-/chemotherapy, hormone therapy, photodynamic therapy, targeted therapy, stem cell transplant, hyperthermia, and immunotherapy[7]. These types of treatments are often used in combination because of their resistance mechanisms in cancer.

This review predicts the future of new-generation cancer therapeutics considering current research and to discuss the factors that may be effective in determining national and international roadmaps.

IMMUNOTHERAPIES

Immunotherapy has become an advanced treatment strategy among the different therapeutic options in various malignancies, including hematological and solid tumors.

In immunotherapies, a patient's own immune system is used to fight cancer, to pave the way for more specific and effective treatments. In comparison to chemotherapy, having comparably fewer side effects, cancer immunotherapy is a promising tool for those with different malignancies[8]. Current immunotherapy therapeutics include inhibitors of immune checkpoint, monoclonal antibodies (mAbs), mRNA vaccines, and adoptive cell transfer in the form of chimeric antigen receptor (CAR)-T cell therapies (Figure 1)[9].

Cancer immunotherapy is classified as passive or active immunotherapy based on the immune response. Passive immunotherapy uses agents that increase the existing anti-tumor response, including lymphocytes, cytokines, or mAbs. Active immunotherapy includes methods such as vaccination, non-specific immunomodulation, or activation of the immune system by targeting particularly designed antigen receptors to tumor cells[10]. Contrary to the successful immunotherapy approaches, limiting factors restrict the activation of tumor-specific immune responses, such as intratumoral heterogeneity, poor production and function of tumor-specific CD8 T-cells, shortage of appropriate neoantigens with defective processing, and antigen presentation[11]. Resistance mechanisms to immune response are mainly related to T-cell immune checkpoint pathways. Thus, investigating molecular pathways and exploring new immune checkpoints can reduce the immune response evasion. To enhance the response to immunotherapeutics, it is crucial to find strategies that will increase arrival to the tumor site, enhance T-cell continuity and proliferation, reduce immunosuppression and prevent T-cell depletion[12].

Monoclonal Antibodies (mAbs) for Cancer Therapy

mAbs produced by B lymphocytes or synthetically are proteins that bind to a specific molecular target[9]. Anti-cancer effects have been achieved in preclinical models and patient studies by designing humanized mAbs against appropriate targets[13]. Recently, mAbs have been highly preferred cancer therapeutics as they are substantially specific and have lower cytotoxic effects[14].

mAbs are one of the rapidly developing immunotherapy produced in the pharmaceutical industry. There are more than 22 US Food and Drug Administration (FDA)-approved immunotherapeutic drugs for oncological diseases, in which several of them are presented in Table 1. Studies have shown that the overall survival of cancer patients could be improved by mAbs[15]. Based on these studies, recovery has been identified through many anti-cancer mechanisms, such as antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), promotion of apoptosis, and suppression of cell proliferation[16]. Hybridoma technology was established in 1975 by Köhler and Milstein to develop therapeutic mAbs. Within the scope of this technology, production is performed using immunized mouse spleen cells with the ability to produce antibodies and immortal cancer B-cell myeloma cells[17]. Although hybridoma technology-based mAbs have a great advantage in having low aggregation and high antigen binding *in vivo*, murin mAbs have a short half-life as well as low biological activity and effector function onset[18]. The developed anti-rejection monoclonal antibody muromonab-CD3 is the first therapeutic monoclonal antibody approved for clinical use by the FDA in 1985[19].

With recent developments, the most preferred method to develop mAbs for use in clinical applications is antibody engineering. The best examples of these studies are the design of murine mAbs as humanized, fully human, chimeric, and bispecific antibodies using cloning and sequencing methods. The development of a fully human mAb has been achieved with the phage display method and transgenic animal technology[20]. Compared to murine mAb, the constant region found in humanized and human mAbs has reduced immunogenicity, improve effector functions, and significantly prolong serum half-life[21].

mAbs are applied for cancer therapy as immune checkpoint inhibitors (ICIs), antibody drug conjugates, and bispesific T-cell linkages. It is also used for targeting pro-tumorigenic compounds and direct tumor cells. The mechanisms of action of targeted mAbs are receptor blocking, ligand blocking, as well as CDC, antibody-dependent cellular phagocytosis, and ADCC, which occur with the activation of host immune system components. In 1997, the first anti-cancer chimeric mAb, anti-CD20 rituximab, has been approved by the FDA for use for treating patients with non-Hodgkin lymphoma[22].

mAbs are conjugated with strong chemotherapy methods to form antibody-drug conjugates (ADCs). Considering the large number of mAbs evaluated in ongoing clinical trials, it could be hypothesized that the market share of ADCs will gradually increase. The development of new cancer-targeted mAbs, and the design of new linkers to enable controlled drug release will further advance ADC technologies.

Immune Checkpoint Inhibitors

As cancer cells can evade the tumor-reactive T-cell response, it is necessary to increase the effectiveness of anti-tumor immune responses[23]. Recent advances in understanding T-cell immunobiology has been particularly influential in identifying therapeutic plans against the immune escape mechanisms of tumors. Therefore, one of the most promising therapeutic modalities for patients recently has been immune checkpoint inhibition[24]. T-cell activation plays an important role in the regulation of anti-tumor immunity. The immune system includes several checkpoint pathways that focus on T-cell activation. Significant molecules in checkpoint arrangements include T-cell surface molecules, T-cell immunoglobulin, and mucin domains. Expression of these molecules causes an excessive immune response. Therefore, they are important targets for cytotoxic T-cells to attack cancer cells and abolish inhibition[25]. ICIs are mAbs that can block immune cell receptors or immune

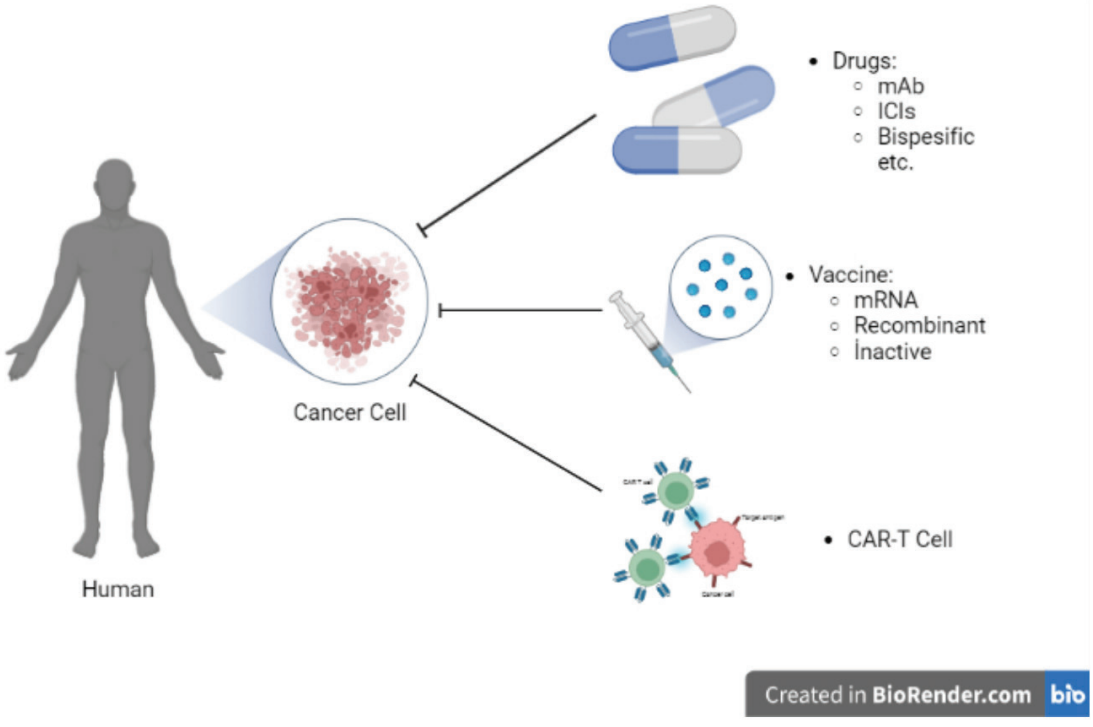

Figure 1. Current advances and future prospects in cancer immunotherapies.

ICI: Immune checkpoint inhibitors, mAb: Monoclonal antibody

checkpoints. Tumor cells tend to overexpress ligands that activate these inhibitory receptors. Therefore, the T-cells evades the immune response and multiplies uncontrollably. The programmed cell death protein 1 (PD-1) and T-cell surface molecule CTLA-4 are examples of the immune checkpoint systems that are in the center of antibody development for blockage. CTLA-4, when activated, transmits inhibitory signals that block the proliferation of T-cells and secretion of cytokine IL-2 for maturation. The CTLA-4 inhibitor ipilimumab[26] positively affected the survival rate in a clinical trial on stage III and IV melanoma patients and became the first ICB drug to receive FDA approval in 2011[27].

PD-1, unlike CTLA-4, suppresses T-cell activity by promoting T-cell depletion. Nivolumab, the first PD-1 drug to target immune checkpoint blockade, was approved by the FDA in 2014. Pembrozilumab, an anti-PD-1 immune checkpoint blocker, and cemiplimab are other drugs. The latest FDA-approved immune checkpoint blocking drugs, including atezolizumab and durvalumab, target the PD-1 ligand, PD-L1, thereby providing the same inhibition of PD-1 activation with a different chemical approach[28].

With recent studies, different targets such as *lymphocyte activation* gene-3 (*LAG-3*), V-domain Ig suppressor of T-cell activation, T-cell immunoglobulin and mucin domain-containing-3 (TIM-3), ITIM domain (TIGIT), and T-cell immunoglobulin are identified as new

Table 1. FDA-approved immunotherapeutic drugs for different cancer types.

Name	Target	Cancer (year of first approval)*
Adagrasib	RAS GTPase family	Non-small cell lung cancer (2022)
Atezolizumab	PD-L1	Urothelial carcinoma, non-small cell lung cancer (2016)
Avelumab	PD-L1	Merkel cell carcinoma (2017)
Bevacizumab	VEGF	Colorectal, lung, cervical, renal cell cancers, glioblastoma (2018)
Cemiplimab	PD-1	Cutaneous squamous-cell carcinoma (2018)
Ciltacabtagene autoleucel	BCMA	Multiple myeloma (2022)
Dostarlimab-gxly	PD-1	Advanced endometrial cancer (2021)
Durvalumab	PD-L1	Bladder cancer (2017)
Elacestrant	ER, HER2	Breast cancer (2023)
Enfortumab vedotin	Nectin-4	Bladder cancer (2019)
Fam-trastuzumab deruxtecan-nxki	HER2	Non-small cell lung cancer (2022)
Futibatinib	FGFR2	Cholangiocarcinoma (2022)
Isatuximab	CD38	Multiple myeloma (2020)
Lisocabtagene maraleucel	CD19	Large B-cell lymphoma (2021)
Mirvetuximab soravtansine-gynx	FRα	Peritoneal cancer (2022)
Mosunetuzumab-axgb	CD20	Lymphoma (2022)
Nadofaragene firadenovec-vncg	IFNα2b	Bladder cancer (2022)
Nivolumab and relatlimab-rmbw	PD-1 and LAG-3	Metastatic melanoma (2022)
Olutasidenib	IDH1	Acute myeloid leukemia (2022)
Pirtobrutinib	BTK inhibitor	Lymphoma (2021)
Sacituzumab govitecan-hziy	ER, HER2	Breast cancer (2020)
Tebentafusp-tebn	CD3	Metastatic uveal melanoma (2022)
Teclistamab-cqyv	CD3	Multiple myeloma (2022)
Trastuzumab deruxtecan	HER2	Breast cancer (2019)
Tremelimumab-actl	CTLA-4	Non-small cell lung cancer (2022)
Tucatinib	HER2	Breast cancer (2020)
Zanubrutinib	BTK	Small lymphocytic lymphoma or chronic lymphocytic leukemia (2019)

FDA: US Food and Drug Administration

*The first year of approval and the indications for each antibody were accessed using the FDA drug database. (https://www.accessdata.fda.gov/scripts/cder/daf/)

immune checkpoints[29]. In March 2022, Opdualag, a fixed-dose combination of programmed death receptor-1 blocking antibody nivolumab and LAG-3 blocking antibody relatlimab, received FDA approval[30].

CAR-T-Cell Therapy

In the last decade, chimeric antigen receptor-T cells have become a new form of as a cell-based immunotherapy in which T-cells from cancer patients are genetically modified and are used to target tumors. With the recent developments in genetic engineering, a chimeric receptor is expressed and cancer cells with potent anti-tumor effects are targeted. CAR-T gained much attention as a novel treatment option for particularly hematological cancers recently[31].

CAR-T-cell therapy uses patients' autologous T-cells to generate a tumor antigen-specific CAR *ex vivo*, and then infused CAR-T-cells back into patients[32]. In more recent studies, nanocarriers loaded with gene editing tools and CAR genes have been promising for leukemia regression by inducing CAR-T-cells *in vivo*[33]. Currently, most clinical studies involving CAR-T-cells are early phase studies in B-cell malignancies. The most common target is CD19, mostly alone, but more recently along with other antigen targets[34].

Because of CD19 expression, blood cancers are the most amenable disease group to occur in the future of CAR-T-cell therapies. High level of tumor expression of the target antigen, the ease of accessing tumor cells via blood and lymphatics and the tolerability of the non-tumor effect of B-cell aplasia on the target make CD19 a good candidate for targeted therapy[35]. In addition to CD19, BCMA is the other antigen that CAR-T-cell treatment is approved by FDA[36].

CAR-T-cell therapy has shown effective clinical results, particularly against B-cell acute lymphoblastic leukemia. However, its effects are limited in solid tumors due to tumor histopathological features, lack of tumor-specific antigens, immunosuppressive tumor microenvironment, and potentially life-threatening tumor toxicity[37]. Nevertheless, scientists attempt to be made to overcome some of these barriers, particularly by engineering CAR-T agents[38]. As research in CAR-T therapies expands, promising results will continue to emerge alongside challenges. Thus, CAR-T will continue to positively influence, direct, and influence its potential.

Cancer Vaccine

Cancer vaccines are designed to induce an immune response against tumor antigens. Although it has been long years of research and development, only a small group of cancer vaccines have been transferred into clinical use[39]. The success of cancer vaccine depends on diverse factors, including the microenvironment of the tumor, the type of antigens used, several vaccine formulations and the immune makeup of the tumor[40]. Cancer vaccines can be used preventively or therapeutically[41]. The first preventive cancer vaccines were against viral infections associated with cancer development. Hepatitis B virus (HBV) is the major cause of hepatocellular carcinoma, and HBV vaccine was first licensed in 1986 in the US. Since then, it has become available in many countries around the world. For long-term immunity against chronic HBV infection, three doses of the vaccine are recommended[42].

Several cancers are associated with human papillomavirus (HPV), including cervical, oropharyngeal, anal, penile, and vulvovaginal cancers[43]. Recently, there are three approved HPV vaccines available since 2006, and men and women over 11 years of age are recommended for vaccination to prevent HPV-related disorders. However, currently there is no preventive vaccine for non-viral cancers approved for use in humans. In part, this is due to a lack of tumor-associated antigens (TAAs) along with a risk of autoimmunity on healthy tissues because of cross-reactivity. However, safer TAAs are now tested in therapeutic vaccine trials without causing autoimmune reactions[44].

Additionally, pre-clinical and clinical trials of mRNA vaccines as a therapeutic strategy against cancer are based on years of research[45]. mRNA vaccines have been a rapidly growing area of research as they have good tolerability, degradability, non-integration into the host genome, non-infectious potential, and the potential to induce both cell-mediated immunity and humoral[46]. The use of mRNA vaccines along with other immunotherapeutic treatment modalities, such as oncolytic viruses, ICIs, and adoptive cell transfer, has increased therapeutic success[47].

Decades of research have proven that cancer vaccines can indeed improve systemic tumor regression and lasting remission. However, the reasons for its failure in clinical practice include loss of antigen from the tumor, loss of MHC, inclusion of soluble factors or immunosuppressive cells in the microenvironment, and lack of a strong anti-tumor immune response. Additionally, cancer vaccines have limited clinical application as they cannot induce T-cell responses with high enough avidity to efficiently eradicate tumors. It may be due to its own immune avoidance and escape mechanisms, including the inability to induce research that advances our immunological understanding and is

on the verge of using it to develop rational and effective cancer vaccines is promising for the future. The success of any cancer vaccine as a target relies on overcoming the immunosuppressive tumor microenvironment and transforming "cold" tumors into "hot" tumors, thereby inducing a potent tumor-specific immune response that can kill cancer cells. In the future, with the investigation of new target antigens, adjuvants, and delivery systems, current challenges will be overcomed effectively[48].

CONCLUSION

Recently, immunotherapy has become a remarkable cancer treatment method with the development of CAR-T-cells, ICIs, and cancer vaccines. In preclinical studies, it has been determined that the combination therapy of CAR-T-cells and ICI is effective on various malignancies and is more effective than the treatments used alone[49]. For this reason, it is thought that it will be a promising method for their use in clinical studies. Antibody-based cancer therapy has also been highly effective in the clinic. There are different mAb constructs, there are different mAb structures, such as mAbs for clinical trials with optimized pharmacokinetic properties, and mAbs conjugated with small molecule drugs. With the increase in studies on understanding the mechanisms, problems such as resistance to treatment, identification of potential targets, analysis of biological systems, and individual variations will be minimized. With the use of different immunotherapy approaches in the future, cancer patients will have a treatment method with the highest immune response rate and the lowest side effects.

As new genomic and molecular therapies are discovered, it is increasingly important to construct and accurately interpret molecular tumor profiles to deliver effective cancer therapy. However, the remarkable development of molecular techniques and the precision of the information obtained with these tools are important. To convert these molecular profiles to clinical benefit, clinical cases and results obtained from molecular analysis need to be discussed. Artificial intelligence-based clinical decision support tools might be a solution for this problem in the near future[50].

Ethics

Peer-review: Externally peer-reviewed.

Author Contributions

Concept: B.Y., Design: B.Y., Literature Search: Z.D., K.T., T.K., Writing: Z.D., K.T., T.K., B.Y.

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