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Overview of current approaches in cancer immunotherapy and personalized opportunities for future aspect

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Abstract

Cancer refers to a group of diseases characterized by a rapid and uncontrolled proliferation of cells in the body after undergoing a series of structural variations. Non-specific methods such as surgery, radiotherapy, and chemotherapy are used widely in cancer treatment. Recently, there is a special focus on specific methods such as immunotherapy that targets certain parts of the patient's immune system. New treatment options are needed in this respect because nonspecific methods are insufficient in curing the disease, do not increase patient's survival, and healthy cells are damaged as well as cancer cells. Immunotherapy has less toxicity, fewer side effects during treatment, and is a patient-specific individualized treatment modality. Due to the fact that human tumors occur with a combination of genetic and epigenetic changes, cancer cells manage to recognize immunity and escape subsequent destruction. The main goal of cancer immunotherapy is to reactivate the immune system to neutralize tumor cells. Immunotherapy has many advantages such as preventing the side effects of chemotherapy/radiotherapy, avoiding metastases, and targeting cancer stem cells. The main treatment methods used in cancer immunotherapy, are cancer vaccines, adoptive cell therapy, cytokines, and monoclonal antibodies. In this review, we outline some of the main strategies in cancer immunotherapy and discuss the progress in personalized cancer therapy.

Introduction

Cancer, which is a global problem, is known to be one of the leading causes of mortality in the world. Every year, approximately 14 million new cases of cancer are diagnosed worldwide. About half of them die 10 years from diagnosis (Callahan et al., 2016). Studies efforts to improve cancer survival, early diagnosis, treatment options, and to prevent metastases, have nearly doubled in the last 40 years (Walk et al., 2020). Cancer immunotherapy has revolutionized the field of oncology by increasing survival rates of patients. It is reported that the human immune system is properly activated and has a therapeutic capacity that can provide complete healing for the patient as it is effective on common metastatic cancer cells (Hanahan and Weinberg, 2011; Callahan et al., 2016; Walk et al., 2020).

Advances in immunotherapy were reported to have transformative effects on the fields of oncology, radiology, and cancer drug development. More than 2000 cancer immunotherapy agents approved by the Food and Drug Administration (FDA) are currently in the clinical trial phase. Despite the positive clinical outcome data of the agents to be used for immunotherapy, cancer immunotherapy is currently claimed to benefit only for a small subset of cancer patients, and indications for cancer evaluated in clinical trials are reported to be approximately 20% on average. Biomarkers with predicted efficacy of treatment are crucial for current clinical trials since not all patients respond to cancer immunotherapy, and some of them have even experienced severe immune reactions. Today, although the knowledge obtained in the field of tumor biology has increased, there are few tumor biomarker tests that are reflected in standard clinical practices. Programmed Death Ligand-1 (PD-L1), Immunohistochemistry (IHC-Immunohistochemistry), Mismatch Repair (MMR), Microsatellite Instability (MSI) Test, Tumor Infiltrative Lymphocyte (TIL), and the multiplex assessment of the tumor microenvironment are helping to guide the cancer immunotherapy (Walk et al., 2020). Cancer is defined as the accumulation of multiple genetic modifications and the loss of regulatory processes at the cellular level. The first stage of immunotherapy to be used after cancer development involves the expression of neoantigens, which are effective in the anticancer immune response against cancer cells and are captured by dentritic cells (DC) (Tian et al., 2011).

The stage of cancer immunotherapy include 1) the release of immunological signals such as proinflammatory cytokines, 2) the presentation of antigens captured by dendritic cells to T cells, 3) the activation of effector T cells against tumor-specific antigens, 4) the activation of the activated T cells, such as CD8+ (Cluster of Differentiation 8) effector T cells, and target the tumor, recognizing and killing cancer cells (Fig. 1) (Chen and Mellman, 2013; Pardoll, 2012).

So, cancer immunotherapies aim to apply therapeutic interventions to promote anti-tumor immunity by elucidating the molecular and cellular mechanism by which cancer cells can escape from the immune system (Taefehshokr et al., 2020). By targeting the tumor microenvironment with immunotherapy applications, it is possible for patients to benefit from individualized treatment with minimal side effects (Harris and Drake, 2013; Seledtsov et al., 2015).

Definition of immunotherapy

Immunotherapy, which is one of the most powerful tools for cancer treatment, is effective in targeting cancer cells using the immune system of the body and creating a lasting anti-tumor response. It also prevents the metastasis and recurrence of cancer cells along with this effect (Rosenberg et al., 2004; Song et al., 2017; Zhang et al, 2019).

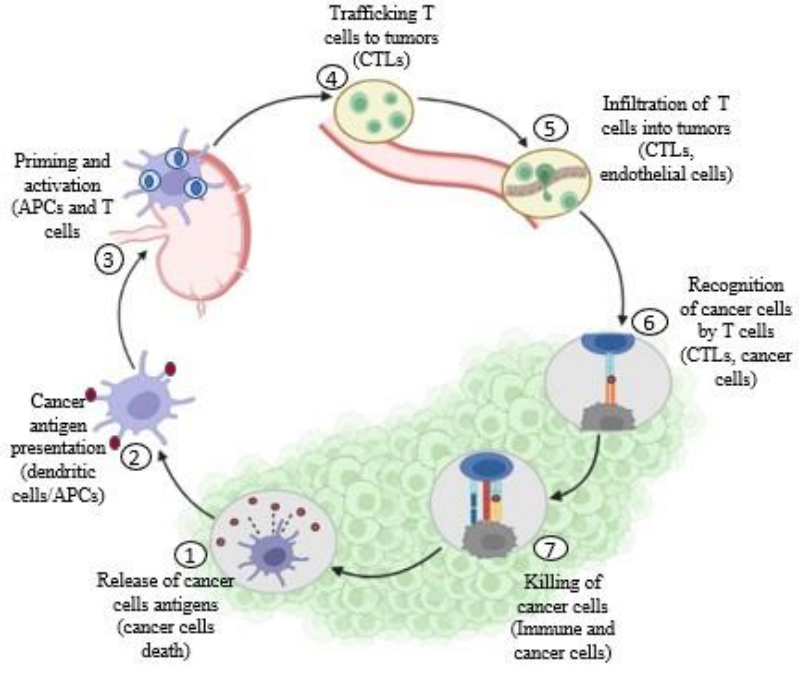

Figure 1. Cancer immunity cycle: The cycle consisting of seven steps; In the first step, it starts with the release of tumor-associated antigens from cancer cells and is completed with the death of the cancer cell in the last step. The cell types and activity location involved in each step are shown in the figure (Chen et al., 2020).

For a strong immunotherapeutic result, the immune system that can successfully recognize and eliminate the cancer niches lurking in the human body is needed (Taefehshokr et al., 2020). The immune system is divided into two different response components, natural (innate) and adaptive. The natural immune system includes neutrophils and macrophages, among other type of cells, reacting rapidly but indiscriminately, recognizing foreign antigens such as receptors and microbial products. Basically, innate immunity is a non-specific defense mechanism that immediately responds to the emergence of antigens (Lobenwein et al., 2021). Adaptive immunity, on the other hand, is a more complex immune response that exhibits antigen-specific immune responses requiring the processing and recognition of an antigen. The adaptive immune system encourages immune cells to attack against an antigen after it recognizes an antigen (Walk et al., 2020). This process, which depends on the adaptive immune system; begins with the release of immunogenic neoantigen proteins into the tumor microenvironment. The released neoantigens are processed by dendritic cells that migrate to lymph nodes to activate tumor-specific cytotoxic T cells. Tumor-specific CD8 cytotoxic T cells return back to the tumor cell to destroy the cancer cells and

renew the immune cycle (Leach et al., 1996). The success of cancer immunotherapy so far has resulted from the careful elucidation of this cycle, including the mechanisms and specific parameters underlying immune responsiveness and resistance. The first thing required to understand the immune mechanisms in cancer treatment and to successfully target cancer cells is the presence of immune regulatory checkpoints. While these checkpoints function to activate the immune system, some of them also function to down-regulate immunity (Walk et al., 2020).

Personalized medicine and cancer immunotherapy

Personalized medicine is the medical treatment adapted mainly to the individual genetic characteristics. In general, the drugs used in personalized medicine lead to the medical approach that suggests the customization of the health system with medical decisions, clinical practices or products adapted to the individual characteristics of patients (Bhambre et al., 2021). In the last decade, the developments in the next-generation sequencing technology have been effective in identifying individual's genomes and planning personalized therapies, including gene expression and epigenetic profiles (Kiyotani et al., 2021). Personalized treatment approaches based on cancer genome information of individuals are guiding in identifying target molecules and selecting appropriate treatments for cancer patients (Kiyotani et al., 2021; Maciejko et al., 2017). The determination of effective treatment methods in cancer treatment has led to a great innovation in immunotherapy cancer treatment, which is a more effective model among other treatment methods applied. Also, these treatments are customized for each individual (Bhambre et al., 2021; Maciejko et al., 2017). Targeted cancer drugs act by targeting the differences in cancer cells that help them grow, divide, and spread.

One of the first examples of targeted cancer therapy was use of trastuzumab as treatment for HER2-positive metastatic breast cancer (Garattini et al., 2015). Trastuzumab opened the door to the development of personalized treatment systems in cancer immunotherapy, and even if HER2 is expressed at low levels on tumor cell surfaces, currently, it is possible to send the drug directly to tumor cells with trastuzumab deruxtecan, also known as T-DXd (Modi et al., 2022).

The effect of cancer on the immune system

The immune response to tumors

It is important to understand how cancer interacts with the immune system to identify the underlying basis for immune avoidance from cancer and to design effective immunotherapies. Cancer, which is known as uncontrolled cellular proliferation, develops several characteristic features that contribute to the onset and progression of the disease. Transformation of a normal cell into a cancerous cell include the production of new forms of host molecules known as cancer antigens or tumor-associated antigens (TAAs) (Schreiber et al., 2011; Kakimi et al., 2017; Yang, 2015). The new host molecule forms that are produced in this way allow the immune system to recognize the cancerous tissue by separating cancer cells from normal and healthy cells. Although immune cells are effective in killing most tumor cells, they also leave out the variants that can hide from the immune system or suppress it. The resulting resistant tumor cells are then transformed into clinically significant tumors (Yang, 2015). The immune system must be able to recognize exogenous stimuli and fight them without affecting the tissue itself under homeostatic conditions. Any disorder in this balance causes various pathologies with excessive immune reactivity leading to autoimmune diseases or allergies, tumor progression, and excessive tolerance that promote infections (Escribese and Barber, 2017). In the

case of cancer, tumor cells, which were originally self-cells, are recognized by the immune system because of the expression of tumor-associated antigens (Ward et al., 2016). The recognition of these molecules by the immune system triggers the activation of effector CD8 T cells, Natural Killer (NK) cells, and M1 macrophages. However, this does not always happen (Ward et al., 2016; Teng et al., 2015). In some cases, the constant interaction of immune cells with tumor cells induces the "immunoediting", and results in the inactivation of the immune system by tumor cells (Merlo et al., 2016). Usually, this is caused by the ability to reduce the expression of tumor antigens and the expression of the Major Histocompatibility Complex (MHC) on the cell surface and to induce the secretion of immunosuppressive mediators such as Transforming Growth Factor Beta (TGFb) and Interleukin-10 (IL10). All these "immunoeditions" facilitate the loss of immunogenicity and induction of immunosuppression, which accelerate tumor progression (Ribatti et al., 2016).

Because of the important role of the immune system in tumor progression, different strategies and therapeutic agents managed to re-direct or activate/inhibit the immune response in cancer were studied in previously. Cancer immunotherapy is divided into 3 approaches; cancer vaccine, cell transfer therapy, and immune checkpoint therapy. All modalities depend on the cellular immune response to control tumor cells (Kakimi et al., 2017; Escribese and Barber, 2017).

Antibody and antibody fragments for cancer immunotherapy

Antibody-based drugs are among the fastest developing biopharmaceuticals. With the approval of Rituximab in 1997 and its worldwide commercial success as an antitumor drug, more than 50 therapeutic antibodies have been approved for clinical use (Ayyar et al., 2016). In the first stage of antibody development studies, mouse-derived antibodies, which were very promising, caused an immune response called HAMA (human anti-mouse antibody), which caused a decrease in the effectiveness of the antibody structure during their therapeutic applications in humans. Antibody structures for the resolution of the HAMA response with the help of DNA technology, 30-35% of mouse origin and 65-70% human origin chimeric antibodies were developed. Due to the detection that the HACA (human anti-chimeric antibody) response encountered during the use of chimeric antibodies can be improved, studies have accelerated to make the antibody structures as similar to human structures as possible. For this purpose, first of all, CDR (complementary determination regions) located in the variable regions of the antibody structures were left of mouse origin, and humanized antibody structures, 5-10% of which were mouse origin, were developed with the other parts of human antibody structures. Due to the mouse-derived protein structures of the humanized antibody undesirable side effects may occur against these antibodies (Ni J, 2009). Therefore, the last two decades have focused on the development of human-derived antibodies in different forms using antibody engineering (Roth K, 2021). Furthermore, it is enabled to generate structurally modified antibodies or antibody derivatives using advanced prokaryotic and eukaryotic expression systems and transgenic plants and animals using a variety of imaging platforms and in vitro selection methods (Winter and Milstein, 1991). Current trends in antibody-based cancer therapeutics suggest a major focus on immune-modulating antibodies that regulate or redirect T-cell functions. Recent advances in antibody technology have resulted in a revival of old concepts that have led to the generation of new therapeutics for cancer therapy such as bsAb, ADCs and ICIs (Ayyar et al., 2016).

Due to the increase in knowledge about antibody structures and advances in recombinant DNA techniques, the construction of various antibody fragments, especially single-chain variable fragments (scFv, ~30 kDa) and single-domain antibodies (sdAbs, ~15 kDa) has been made possible ScFv constructs consist of one heavy chain variable (VH) and one light chain variable (VL) region of the antibody structure that are linked by a fexible polypeptide linker. SdAb, known as the smallest antibody fragment, has only one variable domain Another of the antibody structures used in cancer immunotherapy is fragment antigen binding (Fab) structures. Fab consists of one complete light chain and one variable and constant(C) portion of heavy chain.

These antibody fragments have an advantage over all whole mAbs in penetrating tumor tissues due to their small size. As shown in Figure 1 (Hoogenboom, 2005). On the other hand, shrunken sdAb generally provide high intratumor penetration capacity and can bind some epitopes that full-length antibodies cannot reach. Antibody fragments can be utilized in different applications in cancer immunotherapy due to their different structures (Chen et al., 2020).

Apart from conventional antibodies consisting of both antigen-binding domains and constant regions, antibody fragments consisting only of variable domains also has potential in tumor immunotherapy. ScFv fragments, consisting of a variable domain in the heavy chains and a variable domain in the light chains, are derived from conventional antibodies and are widely used in CAR T cell-based immunotherapy (Fig.2). The sdAb fragment is the smallest antibody fragment containing only one variable domain from the heavy chain antibodies. Due to its miniature size, antibody fragments such as scFv and sdAd show better penetration abilities than conventional antibodies, making it easier to generate bispecific or multi-targeting antibodies and provide more opportunities for anti-tumor immunotherapy for solid tumors (Fig. 3) (Chen et al., 2020; Ji et al. 2019). Antibody-mediated cancer immunotherapy includes immunosuppressive signal blocking and Fc-mediated ADCC, ADCP and CDC activities.

When signaling pathways are involved in the immune system (for example, when antigens are immune checkpoints), antibodies can mediate the immune response against tumors by activating tumor immunity (Fig. 2) (Chen et al., 2020; Ji et al. 2019; Marshall and Djamgoz, 2018).

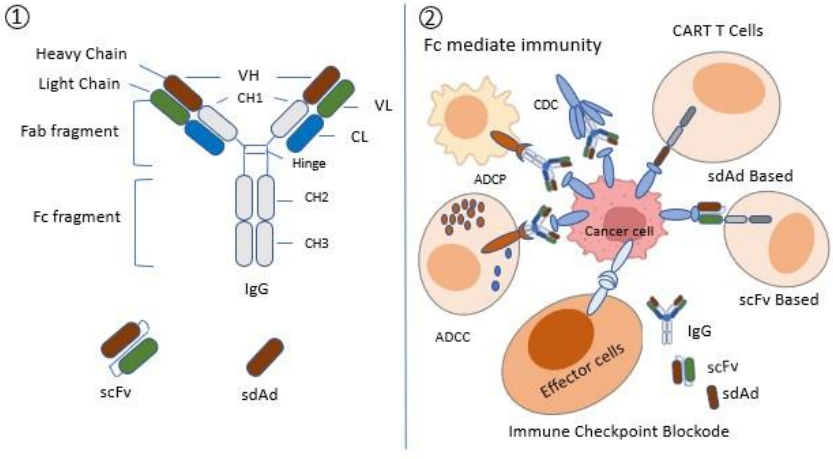

Figure 2. (1) Structure and applications of antibodies and antibody fragments for cancer immunotherapy: The full-length antibody (IgG) consists of Fab fragments and Fc fragments. Antibody fragments include single chain variable fragment (scFv) and single domain antibody (sdAd) and consist of antigen binding domains only. (2) Application of antibodies and antibody fragments in cancer immunotherapy: conventional antibody-mediated immunotherapy, including Fc-mediated immunity and immune checkpoint blockade. Antibody fragments are mainly applied in CAR T cell engineering and immune checkpoint blockade (Chen et al., 2020).

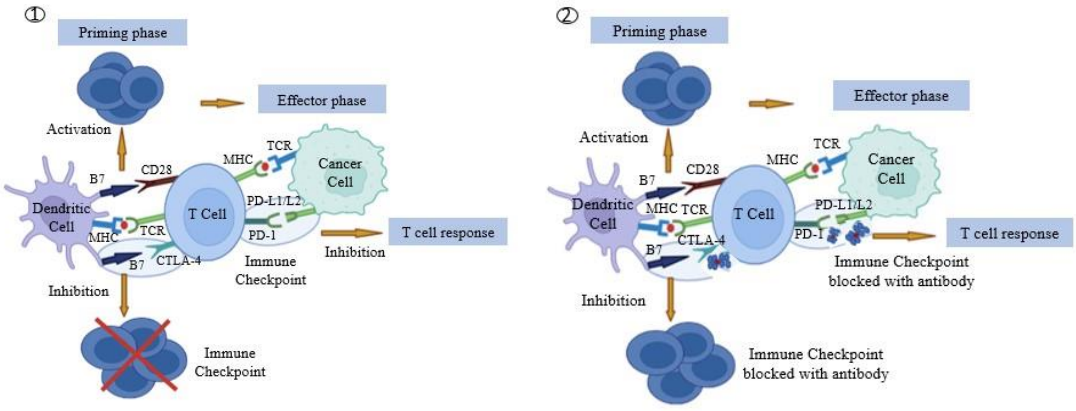

Figure 3. Mechanism of action immune checkpoint inhibitors: (1) For T cell activation; Stimulatory signals produced by the interaction of T cell receptor (TCR), histocompatibility complex (MHC) and CD28 with B7 are required. Interaction of CTLA-4 with B7 instead of CD28 inhibits T cell activation resulting in the cell evading cellular immunity. Programmed cell death protein 1 (PD-1) is a secondary checkpoint. PD-1 binds to PD-L1/L2 ligands expressed in tumors and certain inflammatory tissues and reduces the cellular immune attack on tumor cells. (2) During the priming step required for T cell activation; Antibodies that block CTLA-4 will block the immune checkpoint, allowing CD28/B7 interaction. Antibodies that block PD-1 and its ligands PD-L1/L2 assist in tumor destruction by T cells by blocking the checkpoint during the T cell effector phase (Ayyar et al., 2016).

Immunotherapy classes in cancer

Immunotherapy is considered as the treatment that aims to restore or intensify the immune response of patients. In cancer, immunotherapy is divided into two groups: passive immunotherapy and active immunotherapy depending on the therapeutic agent used and the condition of the immune system of patients (Lobenwein et al., 2021; Papaioannou et al., 2016). In general, passive immunotherapy is used when the immune response of the patient is weak or unable to respond. It involves the use of molecules or cells that can compensate for the immunological deficiency in the patient's body (Meiliana et al., 2016). Active immunotherapy aims to stimulate the effector functions of the recipient immune system. The patient's immune system shows functionality and sensitivity to the stimuli received in active immunotherapy (Lobenwein et al., 2021).

Active Cancer Immunotherapy

Active immunotherapy focuses on the design of anti-tumor vaccines to generate an immune response to fight cancer cells in the cancer patient. For successful treatment with anti-tumor vaccines, several experimental approaches are applied by using tumor peptides, DH vaccines, or whole tumor cell lysates. However, the success of active cancer immunotherapy applications may be limited. due to the complex nature of cancer and its genomic heterogeneity with the immunosuppressive microenvironment (Lobenwein et al., 2021). For this reason, current studies on cancer immunotherapy are gaining weight instead of universal active cancer vaccine applications to manipulate the patient's own immune system against cancer (Farkona et al., 2016). Today, the most promising immunotherapy strategy used in clinical practice is the use of monoclonal antibodies as inhibitors of "immunological checkpoints" controlling the initial and effector phases of T cells in response to tumor antigens which also denotes a major advance in the treatment of various cancers (Murciano-Goroff et al., 2020).

Cancer Vaccines: Despite significant interest in the development of effective therapeutic vaccines for

cancer, the clinical application of cancer vaccines is complex because of the low immunogenicity of most tumor-associated antigens. Cancer vaccines are designed to induce a tumor-specific immune response (anti-tumor T cells) in vivo against tumor-associated or tumor-specific antigens (Schuster et al., 2006; Seledtsov et al., 2015; Farkona et al., 2016; Taefehshokr et al., 2020).

Human Gene therapy: It is defined as a medical technique that uses a gene(s) to prevent, treat, and cure a medical disorder or disease. A gene sequence's controlled modification helps to substantially understand its function within cells. Gene regulation enzymes imply zinc finger nucleases (ZFNs), targeted meganucleases, transcription activator-like effector nuclease (TALENs), and clustered regular interval short palindromic repeats (CRISPR)/CRISPR-associated nuclease 9 (Cas9) (Yahya et al. 2022). CAR T treatment, which is effective in the hematological malignancies treatment, may be insufficient as an effective mechanism in the treatment of some solid tumors (Salas-Mckee et al., 2019). Sensitive genome arrangements performed using the CRISPR/Cas9 technique are effective in increasing the success of CAR T in cell therapy (Eyquem et al., 2017). In this technique, CRISPR/Cas9 is used to cut many regions in T cell receptors used for the formation of CAR-T cells. As the Fas receptor, one of the receptors targeted by CRISPR/Cas9, is linked with the Fas receptor-ligand and increases T cell apoptosis, CAR-T cell with the potential of killing tumor cells is produced through Fas-targeted suppression by CRISPR/Cas9 (Yahya et al., 2022).

Checkpoint Inhibitors: So far, checkpoint inhibitors have been the most extensively investigated immunotherapy class. The two most common checkpoint inhibition strategies are PD-1/PD-L1 blockade and the inhibition of Cytotoxic T Lymphocyte-Associated Antigen-4 (CTLA4). Physiologically, immune checkpoints protect healthy tissues from immune attack by maintaining proper immune responses (Granier et al., 2017; Alsaab et al., 2017). For example, when T cells are activated, they express PD-1, which enables them to recognize abnormal cells and cancerous cells in response to inflammation. T cell-mediated tumor cell death is achieved by blocking this interaction with mAbs targeting PD-1 or PD-L1 (Munn and Bronte, 2016; Alsaab et al., 2017). CTLA4, which is another immune checkpoint, is a co-inhibitory molecule regulating the degree of T cell activation. The interactions between CTLA4, CD80, and CD86 ligands express tumor progression by inhibiting T cell activity. CTLA4 is effective in keeping T cells active, and in recognizing and eliminating tumor cells by blocking the interaction between these ligands. Some anti CTLA4 antibodies can both deplete regulatory T cells and inhibit checkpoint functionality. The clinical effects of PD-1, PD-L1, or CTLA4 checkpoint blocking strategies has increased significantly over the past few years (Webb Es et al., 2017). To date, many PD-1 and PDL-1 inhibitors, and CTLA4 inhibitors have been approved because they are proven to treat a variety of cancers (Table 1) (Taefehshokr et al., 2020). However, there are also important limitations in their use. Checkpoint inhibitors administered systemically can have serious side effects in many organs and many patients may not respond to treatment with checkpoint inhibitors (Fig. 3) (Ayyar et al. 2016; Taefehshokr et al., 2020; Riley et al., 2019). The factors underlying the responsiveness to checkpoint inhibitors are under intense investigation. However, in all these studies, there may have been low numbers of tumor-infiltrating T cells, the deregulation of checkpoints in both tumor cells and T cells, and adapted resistance to checkpoint inhibition (Riley et al., 2019).

Passive Cancer Immunotherapy

The use of tumor-specific monoclonal antibodies has been known for years to be the most popular method for cancer treatment among the passive

immunotherapy approaches. Monoclonal antibodies (mAbs) that target tumor cells are best characterized by anticancer immunotherapy and are the most widely used treatment in the clinical practice (Lobenwein et al., 2021; Meiliana et al., 2016). Within this treatment, the purpose is to recognize the cancer cells by "tumor-associated antigen" and programmed cell death by Antibody-Dependent Cellular Cytotoxicity (ADCC) or Antibody-Dependent Cellular Phagocytosis (ADCP) in response to changing the signaling functions of expression receptors, especially on the surface of malignant cells (Papaioannou et al., 2016; Escribese and Barber, 2017).

Cytokine Treatment: Cytokines regulate both innate immune system cells (e.g. NK cells, macrophages, and neutrophils) and adaptive immune system cells (T and B cell immune responses).

Cytokines also act in an autocrine and paracrine manner by showing its effects after binding to the relevant receptors on target cells. The cytokines Interleukin 2 (IL-2) and Interferon-α2b (IFN-α2b) were approved by the FDA for the treatment of various cancer indications (Schuster et al., 2006).

IL-2 is used in the treatment of renal cell carcinoma, lymphoma, and leukemia. IFN-α2b was approved for the treatment of Kaposi's sarcoma and various types of leukemia. It was found that the infusion of cytokines is associated with significant side effects (Kammula et al., 1998; Panelli et al., 2004; Carson et al., 2000).

Synchronized use of several cytokines rather than single cytokine is clinically recommended for optimal induction of an immune response. Previous studies using combined cytokines indicate that such combinations may have synergistic effects.

Cytokine combinations can also be employed to enhance the effects of vaccines that are designed to create cancer cell-specific immune responses of the immune system (Schuster et al. 2006).

Table 1. FDA-approved immune checkpoint inhibitors (Taefehshokr et al., 2020)

Medication	FDA approval	Target	Indication	Combinatorial therapy
Ipilimumab (Yervoy)	2011	CTLA-4	Resectable or metastatic melanoma, Renal cell carcinoma, metastatic colorectal cancer	Advanced renal cell carcinoma and mismatch repair deficiency or metastatic colorectal cancer with high microsatellite instability in combination with nivolumab for resectable or metastatic melanoma.
Pembrolizumab (Keytruda)	2014	PD-1	Metastatic melanoma, Metastatic Merkel-cell carcinoma, Metastatic nonsquamous small cell lung cancer, Head and neck squamous cell cancer, Classical Hodgkin Lymphoma, Primary mediastinal large B-cell lymphoma, Metastatic urothelial carcinoma, breast cancer, cervical cancer, metastatic stomach or gastroesophageal junction adenocarcinoma, Hepatocellular carcinoma.	In combination with platinum and pemetrexed chemotherapy for the first-line treatment of metastatic non-squamous non-small cell lung cancer, in combination with paclitaxel or nab-paclitaxel and carboplatin for first-line treatment of metastatic squamous non-small cell lung cancer.

Nivolumab (Opdivo)	2014	PD-1	Metastatic melanoma, metastatic non-small cell lung cancer, metastatic small cell lung cancer, renal cell carcinoma, Classical Hodgkin Lymphoma, breast cancer, head and neck squamous cell cancer, microsatellite metastatic colorectal cancer, Hepatocellular carcinoma.	In combination with nivolumab for resectable or metastatic melanoma, advanced renal-cell carcinoma and mismatch repair deficiency or metastatic colorectal cancer with high microsatellite instability.
Atezolizumab (Tecentriq)	2016	PDL-1	Metastatic or locally advanced urothelial carcinoma, non-small cell lung cancer, triple-negative breast cancer.	In combination with Carboplatin, Bevacizumab, and Paclitaxel for the first line-the treatment of metastatic non-squamous small-cell lung cancer in adult carcinoma.
Avelumab (Bavencio)	2017	PDL-1	Metastatic Merkel-cell carcinoma, metastatic or locally advanced urothelial carcinoma.	In combination with Axitinib for the first-line treatment of advanced renal cell carcinoma.
Durvalumab (Imfinzi)	2017	PDL-1	Metastatic or locally advanced urothelial carcinoma, non-small cell lung cancer.	None
Cemiplimab (Libtayo)	2018	PD-1	Metastatic or locally advanced cutaneous squamous cell carcinoma.	None

Adoptive T Cell Treatment: Adoptive Cell Therapy (ACT) is the process of administering immunologically active cells to patients to treat and prevent the disease. ACT involves harvesting immune cells from the patient's peripheral blood, isolation of cells, ex vivo replication of tumor-specific immune cells, and reinfusion of activated T cells into the patient (Mayor et al., 2016; Neves and Kwok, 2015). The T cells used for this purpose are Tumor Infiltrative Lymphocytes (TIL), the T cells designed to express cancer-specific T Cell Receptor (TCR) and to express Chimeric Antigen Receptor (CAR) that combines the extracellular portion of the antibody. Furthermore, dendritic cells (DCs) which are highly effective in inducing T cell immunity, are also used in this approach (Harris and Drake; 2013; Farkona et al., 2016; Kimiz Gebologlu et al., 2018; Yang, 2015; Hayes, 2021).

Monoclonal antibodies: As a result of the entry of a foreign substance into the body, B lymphocytes are activated and antibody production takes place. Antibodies recognize epitope sites on the antigen. If an antibody against a single epitope is produced instead of the entire epitope, this antibody is called a monoclonal antibody (mAb) (Bean, 2000; Kohler, 2000). Firstly, mAbs were produced with hybridoma technology (Kuhn and Weiner, 2016; Pandey, 2010). The first mAbs developed as human therapeutic agents are known as mouse antibodies (Liu, 2014). When mouse mAbs were repeatedly administered to humans in clinical studies, it was observed that the half-life of the antibody was reduced and the products became more ineffective with each injection. The reason for this is the high immunity of mouse antibodies in the human body and the development of human anti-mouse antibody (HAMA-Human Anti-Mouse Antibody) response in patients (Liu, 2014; Teillaud, 2012). The HAMA response in therapeutic mAb production was resolved by Recombinant-DNA technology, in which mouse antibodies were replaced with chimeric, humanized, or human antibodies (Levene et al., 2005; Simpson and Caballero, 2014). It is accepted that mAbs are the most widely used and approved cancer immunotherapy method in clinical practice. The most common types of cancer targeted by

mAbs are breast and colon cancers, lymphomas, and other types of cancer (Sathyanarayanan and Neelapu, 2015). However, mAbs treatment causes various side effects such as fever, chills, fatigue, headache, myalgia, nausea/vomiting, difficulty in breathing, rash, and bleeding (Oldham and Dillman, 2008). The cancer immunotherapeutic efficacy of mAbs is based on three main mechanisms, which include; (1) the inhibition of factors and receptors activating signaling pathways used by cancer cells in division and angiogenesis by antibody binding, (2) target monoclonal antibodies consisting of chimeric or human antibody components binding to antibody-dependent specific tumor-related antigens, (3) cellular cytotoxicity consisting of Complement-Dependent Cytotoxicity (CDC) and complement activation (Sakalar et al., 2013; Mayor et al., 2016). It is important, for more effective treatments, to understand the mechanisms by which mAbs mediate tumor lysis. Although mAbs have different mechanisms of action, all of these mAbs have become part of the standard treatment protocol in combination with chemotherapy and/or radiotherapy (Papaioannou et al., 2016). In the ADCC mechanism, the mAb first binds to antigens on the surface of target cells, such as tumor cells, and then the Fc receptors of immune cells, such as macrophages and NK cells, recognize the cell-bound mAbs. The cross-binding of the receptors causes the release of cytotoxic agents such as perforin and granzyme into lytic synapses. Finally, tumor cells die with apoptosis (Fig. 4) (Ohaegbulam et al. 2015; Chung et al., 2014; Wang et al., 2015). Monoclonal antibodies that have ADCC characteristics are rituximab, transtuzumab, cetuximab, and pertuzumab (Boyerinas et al., 2015; Glassman and Balthasar et al., 2014). The examples of mAbs that have CDC characteristics include rituximab, alemtuzumab, cetuximab, and ofatumumab. Many mAbs used in cancer immunotherapy target and bind to an antigen on the cancer cell surface, and block the down-regulation signaling pathways and cell proliferation.

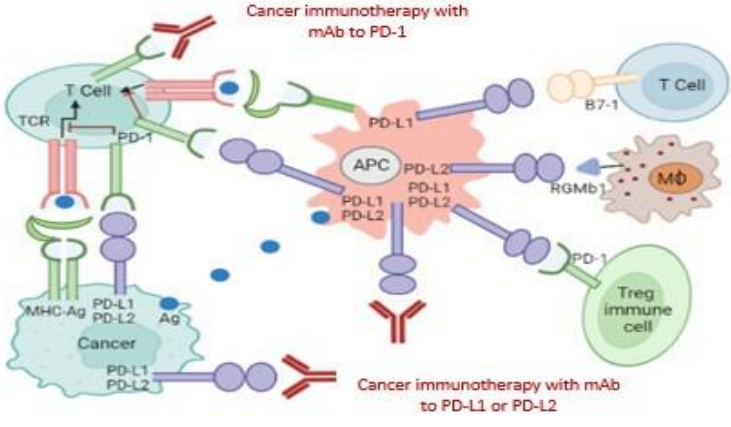

Figure 4. Human cancer immunotherapy with anti-PD-1 and anti-PD-L1/L2 antibodies: Antigen presenting cells (APC) receive antigens (Ag) released from cancer cells and presented to T cells. Cancer cells can also present Ag with MHC to activated T cells. Upon T cell activation, PD-1 receptors are expressed on T cells, inhibiting immune responses by binding of PD-L1 and PD-L2 ligands APC and PD-L1 on cancer cells. Therefore, monoclonal antibody (mAb)-mediated specific blockade of the PD-1/PD-L1/PD-L2 pathway can enhance anti-tumor immunity. In addition to binding to PD-1, PD-L1 and PD-L2 also bind B7-1 and molecule B, respectively (Ohaegbulam et al., 2015).

There are two immunotherapeutic mAb classes, depending on whether they contain drugs or radioactive substances (Table 2). In the first class, there are unconjugated bare mAbs such as an example of conjugated mAbs, and Ibritumomab tiuxetan is an example of (radionuclides) radioactive conjugated mAbs. There are also bispecific antibodies (BsAb) called Blinatumomab, which contain two different mAbs and can bind immunotherapy is to design dendritic cells to target TAA and provide effective immunization against the tumor. The main interest of nanobodies is their high tissue penetration capacity (Chanier and Chames, 2019). Antigen presenting cells (APCs) for regulating adaptive immunity in cancer are CD4+, CD8+ and B cells. Among these cells, CD4+ T cells respond by recognizing the antigen presented to major histocompatibility complex II (MHC-II) molecules on the surface of antigen presenting cells. Enhances adaptive immune response through activation of B cells, NK cells and macrophages. B cells present antigen via MHC-II and T cells secrete signals to differentiate B cells from plasma cells that secrete immunoglobulin (Ig), helping to increase phagocytosis. These functions are mostly realized by cross-linking of Fc receptors. (Verhaar et al., 2021). While the use of PD-1/PD-L1 and CTLA-4 antibodies in cancer treatment has increased the success of immunotherapy, it has also been Alemtuzumab and Transtuzumab associated with antigens on cancer cells, and in the second class mAbs are conjugated with chemotherapeutic drugs or radioactive isotope Gemtuzumab ozogamycin is two different antigens simultaneously (Özlük et al., 2017; Kimiz Gebologlu et al., 2018; Riley et al., 2019; Kozani et al. 2021; Yagishita and Hamada, 2019).

Nanoantibodies: One of the challenges in effective in the development of treatments targeting other immunological pathways. However; It is considered necessary to use combined treatment methods to increase the response rates to immunotherapy, which is effective only in a portion of cancer patients (Stambrook et al., 2017; Hahn et al., 2017). The success of the treatment using this approach is generally based on the presence of immune cells in the tumor and their interaction with immunosuppressive ligands expressed by tumor cells.

In the case of non-infiltrating tumors resistant to checkpoint inhibitors, new immunotherapy approaches tend to use bispecific constructs targeting a tumor antigen and an immune receptor to promote immune cell infiltration and tumor cell specific targeting (Brinkmann and Kontermann, 2017). The first therapeutic nanobody approved by the European Drug Agency (EMA) is Caplacizumab (Duggan, 2018).

Table 2. Monoclonal antibodies approved for cancer treatment (Kimiz Gebologlu et al., 2018; Kozani et al. 2021; Yagishita and Hamada, 2019)

General name	Commercial name	Type	Target	FDA approval	Indication
Rituximab	Rituxan	Chimeric	CD20	1997	B-cell non-Hodgkin lymphoma
Transtuzumab	Herceptin	Humanized	HER2	1998	Breast cancer
Gemtuzumab ozogamicin	Mylotarg	Humanized conjugated with calicheamicin	CD33	2000	Acute myelogenous leukemia
Alemtuzumab	Campath-1H	Humanized	CD52	2001	Chronic lymphocytic leukemia
Ibritumomab tiuxetan	Zevalin	Conjugated murine with radioactive Y90	CD20	2002	B-cell non-Hodgkin lymphoma
Bevacizumab	Avastin	Humanized	VEGF	2004	Metastatic colorectal, non-small cell lung, ovarian, and breast cancer

Cetuximab	Erbitux	Chimeric	EGFR	2004	Metastatic colorectal cancer, squamous cell cancer, and non-small cell lung cancer
Panitumumab	Vectibix	Human	EGFR	2006	Metastatic colorectal cancer
Ofatumumab	Arzerra	Human	CD20	2009	Chronic lymphocytic leukemia
Denosumab	Xgeva	Human	RANKL	2010	Metastatic bone tumors
Brentuximab vedotin	Adcetris	Chimeric conjugated with MMAE	CD30	2011	Hodgkin lymphoma or anaplastic large cell lymphoma
Ipilimumab	Yervoy	Human	CTLA-4	2011	Metastatic melanoma
Pertuzumab	Perjeta	Humanized	HER2	2012	Breast cancer
Ado-transtuzumab emtansine	Kadcyla	Humanized conjugated with DM-1	HER2	2013	Breast cancer
Obinutuzumab	Gazyva	Humanized	CD20	2013	Chronic lymphocytic leukemia and non-Hodgkin lymphoma
Nivolumab	Opdivo	Human	PD-1	2014	Melanoma, non-small cell lung cancer, renal cell carcinoma, and Hodgkin lymphoma
Pembrolizumab	Keytruda	Humanized	PD-1	2014	Melanoma, and metastatic non-small cell lung cancer
Ramucirumab	Cyramza	Humanized	VEGF	2014	Gastric cancer, non-small cell lung cancer, and breast cancer
Dinutuximab	Unituxin	Chimeric	GD2	2015	Neuroblastoma
Elotuzumab	Empliciti	Humanized	SLAMF7	2015	Multiple myeloma
Daratumumab	Darzalex	Human	CD38	2015	Multiple myeloma
Necitumumab	Portrazza	Human	EGFR	2015	Metastatic squamous, non-small cell lung cancer
Atezolizumab	Tecentriq	Humanized	PD-L1	2016	Metastatic non-small-cell lung cancer
Avelumab	Bavencio	Human	PD-L1	2017	Non-small cell lung, ovarian and gastric cancers, and renal cell carcinoma
Durvalumab	Imfinzi	Human	PD-L1	2017	Metastatic urothelial carcinoma
Inotuzumab ozogamicin	Besponsa	Humanized conjugated with calicheamicin	CD22	2017	Acute lymphoblastic leukemia
Rituximab and hyluronidase human	Rituxan Hycela	Chimeric with hyluronidase human	CD20	2017	Follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia
Bevacizumab-awwb	Mvasi	Humanized	VEGF	2017	Colorectal, lung, brain, kidney, and cervical cancer
Transtuzumab-dkst	Ogivri	Humanized	HER2	2017	Breast cancer and metastatic gastric or gastroesophageal adenocarcinoma
Cemiplimab	Libtayo	Unclassified	PD-1	2018	Cutaneous squamous cell carcinoma
Isatuximab	Sarclisa	Chimeric IgG1	CD38	2020	Multiple myeloma
Sacituzumab govitecan	Trodelvy	Humanized IgG1 ADC	TROP-2	2020	Triple-negative breast cancer
Tafasitamab	Monjuvi	Humanized IgG1	CD19	2020	Diffuse large B-cell lymphoma
Belantamab mafodotin	BLENREP	Humanized IgG1 ADC	BCMA	2020	Multiple myeloma
Naxitamab	DANYELZA	Humanized IgG1	GD2	2020	Neuroblastoma and refractory osteomedullary disease

Dostarlimab	Jemperli	Humanized IgG4	PD-1	2021	Endometrial cancer
Amivantamab	Rybrevant	Human bispecific IgG1	EGFR, cMET	2021	Non-small cell lung cancer
Loncastuximab tesirin	Zynlonta	Humanized IgG1 ADC	CD19	2021	Diffuse large B-cell lymphoma

EGFR Epidermal Growth Factor Receptor, HER2 Human Epidermal Growth Factor Receptor-2, MMAE Monomethyl Auristatin E, RANKL Receptor Activator of Nuclear Factor-κB Ligand, SLAMF7 Signaling-Lymphocytic-Activation Molecule Family-7, VEGF Vascular Endothelial Growth Factor, 90Y yttrium-90.

Conclusion

Cancer treatment has long been associated with strategies that directly attack tumor cells. It is argued that cancer immunotherapy will make an important contribution to traditional treatment methods with the treatment strategy using the patient's immune system. In particular, Immune Checkpoint Blockade Treatment has been one of the most impressive advances in cancer therapeutics in recent years. Although studies conducted on cancer immunotherapy are ongoing, practical applications are still insufficient. In recent years, the number of mAbs approved or pending approval for cancer treatment has been increasing. Although mAbs are mostly employed in cancer immunotherapy in clinical practice, better results are obtained with combinations of immunotherapy applications. The main achievements of cancer immunotherapy are the identification of optimal tumor antigens, the development of biomarkers, and the understanding of toxicity issues. In the light of the information obtained to date, it shows that personalized medicine systems will maintain their importance in the future, especially in the development of personalized cancer treatment systems. We hope that ultimately enhanced personalized strategies to regulate the immune suppressive microenvironment will be required to make immunotherapy effective.

Conflict of interest

Authors declare no conflict of interest.

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