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Review Article
Immunotherapy a New Hope for Cancer Treatment: A Review

[1]Fatemeh Nouri Rouzbahani, [1]Mohammad Shirkhoda, [1]Feridon Memari, [1,2]Hassan Dana, [1]Ghanbar Mahmoodi Chalbatani, [1]Habibollah Mahmoodzadeh, [3]Nasim Samarghandi, [1]Elahe Gharagozlou, [4]Mohammad Hosein Mohammadi Hadloo, [1]Ali Reza Maleki, [1]Ehsan Sadeghian, [2]ElhamZainali Nia, [5]Nedazainali Nia, [1]Farimah Hadjilooei, [6]Omid Rezaeian, [6]Saeed Meghdadi, [1]SeyedRohollah Miri, [7]Fatameh Jafari, [8]Elham Rayzan and [2]Vahid Marmari

[1]Cancer Research Center, Cancer Institute of Iran, Tehran University of Medical Science, Tehran, Iran
[2]Department of Biology, Damghan Branch, Islamic Azad University, Damghan, Iran
[3]Depertment of Immunology, School of Medicine, University of Medical Sciences, Isfahan, Iran
[4]Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran
[5]Department of Biology, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran
[6]Department of Biology, Nour Danesh Institute of Higher Education, Isfahan, Iran
[7]Paramedical Faculty, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[8]International Hematology/Oncology of Pediatrics Experts, Universal Scientific Education and Research Network, Tehran University of Medical Sciences, Iran

First, Second and Third author contributed equally to this work

Abstract

Cancer is a major burden of disease worldwide with considerable impact on society. The tide of immunotherapy has finally changed after decades of disappointing results and has become a clinically validated treatment for many cancers. Immunotherapy takes many forms in cancer treatment, including the adoptive transfer of ex vivo activated T cells, oncolytic viruses, natural killer cells, cancer vaccines and administration of antibodies or recombinant proteins that either costimulate cells or block the so-called immune checkpoint pathways. Recently, cancer immunotherapy has received a high degree of attention, which mainly contains the treatments for programmed death ligand 1 (PD-L1), programmed death 1 (PD-1), chimeric antigen receptors (CARs) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Here, this paper reviewed the current understandings of the main strategies in cancer immunotherapy (adoptive cellular immunotherapy, immune checkpoint blockade, oncolytic viruses and cancer vaccines) and discuss the progress in the synergistic design of immune-targeting combination therapies.

Key words: Immunotherapy, CAR-T cell therapy, CTLA4, Combination therapies and programmed death ligand 1 (PD-L1)

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Corresponding Author: Ghanbar Mahmoodi Chalbatani, Cancer Research Center, Cancer Institute of Iran, Tehran University of Medical Science, Tehran, Iran
Seyed Rohollah Miri, Cancer Research Center, Cancer Institute of Iran, Tehran University of Medical Science, Tehran, Iran

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INTRODUCTION

Today, cancer is one of the most widespread diseases with high mortality rates worldwide and as one of the serious problems and challenges of health and treatment [1]. According to global cancer statistics, cancer is the second leading cause of death worldwide. In the 21st century, Cancer has become the number one cause of deaths in developed countries[2,3]. For example, colorectal cancer with more than 1.2 million new cases resulted in 600 thousand deaths annually and ranks fourth in terms of mortality worldwide[4]. Only in the United States, annually about 50,000 people will die of the disease and nearly 135,000 new cases will be diagnosed[5]. 90-95% of cancer cases are a consequence of environmental factors result in gene mutations and the remainder 5-10% are due to inherited genetic alterations[6].Each year, tens of millions of people are diagnosed with cancer around the world and more than half, eventually, die[7]. Among multi-model cancer treatment strategies, including surgery, hormonal therapy, radiotherapy and chemotherapy, immunotherapy has revolutionized the treatment of cancer. Immuno oncology is an exciting field of cancer treatment with the potential for impacting the management of numerous malignancies[8] which has recently received a considerable rise[9]. The major goal of cancer immunotherapy is to alleviate tumor-associated suppression of anti-cancer immune responses[10]. The idea of using patient's immune system against cancer-cells dates back to 1997, since the immune system response versus virulent cells during initial transformation in the immune surveillance process was discovered[11,12]. Cancer immunotherapy, which sometimes called immune-oncology, induces the patient's own immune system[13] and attempts to harness the exquisite power and specificity of the immune system for cancer treatment[14]. Immunotherapies against cancers consist of diverse approaches, ranging from stimulating effector mechanisms to counteracting inhibitory and suppressive mechanisms[9]. By the rapid increase in scientists' knowledge about the immune system, small molecules, peptides, recombinant antibodies, vaccines as well as cellular therapeutic modalities are being applied to manipulate the immune response to treat cancer. Currently, immunotherapies have provided remarkable benefits against cancer[15]. The recent clinical successes in cancer immunotherapies, such as immune checkpoint blockade, have reaffirmed the importance of the host immune system in preventing and eliminating malignancies[16]. Since cancer is still one of the challenges facing human being in the field of treatment and because single-drug therapies are not effective in the treatment of cancers, combining two or more therapies with different mechanisms will bring more success. In cancer treatment, so this article will provide a general overview of current immunotherapy in cancer management and also a series of promising heuristic treatments for cancer that can provide real and more useful research patterns.

Cancer vaccines: Cancer vaccines have been designed since three decades ago[17,18]. The goal of cancer vaccines is to activate and expand cancer-specific T cells, which removes cancerous cells by recognizing their neo-antigens[19].These neo-antigens are created by cancer-specific DNA alterations result in a unique peptide sequence[20,21]. The vaccines are created based on targeting tumor-associated antigens that are preferentially expressed in cancer cells, which are the microscopic markers distinguishing cancer cells from the normal ones[22]. Cancer cells can contain hundreds of neo-antigens which are specific to each patient's tumor for instance growth associated factors or unique antigens to malignant cells owing to somatic mutation[23]. Cancer vaccines are highly specific and are expected to affect only a single individual because they are designated based on the unique cancer antigens and are able to stimulate the immune system in order to reinforce the immunity to response against cancerous cells[24,25]. Scientists have developed two types of cancer vaccines, therapeutic and preventive. Several analyses have been carried out on therapeutic cancer vaccines over past two decades in order to replicate successes and failures, on the way of clarifying future directions for more vaccine efforts[26]. Most cancer vaccines are therapeutic [27] designed to treat an established disease, such as cancer, mainly by evoking cellular (T-cell-based) immune responses[28]. Therapeutic cancer vaccines are used to omit cancerous cells through strengthening patient's immune response, particularly CD8+ T cell-mediated responses, with the assistance of suitable adjuvants[29,30]. Therapeutic cancer vaccines are used to enhance neo antigen's recognition and to decrease the immune tolerance[31]. Preventive vaccines are used for disease prevention and have been developed against the oncogenic viruses. Oncogenic viral antigens have been identified in virus-induced cancers such as human papillomavirus (HPV)-associated cervical cancer, hepatitis B virus-associated hepatocellular carcinoma and human herpesvirus 8-associated Kaposi sarcoma[32]. The HPV and HBV vaccines have significantly decreased the risk of related cancers[33]. Multiple clinical trials[34] have proved that after testing HPV vaccines for the prevention

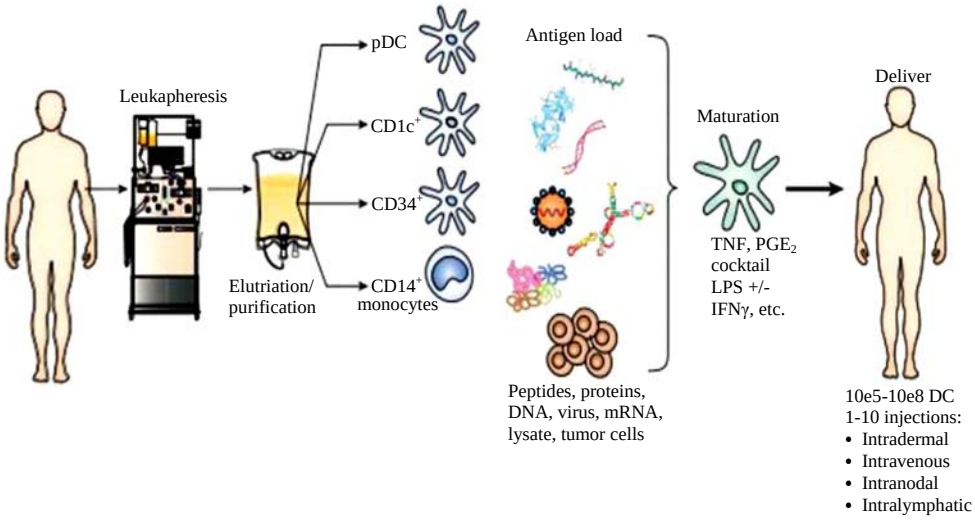

Fig. 1: Schematic picture of the key steps in preparation of cancer vaccines[44]

of cervical and HPV positive oral cancers, HPV prevalence among females aged 14-19 had decreased by 64% and had decreased by 34% in females who were 20-24 years old[35]. Currently approved vaccines, Gardasil (Merck) and Cervarix (GlaxoSmithKline), provide effective protection against chronic HPV infection type 16 and 18 and also prevent cervical intraepithelial neoplasia, adenocarcinoma in situ and cervical cancer[36]. In order to produce cancer vaccines, in some cases, tumor-associated lymphocytes are being isolated and after *in vitro* amplification are being reinjected to patient's body. The same can be done with idiotypic antibodies that are produced by the patient and specifically directed against tumor cells[20]. Several kinds of cancer vaccines exists, such as dendritic cell-based (DC) vaccines[37,38], peptide vaccines[39,40], genetic vaccines[41] and cancer cell vaccines[42]. As DCs are central players in initiating the antigen-specific immune response, it seemed logical to utilize them for cancer immunotherapy[43] (Fig. 1).

During DC vaccine immunotherapy, stem cells are isolated from peripheral blood and will develop into DCs in an *in vitro* cell culture. DCs then are loaded with cancer patients become sensitized. These sensitized DCs are infused intradermal and travel to the lymph nodes. The DCs instruct specific lymphocyte to multiply. Multiple clinical trials have now been conducted using DC vaccines targeting various cancer types, such as metastatic prostate cancer, metastatic lung cancer, renal cell carcinoma, brain cancers, melanoma, acute myeloid leukemia, pancreatic cancer and others[45-48]. Although all cancer vaccines are beneficial, the most important long-term concern is the induction of autoimmunity[49] that depends on the tumor antigen which is targeted and the elicited response. It seems that the coming years will clarify the emergence of cancer vaccines as a major modality for cancer treatment[50].

Oncolytic virus therapy: Oncolytic virus therapy (OVT) as a new development in cancer therapy, has emerged over past few decades[51,52]. The role of viruses in the cancer treatment was discovered about one century ago[53]. Over the course of the 20th century, further anecdotal evidence emerged that viral infections could induce remission in various cancer types[54,55]. Virotherapy is based on the administration of oncolytic viruses[56-60]. Oncolytic virotherapy is a subtype of gene therapy that uses actively replicating viruses[61]. The basis of OV therapy is that certain viruses can selectively infect and lyse cancer cells by exploiting altered signaling pathways in the tumor cells[62] while leaving healthy cells unaffected[63-67]. Oncolytic viruses replicate in cancerous cells and cause tumor cell death[56]. Such oncolysis is mostly an immunogenic type of cancer cell death (ICD)[68]. These viruses destroy tumors through two major mechanisms: selective replication within neoplastic cells, resulting in a direct lytic effect on tumor cells and induction of systemic antitumor immunity[69]. Inside a cancer cell, the virus replicates and secretes GM-CSF until the cell lysis release more viruses, GM-CSF and antigens[70]. The expression of GM-CSF stimulates the manufacture of granulocytes and monocytes that can stimulate adaptive immunity against tumor-associated antigens[71]. The T cells are now programmed to identify cancer cells throughout the body. This approach has a promise of eliminating not only the infective tumor but also secondary tumors that may result from metastatic growth (Fig. 2).

The key advantageous characteristics of any OV are specificity, potency and safety, specificity for targeted cancer,

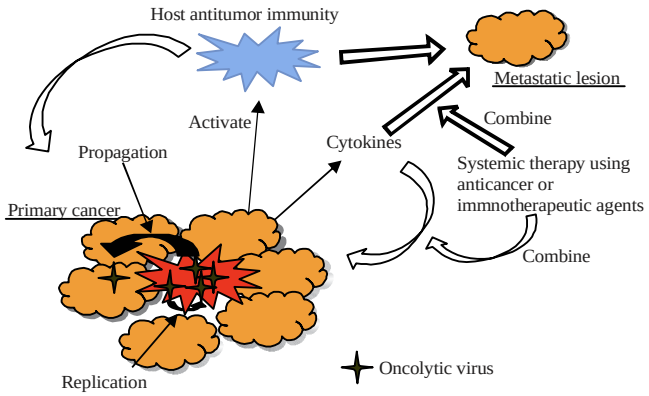

Fig. 2: Mechanism of oncolytic virus therapy[72]

potency to kill infected cells and safety to avoid adverse reactions and pathogenic reversions[73]. Oncolysis can be a natural feature of the virus, such as reovirus or genetically engineered OVs, like adenovirus and renders oncolytic virotherapy[74]. Until now, more than twenty viruses with oncolytic activity have been characterized[75] such as Polio virus which is used for treating glioblastoma that is a very aggressive cancer[76,77]. Picornavirus Seneca Valley virus (Picornavirus and Seneca Valley virus), which can infect neuroendocrine tumors such as small cell lung cancer[73,78,79]. OVs, like reovirus[74], HSV[80,81] or vaccinia virus[82], can induce tumor-specific adaptive immune responses and indirectly cause cancer cell death. The combination of oncolytic viruses with current cancer immunotherapies (such as anti PD1 and anti PDL1 blockades) has the potential to potentiate antitumor effects[83]. An oncolytic adenovirus expressing a mini-antibody that blocks PDL1 improved the antitumor effects of CAR-T cells in a human prostate cancer xenograft model[84]. Oncorine is a modified adenovirus vector that can treat carcinoma in combination with chemotherapy[85]. First HSV based oncolytic virus, talimogene laherparepvec (T-VEK) (IMLYGIC), was approved in 2015 by the FDA which is the modified form of herpes simplex virus, is used for patients with locally advanced or nonresectable melanoma[86-90]. A study has already shown the improved efficacy of T-VEC in combination with CTLA-4 inhibitor ipilimumab[91]. The viral gene encoding ICP47 which blocks antigen presentation by infected cells is deleted in T-VEC and this leads to immune response enhancement[92]. ICP47 blocks the function of the TAP (transporter associated with antigen processing) and thus prevents infected cells from presenting antigen to CD8+ T cells[93]. Ipilimumab enhances T cell priming by inhibiting cytotoxic T lymphocyte-associated antigen 4 (CTLA4), a receptor involved in the negative feedback loop that blocks a costimulatory signal from DCs[94]. Development of oncolytic viruses as promising therapeutic agents, requires careful attention to establish appropriate clinical trial, dosing regimens, pharmacodynamic assays, educational programs addressing biosafety concerns as well as new manufacturing and regulatory pathways[69]. Choosing virus classes to target specific tumor types, should soon become standard practice[95].

Adoptive T cell therapy: The adoptive transfer of T cells was a pivotal experimental technique used more than half a century ago to establish that cellular components of the immune system could reject tumors[96-98]. The goal of adoptive T cell therapy (ACT) is to generate a robust immune-mediated antitumor response through the *ex vivo* manipulation of T cells[99]. The ACT is genetically engineering a patient's T cells to express chimeric antigen receptors (CARs) which recognize and attack cancerous cells[100]. ACT refers to the extraction, *ex vivo* expansion and subsequent return of an individual's native immune cells for the express purpose of treating disease. In the context of cancer immunotherapy, the patient's own T cells are genetically modified so that they can specifically target and kill cancer cells via recognition of specific antigens expressed on the cancer cell surface[101]. Genetic modification of T cells is a quick and reliable process and clinical trials of genetically modified T cells targeting a variety of malignancies have been carried out[102-106]. After the patient's native T cells are harvested and then reprogrammed via genetic modification, they are subsequently reintroduced back to the patient[107]. The two most commonly toxicities with CAR T cell therapies are cytokine release syndrome (CRS), that caused hypotension, high fever, hypoxia, and/or multi-organ toxicity and a CAR T cell-related encephalopathy syndrome (CRES), typically distinguished by a toxic encephalopathic state with symptoms of confusion, delirium, occasionally seizures and cerebral edema[108-111]. To date, CAR T cell therapies have been most efficacious in patients with B cell ALL[112]. The

Table 1: Factors responsible for limited success of CAR T cell therapy against solid tumors

Drawbacks	Reference
Reasons of limited success of CAR T cell therapy	
Lack of a unique tumor-associated antigen (TAA) in most cancers	Brentjens *et al.*[100]
Inability of *ex vivo* expanded CAR T cells to persist and proliferate following adoptive transfer	
Lack of survival and growth factors (e.g., IL-2)	
Presence of immunosuppressive molecules and cells	
Metabolically hostile tumor micro environment	

excitement of cell-based therapy was followed by the use of engineered chimeric antigen receptor (CAR) T cells directed at TAAs expressed on the tumor cell surface, typically CD19 in B cell malignancies[112]. Initial clinical trials using CAR T cells have all focused on targeting CD19-based on its cell surface expression in most leukemia, lymphomas and its function[113,114] which is an ideal antigen because it is ubiquitously expressed on a broad range of differentiated B cells but it is not expressed on hematopoietic stem cells or any other essential cell types[115-117] limiting potential' on target-off tumor' toxicity. Indeed, in 2017, the FDA approved the Tisagenlecleucel, that is CD19 CAR T cell product, for the treatment of pediatric and young adult patients with relapsed and/or refractory B cell precursor acute lymphoblastic leukemia and axicabtageneciloleucel (Yescarta, Kite Pharma, Inc.) to treat adults with certain types of B cell lymphoma[100]. Indeed, CAR T cells are susceptible to PD-1-mediated inhibition and, therefore, the combination of CAR T-cell therapy with monoclonal antibody immune-checkpoint inhibitors is an obvious progression to protect CAR-T-cell function within the tumor microenvironment[118]. The demonstration of clinical efficacy in trials using CAR T cell therapy are, at present, limited to hematological malignancies but this modality is beginning to be explored clinically in the treatment of solid tumors[99]. The limited success of CAR T cell therapy against solid tumors may be due to many factors, such as (i) The lack of a unique tumor-associated antigen (TAA) in most cancers, (ii) The inability of *ex vivo* expanded CAR T cells to persist and proliferate following adoptive transfer, (iii) The lack of survival and growth factors (e.g., IL-2), (iv) The presence of immunosuppressive molecules and cells and (v) The metabolically hostile tumor microenvironment[100] (Table1).

New targets for solid tumors that are beginning to enter clinical studies include mesothelin for the treatment of mesothelioma[119-121] pancreatic[121,122] and ovarian cancer,[116] disialoganglioside GD2[123,124] and EGFRvIII[125] for CNS malignancies and mucin-16[126,127] to treat ovarian cancer. The ACT is a promising treatment modality which can eradicate primary and metastatic tumor cells and people are increasingly learning how to direct it against diverse cancers[128,129]. Better understanding the importance of CAR-T-cell therapy is a priority for future studies[130].

Immune checkpoint blockade: Checkpoint blockade, an approach to trigger antitumor immune responses, refers to the blockade of immune inhibitory pathways activated by tumoral cells[131]. In the 1990s, data from preclinical studies showed that blockade of immune checkpoints bolsters the T cell response and could result in tumor eradication[132]. Immunotherapies such as immune checkpoint blockers (ICBs) are an established therapeutic approach to cancer treatment. These agents are approved for the treatment of several malignancies such as melanoma, urothelial carcinoma, renal cell carcinoma and head and neck squamous cell carcinoma[133]. ICBs act on cancer cells indirectly by removing the "brakes" that serve to regulate T lymphocytes, the main cells responsible for triggering an anticancer immune response[134-142]. ICBs are an established class of immunotherapy that target negative regulators of T cell activation, specifically the immune checkpoints, cytotoxic T lymphocyte-associated antigen4 (CTLA4), programmed cell death1 (PD1) and programmed cell death ligand1 (PDL1). Inhibition of these immune checkpoint molecules prevents the down regulation of immune cells, leading to enhanced T cell activity, which ultimately results in increased antitumor immunity[134]. The two immune checkpoint receptors, CTLA4 (also known as CD152) and PD1 (also known as CD279), which are both inhibitory receptors, regulate immune responses at different levels and by different mechanisms[143]. CTLA4 provides inhibitory signals that may prevent adequate immune response to malignant cells. During early T cell activation CTLA4 is recruited to the plasma membrane, where it competes with the co-stimulatory receptor CD28 to bind to B7 ligands expressed on the antigen presenting cells(APCs)[144,145]. CTLA4 is thought to bind with both higher avidity and affinity than CD28 to B7 ligands[146] (Fig. 3). CTLA4 suppresses T cell activation by competitively inhibiting CD28 binding to CD80 and/or CD86 and inducing downstream inhibitory signaling, which ultimately leads to decreased T cell proliferation and IL-2 secretion[145,147].

Ipilimumab (Yervoy), is an anti CTLA4 antibody, that was approved in 2011 by the FDA as a first-line therapy for metastatic melanoma based on clinical trials that showed prolongation of overall survival[136,139,140]. Like CTLA4, PD1 is a transmembrane protein expressed in activated effector T cells but not in resting T cells[144]. PD1 has two ligands, PDL1

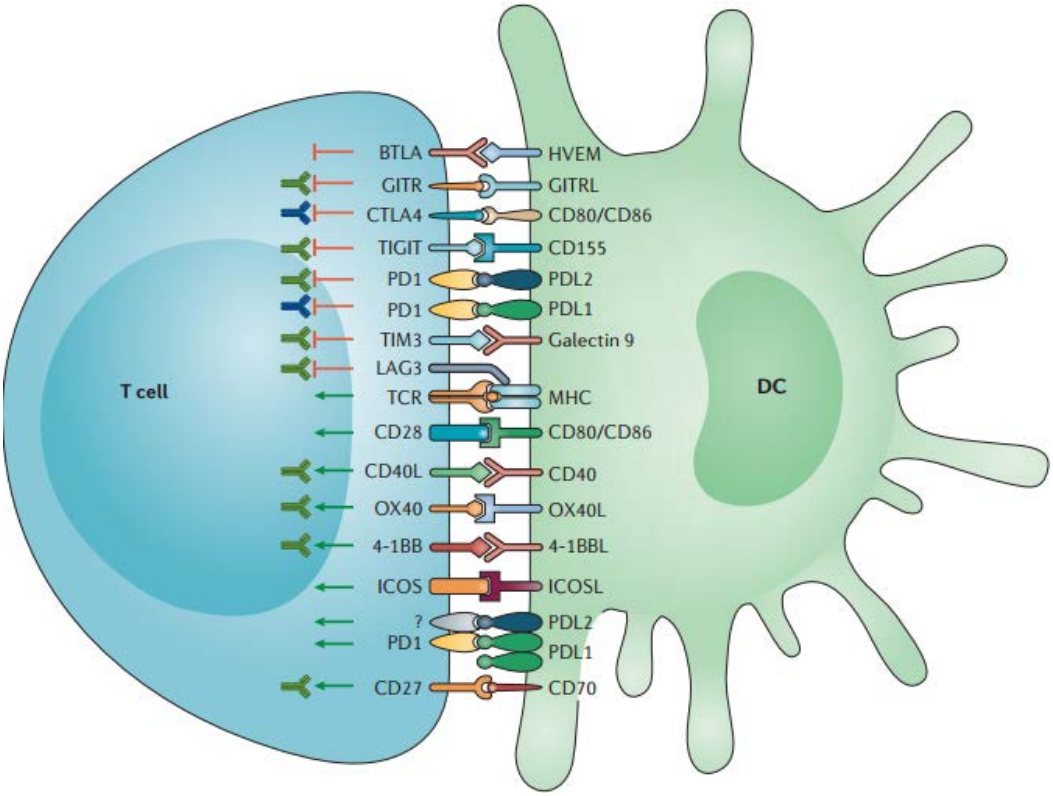

Fig. 3: Interaction between T-cells and antigen presenting cells[148]

and PDL2,[149,150] which can be expressed on a variety of cells, including APCs, tumor cells and T cells themselves. When bound to its ligands, PD1 also inhibits signaling pathways that normally lead to an effective T cell response. In contrast to CTLA4, that seems to mainly function in early activation of T cells, the major role of PD1 is to limit the activity of T cells in peripheral tissues at the time of an inflammatory response to infection and to limit autoimmunity[151-157]. Since 2010, additional immunotherapies have received FDA approval. ICBs including ipilimumab[136,139], nivolumab[140], pembrolizumab[141], atezolizumab[138], avelumab[135] and durvalumab[137,142] approved for a wide range of malignancies, including melanoma, non-small cell lung cancer (NSCLC), RCC, urothelial carcinoma (UC), head and neck squamous cell carcinoma (HNSCC), Hodgkin lymphoma, Merkel cell carcinoma, microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancer, hepatocellular carcinoma and gastroesophageal junction adenocarcinoma. Although all ICBs benefits by enhancing immune system function, they can lead to adverse events (AEs) distinct from chemotherapy[158,159] that include a range of gastrointestinal (GI), dermatologic, endocrine and hepatic toxicities as well as other less common inflammatory events[160]. Immune checkpoint inhibition has already begun to change the standards of care for patients[161] and the future looks very bright for this important class of immunotherapy.

Combination therapy: Combination therapies development for cancer treatment has a long and distinguished history[162-164]. Monotherapy or single agent immunotherapy may be relatively ineffective in most of the patients with advanced cancers[165]. It has been investigated that, in order to achieve complete remission, the combination of multiple therapeutics may be needed. Combination therapies are progressing rapidly that new combinations are being diagnosed almost monthly[166]. Switching to combination therapy as a cancer treatment modality, which is nowadays utilized in adulthood cancer treatments as well as its previous application in childhood cancers, will further prevent mutational escape in malignant cells[167]. Combination therapy is a treatment option when single agent therapy does not seem to be effective. Early results of combination trials suggest that the synergism of combined drugs evoke antitumor responses[168] and make more sustained and durable tumor destruction[169]. Current efforts are focusing on new the potentials of combination strategies with synergistic antitumor activity, using immune checkpoint blockade as a partner of targeted agents[163]. There are many challenges with the development of combination targeted

therapeutics for cancer. First is to assess the relation of the targeting agents and their presumed targets of interest, both in their appropriate disease context and in the wide range of their potential drug interactions with various downstream effectors[170]. The rationale to combine different target therapies is really based on their mechanisms[171]. In the following part, there mentioned some combination therapies which have been gained till now.

A recent clinical trial on CTLA and anti PD1 combination therapy has demonstrated tumor regression in 50% of treated patients with advanced melanoma and in most of the cases with tumor regression of 80% or higher[172]. There are ongoing clinical trials with anti CTLA4 (ipilimumab, BMS or tremelimumab, MedImmune/AstraZeneca) plus anti PD1 or anti PDL1 in other cancer types, with preliminary data indicating promising results[140] that highlight this combination as an effective strategy. Also, Platinum-based doublet therapy (for example, cisplatin in combination with another cytotoxic agent) has been the standard therapy for patients with advanced-stage NSCLC[173]. The combination of dabrafenib and trametinib was FDA approved in 2016 for treating BRAF-V600E-positive NSCLC[174] and also the combination of imatinib with a DC vaccine in a BCR-ABL lymphoma model resulted in decreased numbers of Treg cells, fewer metastases and increased T cell-derived IFNγ production compared with either monotherapy[169]. Combination therapies are likely to be needed in the future that takes advantage of the new genomic technologies to understand the basis in individual tumors. Combination therapies are promising for the management of cancer because of their potential synergy which could lead to deeper responses but more work needs to be done to learn about tumor feedbacks and resistance mechanisms. Many combinational studies are allowed nowadays for the treatment of patients in the upfront setting due to poor overall results[175].

Biomarkers in cancer immunotherapy: Extraordinary advances in scientists' understanding of the cancer biology, underlies the progression and development of cancer as well as potential molecular targets for its treatment[176-179]. Biomarkers are defined by the World Health Organization (WHO) in 1993 as almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be biological, chemical or physical[180,181]. According to the FDA, a biomarker is a characteristic that can be evaluated as an indicator of a physiologic or a pathologic process or a pharmacological response to a therapeutic intervention[182]. Useful biomarkers can be grouped into six subtypes: Those for identifying risk factors, those for the early diagnosis of diseases or abnormalities, those used to predict either prognosis or clinical responses to therapy, those that can identify the patients are most likely to benefit from a given treatment and those used as surrogate endpoints in clinical trials[183]. Biomarkers can be measured alone or in a group, often called a biomarker panel, to infer risk, diagnosis, prognosis and therapeutic response. DNA, RNA, proteins, metabolites, host cells and microorganisms can all function as biomarkers[184]. The biomarker should be able to discriminate between pathologic and physiologic conditions, even if they are similar. Biomarkers should have defined molecular mechanisms of biological activities[185]. Cancer biomarkers are typically evaluated in blood, body fluids or tumor specimens either ex vivo or in situ. To date, biomarkers of response have not served as primary end points for therapeutic trials that supported the approval of cancer therapies, although in selected cases they have been used as components of composite endpoints[180]. They can also localize tumors and detect sites of different stages[181]. Biomarkers should be simple to measure, inexpensive and responsible for high throughput technologies to be used clinically[185-187]. Nowadays, the most frequently recommended biomarkers by clinical practice guidelines for epithelial ovarian cancer (EOC) (despite its low specificity), is Cancer antigen-125 (CA-125) (MUC 16)[185,188]. Human epididymis protein 4 (HE4) has demonstrated good sensitivity and specificity in detecting EOC, overcoming the traditional role of CA-125[189]. Both CA-125 and HE4 have been approved by the FDA for monitoring the treatment and disease recurrence[190]. Alpha-fetoprotein (AFP), one of the first discovered protein tumor markers, is the main serological marker used in the diagnosis of hepatocellular carcinoma (HCC) since it is secreted by about half of HCC tumors[191-193]. The most extensively validated and commonly used serum biomarker for detecting pancreatic cancer is carbohydrate antigen 19-9 (CA 19-9) which is a sialylated Lewis blood group antigen[194]. It is also elevated in a variety of other malignancies such as hepatocellular carcinoma, cholangiocarcinoma and colorectal adenocarcinoma[195]. The glycoprotein PSA is a well-recognized biomarker for detection of prostate cancer[196], which has changed the way of prostate cancer management after its FDA approval in 1984[197,198]. Many studies have shown that miRNAs are a novel class of biomarkers for early detection of human cancers[199,200], due to their abundance and ease of detection in the bloodstream[185]. CEA is also the most well-known and validated serum biomarker for epithelial malignancies[201]. Molecular imaging technology provides a noninvasive mechanism to evaluate tumors and may be an ideal candidate for these purposes[8]. The promise of biomarker science and its successful application resides in the numerous

Table 2: List of biomarkers and surrogate end-points

Biomarkers	Related malignancy	References
CA-125 (MUC 16)	Epithelial ovarian cancer (EOC)	Strimbu and Tavel[185] and Montagnana *et al.*[188]
HE4	Epithelial ovarian cancer (EOC)	Chen *et al.*[204]
	AFP	hepatocellular carcinoma (HCC)Song *et al.*[191],Goggins[192], Ballehaninna and Chamberlain[193], Lukes *et al.*[194], Allhoff *et al.*[195], Cooner *et al.*[196], Motawi *et al.*[197], Bertoli *et al.*[198], Nakamura and Nishimura[199], Kelloff and Sigman[200], Das *et al.*[201], Anastasi *et al.*[202] and Hanash *et al.*[203]
CA 19-9	Pancreatic cancer Hepatocellular carcinoma Cholangiocarcinoma Colorectal adenocarcinoma	Lukes *et al.*[194] and Allhoff *et al.*[195]
PSA	Prostate cancer	Nakamura and Nishimura[199] and Kelloff. and Sigman[200]
miRNAs	human cancers	Patz *et al.*[205] and Finn[24]
CEA	Epithelial malignancies	Das *et al.*[201]
CEA, RBP, SCC and α-1 antitrypsin	Lung cancer patients	Patz *et al.*[205] and Mellman *et al.*[206]

scientific disciplines and cancer research projects[202]. Biomarkers have significant potential for preventing and diagnosis the human cancers in different stages[203]. Promising and emerging biomarkers should routinely be implemented as exploratory end-points into ongoing clinical trials, in order to permit full validation and broader application[180] (Table 2).

CONCLUSION

Immuno oncology is an exciting field of cancer treatment with the potential to impact the management of numerous malignancies. Cancer immunotherapy restrains the patient's immune system to fight against cancer and is emerging as a significant modality in combination with conventional therapies recent results have allowed cancer immunotherapy to finally come of age, therefore it merits serious consideration of the clinical oncology communities. In the last 25 years, remarkable progress has been made in the field of cancer immunotherapy. In particular, several immunotherapy drugs have been approved for the treatment of several types of cancer with impressive and durable clinical responses. The present review has illustrated some of the mechanisms and latest approaches to cancer immunotherapy. In summary, immune checkpoint inhibitors and antiangiogenic drugs are widely and increasingly prescribed and are under review for application in solid tumor management. The goal of cancer vaccines is to activate and expand cancer-specific T cells. This review had identified the top ranking immunotherapies that are the focus of ongoing validations and clinical translational works in specific types of cancer. It was also noted that combination strategies, due to their synergistic anti-cancer activity are promising for the treatment of advanced types of cancer. The ability of the immune system to specifically attack cancer cells coupled with its ability to adapt to an evolving tumor and its built-in function of memory, make it the most powerful weapon for long-term control of cancer. Also anticipated that the development of predictive biomarkers as well as the competition among their manufacturer companies, will help to control the costs associated with these treatments in the future. Cancer immunotherapy seems to be competent in the treatment of advanced types of cancer and hence more effort is needed in order to develop this important field of science.

SIGNIFICANT STATEMENT

This study considered current strategies in a cancer vaccine, immune checkpoint blockade, oncolytic viruses and immune combination therapy. This study will help the researcher to uncover a critical area of cancer immunotherapy, Thus a new theory on the answer to the obstacle relates to the immunotherapy such as Car-T cell therapy, CTLA4 and PD-1 checkpoint blockade.

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