Review Article

Immunotherapy for Treatment of Cancer: A Review

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ABSTRACT

Cancer is the leading cause of morbidity and mortality worldwide and has put heavy burden on public resources. The incidence of cancer and cancer related deaths are both increasing in trend. The conventional treatment for cancer includes surgery, radiation therapy and chemotherapy. However, the use of radiotherapy and chemotherapy, though effective, can be limited for their toxicities. Better understanding of human immunological system has enabled researchers to develop novel immune-based therapeutic agents for cancer. The effectiveness of immunotherapy, either as a single or combination therapy with conventional treatment has been proven through numerous studies. Immunotherapy also has the advantages over radio-chemotherapy for being less toxic, and more target-specific. There are many types of immunotherapies established for treatment of cancer. These include monoclonal antibodies, prophylactic vaccines, immune adjuvants, and cytokines. Beside the existing therapy, various investigational immunotherapy candidates are currently undergoing active development, such as therapeutic cancer vaccines and CAR-T cell therapy, providing better option for treatment of cancer in the near future.

Keywords: cancer, immunotherapy, monoclonal antibodies, vaccines, cytokines, chimeric antigen receptors

INTRODUCTION

Cancer is one of the leading cause of morbidity worldwide and associated with high fatality rate. It affects the overall quality of life and substantially burden the public health care expenditure. The incidence of numerous type of cancers shows an increasing in trend. In 2012, 14 million new cases of cancer have been documented. However, the incidence is expected to increase up to 21 million by 2030.[1, 2] Despite the advances made in development of cancer treatment, it remains as one of the major cause of death. About 8 millions of people died due to cancer in 2012, and it is expected to rise to 13 million by 2030.[3]

Breast, lung, cervix, stomach and colorectal cancers are among the most common cancers in women. While for men; lung, prostate, colorectal, stomach and liver cancers are the commonest. Tobacco use contributes about 20% of cancer death, and in developing countries, 20% of infection-associated cancers are contributed by HBV/HCV and HPV infection.[3]

There are varieties of treatment modalities available for cancer, with indication depends on the type and stage of cancer, general well-being of patient, as well as socioeconomic factors. Conventional treatments for cancer include surgery, radiotherapy and chemotherapy. The use of cancer chemotherapeutic agents often limited for their toxicities.[4]

Advance research made in immunological field has enable a breakthrough discovery of development of novel cancer immunotherapy. This therapy works through either manipulation of human own immune system or by administrating exogenous laboratory-made immune cells into human body to fight against cancers.[5] The advantages of immunotherapy compare to conventional treatment include, it causes less adverse effect, more target-specific and some immune cells have the 'long-term memory' to prevent cancer recurrence.[6]

In history, William Coley is the first person who realised the potential use of immune cells to fight against cancers.[7] He noticed that, some of his patients who acquired post-surgical infection, showed better improvement in their cancer progress. He continued the discovery by treating his cancer patients through provoking immune system by using specific

cultured bacteria, known as *Coley toxins*.[2] Since then, more researches have been carried out and discoveries being made in developing immunotherapy. In recent decades, there is increase in number of immunotherapy receiving approval for cancer treatment. It has become a vital component of treatment regimen for certain types of cancer.[8]

UNDERSTANDING CANCER IMMUNOLOGY

Tumour-associated antigen (TAA) is a specific antigen expressed by most cancer cells. TAA can come from various sources which elicits different immune responses. The examples include TAA derived from oncogenic viruses, overexpression of cellular proteins, and mutated genes and onco-suppressor by-products.[9]

Activation of cytotoxic T-cells (CTL) is the key element of immunological reaction towards cancer cells. CTL is produced by cancer infiltrating lymphocytes. It recognizes TAAs which present on the MHC Class I molecules on tumour cell surface. Subsequently the Fas/FasL pathway will be activated by CTL and initiate the programmed-cell death of the malignant cells.

However, cancer cells can develop mechanism to escape human immune attack to be manifested clinically. This can be achieved by several means include by reducing number of MHC Class I on surface to avoid immune cells recognition, inhibitory signalling, and activation of immunosuppressive activity.[9] Thus, the principal mechanism of cancer immunotherapy is through improving the ability for cancer cells recognition or by introducing the missing immune system components. .

DIFFERENT MODALITIES OF IMMUNOTHERAPY

Cancer immunotherapy can be "passive" or "active" therapy. "Passive" immunotherapy includes treatment with monoclonal antibodies, tumour adjuvant, and delivery of cytokines which directly initiate anticancer activity.[10] "Active" immunotherapy refers to the use of vaccination to stimulate patient own immune system; as a treatment, itself or as a cancer prophylaxis.[11] However, this is an ambiguous term, as some immunotherapy can be both active and passive therapy (e.g. monoclonal antibodies therapy).

Immunotherapy can be further classified into specific; which triggers T-cells responses against tumour-associated antigens and non-specific therapy; which not targeting to any specific antigens (Table 1).[10, 12]

Table 1 Classification of cancer immunotherapy[12]

Immunotherapy	Active	Passive
Specific	Cancer vaccines; tumour-associated or viral antigens	Injection of monoclonal antibodies
Non-specific	Immune adjuvants Cytokines therapy	Chimeric Antigen Receptor T-cell therapy (CAR T-cell)

I. Monoclonal Antibodies

Monoclonal antibodies therapy is one of the most successful forms of immunotherapy for both solid and haematological cancers. The production of monoclonal antibodies is based on the selection of specific antigen for specific tumour growth (Table 2).

Table 2 Tumour-associated antigen targeted by monoclonal antibodies[13]

Antigen category	Examples of antigen	Tumour types expressing antigen
Cluster of differentiation (CD) antigens	CD20	Non-Hodgkin's lymphoma
	CD30	Hodgkin's lymphoma
	CD33	Acute myelogenous leukaemia
Glycoproteins	EpCAM	Epithelial tumours (breast, colon, lung)
	CEA	Epithelial tumours (breast, colon, lung)
	gpA33	Colorectal carcinoma
Glycolipids	Gangliosides	Neuroectodermal tumours
Carbohydrates	Lewis-Y[2]	Epithelial tumours (breast, lung, prostate)
Vascular targets	VEGF	Tumour vasculature
	VEGFR	Epithelium-derived solid tumours
Growth factors	ErbB1/EGFR	Glioma, lung, breast head and neck tumours
	ErbB2/HER2	Breast, colon, lung, ovarian
Stromal and extracellular antigens	FAP	Epithelial tumours (colon, lung, pancreas)
	Tenascin	Glioma, epithelial tumours

Monoclonal antibodies can be produced in the form of murine, chimeric, humanized or human antibodies (Table 3). Murine monoclonal antibody is the first generation of antibodies produced by hybridoma technology. It is prepared in the laboratory by injecting human cancer cells or its antigen protein into mice. This will activate immune reaction and production of antibodies. These antibodies will then be fused with laboratory-grown cells to form hybridomas, which allows massive production of antibodies.[10] Nevertheless, the use of murine form of antibodies can be limited due to the risk of immune activation against these antibodies.

Table 3 Examples of different forms of monoclonal antibodies approved for treatment of cancer[14]

Monoclonal antibodies	Target	Type	Indication(s)
Cetuximab	EGFR	Chimeric IgG	Colorectal cancer
Panitumomab	EGFR	Human IgG	Colorectal cancer
Trastuzumab	HER2	Humanized IgG	Breast cancer, gastric cancer
Pertuzumab	HER2	Humanized IgG	Breast cancer
Alemtuzumab	CD52	Humanized IgG	Chronic lymphocytic leukaemia
Rituximab	CD20	Chimeric IgG	Chronic lymphocytic leukaemia
Ipilimumab	CTLA-4	Human IgG	Melanoma
Nivolumab	PD-1	Human IgG	Melanoma
Denosumab	RANKL	Human IgG	Breast cancer, prostate cancer
Ibritumomab	CD20	Murine IgG	Non-Hodgkin's lymphoma

Improvement in efficiency of immune reaction while at the same time reducing immunogenicity can be achieved through production of chimeric, humanized and fully human antibodies. The humanized monoclonal antibody developed by replacing Fc and Fv regions with human germline amino acid and production of fully human antibodies achieved through transgenic mice and phage display technique.[13]

Monoclonal antibody can cause direct cell deaths by inducing apoptosis of cancer cells through inhibition of signalling pathway for cells growth.[13] It also indirectly induces cells death by recruiting cytotoxic cells such as monocytes and macrophages, and mediates cancer cell death through antibody-dependant cell mediated cytotoxicity (ADCC) or by binding to complement and mediate cancer cell death through induction

of complement dependent cytotoxicity (CDC).[13] Another mechanism action of monoclonal antibody is through vascular and stromal ablation thus retarding the tumour growth and vascularisation.[15] Monoclonal antibodies also can be conjugated with radioactive substances, toxins or chemotherapeutic drugs targeting specific cancer cells improving its efficacy.

Various Types of Monoclonal Antibodies

A. Naked Monoclonal Antibodies

It is the most common type of monoclonal antibodies used for cancer treatment. It acts without being conjugated with other material. In the body, it will attach to antigens on tumour cells or some non-cancer cells or can be free floating (Table 4).

Table 4 Examples of naked monoclonal antibodies[16]

Example	Mechanism of action	Description
Alemtuzumab	Attaches and recruits immune cells to kill tumour cells	• For chronic lymphocytic leukaemia • Target CD52 protein
Trastuzumab	Attaches and inhibits signalling pathway for tumour growth	• For HER2-positive breast cancer • Target HER2 protein

Trastuzumab is used as adjuvant chemotherapy for breast cancer patients with HER2-positive subtype (account for 20 – 30% for overall breast cancer incidence). Studies have shown that trastuzumab significantly contributed towards improvement in patient's outcome and cost-effective in long term. Valachi et al. in their study demonstrated that treatment regimen consisting of trastuzumab and chemotherapy for HER-2 positive breast cancer, gave higher therapeutic outcome in term of pathological response rate (38%) compared to chemotherapy alone (21%).[17] Although, initially, this treatment regimen could increase the treatment cost, however in the long run it is proven to be more cost-effective.[18]

B. Conjugated Monoclonal Antibodies

Conjugation of monoclonal antibodies with active substances such as chemotherapy drugs, radioactive particles or toxins provides transport mechanism for the drug to reach the specific target. It increases the efficiency of drug delivery avoiding toxic effects on normal cells (Table 5). Conjugated monoclonal antibodies are also useful for study of distribution of specific tissue in the body. For example, monoclonal antibody-213-immunoreactive (Mab 213-I) has been used to detect the details distribution of immuno-reactive olfactory and glomeruli cells in the rat olfactory system.[19]This is based on the Mab 213-I immune reaction against TGFα; an antigen that also highly expressed in variety of cancer cells. Thus, it could potentially provide a basis for better detection of cancer cells distribution.

Table 5 Different forms of conjugated monoclonal antibodies[10, 16]

Type	Example	Description
Chemolabelled	Brentuximab vedotin	• Conjugated to chemotherapy • Target CD30 protein • For refractory Hodgkin's Lymphoma
Radiolabelled	Ibritumomab tiuxeta	• Attached with small radioactive particles • Target CD20 antigen • B cells carcinoma, Non-Hodgkin Lymphoma
Immunotoxins	Moxetumomab pasudotox	• Conjugated with anti-CD-22 exotoxin • Target specific antigens on surface cancer cells • Under clinical trials for B-cell malignancies

C. Bi-specific Monoclonal Antibodies

Two distinct types of monoclonal antibodies were bind together to two different types of cancer surface antigens. Blinatumomab as example, targets CD19 protein on leukaemic/ lymphoma, while cells with another antibodies target CD3 on T-cells. Direct target for both proteins initiates a greater immune response attack against the tumour cells.[20]

Adverse Effects of Monoclonal Antibodies

Generally, monoclonal antibodies cause less adverse effects in comparison to conventional treatment such as chemotherapy. The potential adverse effects of monoclonal antibodies associated with the possibility of triggering immunological reaction following the therapy. It is relatively uncommon. However, monoclonal antibodies may prompt type I immune reaction (anaphylactic), mediated by IgE antibodies. Immediate immunologic reaction may affect specific organ and present with symptoms of allergic rhinitis, conjunctivitis, angioedema, asthma, urticarial, eczema, etc. or could affect multiple organs leading to anaphylactic shock.[14] Administration of prophylactic antihistamine prior to infusion can prevent immediate hypersensitivity.

Type II hypersensitivity also can occur in treatment with monoclonal antibodies. The patient may develop depletion in number of platelets, white blood cells and anaemia due to haemolysis. Patients also risk for type III characterized by vasculitis, serum sickness and respiratory problems. In delayed hypersensitivity (type IV), tumour lysis syndrome or cytokines release syndrome may occur.

II. Cancer Vaccines

Cancer vaccines can be classified either as prophylaxis or therapeutics (Table 6).

Table 6 The classification of cancer vaccines[12]

Vaccine type	Name of agent	Indication
Preventative	Hepatitis B virus vaccine	• Hepatocellular carcinoma
	Human papilloma virus vaccines; Gardasil and Cervarix	• Cervical cancer
Therapeutic	Vitespen	• Melanoma and locally renal cell carcinoma • Prostate cancer
	GVAX	• Advance metastatic prostate cancer
	Sipuleucel-T (Provenge) ProstVac-VF	• Prostate cancer
	BiovaxID	• Non-Hodgkin's lymphoma

A. Prophylactic Cancer Vaccines

Certain chronic and persistent viral infection can predispose the development of cancers in human. For example, chronic Hepatitis B and C virus infection predispose human for development liver cancer while Human Papilloma Virus (HPV) infection contributes for development of cervical cancer.[21] Vaccination against these infections could provide protection against development of these cancers.

Another approach of cancer vaccine is to prevent the recurrence rather than occurrence of a cancer. A personalised vaccine is formulated according to patient tumour's mutant protein and indicated to patient who had received surgery and at high-risk of cancer recurrence. Several studies have demonstrated that it is effective in preventing cancer recurrence and inducing complete remission.[22]

HPV vaccines for Cancer of Cervix

Cervical cancer is one of the most common cancers among women. The incidence of cervical cancer is almost 500,000 worldwide and responsible for 250,000 casualties every year.[23] Seventy per cent of overall cervical cancer is associated with HPV 16 and 18 infections. These infections also linked to the development of cancers of anus, vulva, vagina, and penis.[24]

Gardasil and Cervarix are the two examples of HPV vaccines currently available in the market. Gardasil consists of purified proteins of 4 subtype of HPV (HPV 6, 11, 16, 18). Cervarix is made up of purified proteins of 2 subtype of HPV 16 and 18.[25, 26] Exposure to these proteins provokes the immune response and production of antibodies. These antibodies will provide protection against active infection and enhance immune attacks when active infection is present.

HPV vaccines can effectively reduce the incidence of cervical cancer in young women, especially when given at their early age or before sexually active.[27] HPV vaccines can provide up to 98% preventive efficacy against cancer of cervix caused by HPV 16 and 18.[28] Vaccination for HPV should not be limited to women. HPV vaccines is also recommended to men as it provides protection against development of genital warts, which is one of the predispose condition for genital cancers, and to reduce the risk of spread of infection from men to women.[29]

B. Therapeutic Cancer Vaccines

Therapeutic cancer vaccine is relatively a novel concept. It differs from prophylactic vaccines as therapeutic cancer vaccine is used to direct immune system attack against pre-existing tumour cells. Currently, there are many therapeutic cancer vaccines under active researches. Sipuleucel-T is the only therapeutic cancer vaccine received approval from US FDA (since 2010).

The indication of Sipuluecel-T is for treatment metastatic hormone refractory prostate cancer.[30] It mainly consists of autologous peripheral blood mononuclear cells (PMBCs). PMBCs are exposed to prostatic acid phosphatase linked to GM-CSF (PAC-GM-CSF), to provoke immune system attack against prostate malignant cells. A multicentre, double blind placebo-controlled phase 3 clinical study has shown that Sipuluecel-T significantly prolonged overall survival and death risk reduction among hormone refractory prostate cancer patients.[31]

Another potential therapeutic vaccine for prostate cancer is ProstVac, an investigational candidate currently in phase 3 study. It is a vector-based vaccine regimen consists of transgenes for prostate-specific antigen and multiple T-cell co-stimulary molecules (PSA-TRICOM). It works by disrupting the immunological tolerance to PSA and mediates a strong immune response against prostate cancer cells.[32, 33] Preliminary study has shown that this vaccine produced significant immunologic reactivity with negligible toxicity while phase 2 study has demonstrated the overall patient survival benefit.[34]

III. Immune Adjuvants and Cytokines

A. Immune Adjuvants

Immune adjuvant is a non-specific immunotherapy, which instead of targeting tumour cells directly, it works as a booster for immunological reaction against malignant cells. This will lead to reduction in tumour growth in otherwise would not regress by normal immune responses.[8, 16]

Intravesical Bacille Calmette-Guerin (BCG) is an example of effective adjuvant to surgery for superficial or carcinoma-in-situ (CIS) bladder cancer. It contributes towards reduction of cancer growth and prevention of recurrence – reducing more than 20% of cancer growth and up to 40% of recurrence rate in comparison to surgery alone treatment.[35] Other studies also support the finding, which shows that the use of adjuvant BCG increases 10-year progression-free rate by 60%.[36, 37]

The mechanism of action of BCG is through induction of local immunological system, principally mediated by T-helper cells responses. The most efficient regimen of BCG as adjuvant therapy is initial 6 weeks treatment followed by one-year maintenance course. Though it is effective, the use of BCG as adjuvant therapy for bladder cancer can be limited for its potential adverse effects on urinary system (patient complained of dysuria, urgency and frequency). Thus, to optimise the treatment it is important to manage these adverse effects properly.

B. Cytokines Immunotherapy

Immune cells secrets glycoproteins known as cytokines. Cytokines are important proteins that help in regulating activity of immune cells as well as tumour growth. One of the examples of laboratory-made cytokines is Interleukins-2 (IL-2). IL-2 has been approved for treatment of melanoma and renal cell carcinoma, particularly useful when the cancer is refractory towards conventional treatment.[8, 16] It can be administered as a single or as combined therapy with interferon-alpha to improve the efficiency. Adverse effects of IL-2 include fever, chills, malaise, gastrointestinal symptoms, weight gain, and rare but serious, cardiovascular toxicity.

Interferon alpha (IFN-alpha) is the most useful interferon therapy for cancer. It is a form of cytokines which build from 150 amino acids. IFN-alpha works by binding to immune cells surface receptor and mounting an immune reaction towards malignant cells. This is achieved by several means; promoting B and T cells activity and upregulating gene like MHC Class 1, tumour antigen and adhesion molecule against cancer cells[38]. IFN-alpha also exhibits anti-angiogenic activity as well as interfering the cell division causing the shrinkage in tumour growth.

IFN-alpha is indicated for various cancers including melanoma, renal cancer, AIDS-related Kaposi's sarcoma, haematological cancer such as hairy cell leukaemia and follicular non-Hodgkin's lymphoma. Adverse effects of

interferon alpha include flu-like symptoms in initial week of therapy, gastrointestinal disturbances, headache, skin rashes, thinning hair, pancytopaenia and increased risk of autoimmunity.[39] These side effects are dose-related and can be severe, and one of the limiting factor for its usage.

IFN-alpha as adjuvant therapy particularly useful in early stage or locally infiltrating cancer. In a study conducted by Kirkwood and colleagues, it has been shown that IFN-alpha prolongs the relapse free and overall survival of patient with high-risk resected melanoma.[40]

GM-CSF is another example of cytokine therapy. It is frequently being used as a form of supportive treatment after chemotherapy. This therapy is usually done as complimentary to stem cells or bone marrow transplant to replenish the myeloid series. Study of the potential use of GM-CSF as combination therapy for melanoma also has been carried out. A multicentre, phase II trials of treatment of metastatic melanoma with GM-CSF and ipilimumab vs ipilimumab alone has found that the combination therapy had significantly prolonged overall survival rate of the patient.[41] Among side effects of GM-CSF include fever, nausea, vomiting, skin rash and bone pain.

IV. CAR T-cell Therapy

Chimeric antigen receptors (CAR)-T cell therapy is a newer and promising approach of immunotherapy currently under development. It involves a procedure called adoptive cell transfer (ACT). In this procedure, the patient's blood will be withdrawn and filtered for T-cells. These T-cells then will undergo genetic modification to be attached with chimeric antigen receptors (CARs) to specific cancer. These new genetically engineered T-cells will be multiplied before re-administered to the patients' circulation. Inside the circulation, these cells will proliferate and further amplify immune response, thus providing better clinical outcome than conventional therapy.[42]

One potential disease studied with CAR T-cell therapy is acute lymphoblastic leukaemia (ALL). A series of clinical trials of an investigational immunotherapy CD19-specific CAR-T cells (CTL019) demonstrated that paediatric and young adult with relapse/refractory ALL achieved complete remission, prolonged persistence and sustained response after the treatment.[43] In July 2017, CTL019 had received recommendation from US Food and Administration Advisory Committee for approval; set to become the first commercially available CAR-T cell therapy.[44]

CHALLENGES OF CANCER IMMUNOTHERAPY

The ability of cancer cells to evade immune attack; either through intrinsic or extrinsic mechanism is one of the biggest obstacles in cancer immunotherapy. The intrinsic mechanism includes causing antigen or MHC loss, release of immunosuppressive cytokines, or expressing marker that can interrupt T-cell function such as programmed-death-receptor-1 (PD-L1). Whereas, the extrinsic factors which help cancer cells to survive include formation of physical barrier for the drug in reaching the target and existence of regulatory immune cells such as regulatory (Treg) in tumour microenvironment which able to reduce the immune responses against cancer cells.[45]

One approach to overcome this challenge and improving the treatment outcome of immunotherapy is through inhibition of immune-inhibitory pathway activated by cancer cells, known as "checkpoint blockade". Anti-CTLA-4 antibodies (ipilimumab) act by down-regulating the initial stages of T-cell activation, an initial target for checkpoint antibodies[46] whereas, anti-PD-1antibodies (pembrolizumab) inhibit the expression PD-1 which responsible for downstream signalling to inhibit T-cells proliferation[47]. These drugs have received FDA approval for treatment of metastatic melanoma and other various cancer conditions.

CONCLUSION

Better understanding of human own immunological system has led to discovery of immune-based therapy for cancer. Recruiting and manipulating human own immune system has become the basis of development of immunotherapy against cancer cells. Various kinds of immunotherapy have received market approval over the years; monoclonal antibodies, prophylactic and therapeutic tumour vaccines, immune adjuvants and cytokines are among the examples. The effectiveness of immunotherapy in treating cancer has been established through many clinical studies. Immunotherapy improves the overall survival rate of the patient and reduces cancer recurrence. Immunotherapy superior to conventional treatment for being more target-specific, cause less adverse effects, better tolerability to the patients and cost-effective for long-term usage.

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