

Immunotherapy options for cancer

Abstract

Cancer is a heterogeneous disease originated from various parts of the body and characterized mainly based upon the type of cells or tissue it originated from. In early years of cancer research, it was considered that a “magic drug” can be developed to treat all types of cancers. However, this notion was proven wrong through years of research as various forms of cancer emerged that are variant between individuals and are hard to treat or even control. Clonal survival of cancer cells is the major hurdle limiting the therapeutic response in patient. Cancer progression leads to immunocompromised state in patients resulting in fast disease progression and higher susceptibility to infections. Tumor infiltrated T cells, tumor associated macrophages, mesenchymal stem cells and other immune cells support the clonal development in cancer tissue leading to its rapid growth and metastasis. In recent years, immunotherapy of cancer is the major interest among researchers. Chimeric antigen receptor (CAR) T cell therapy, immune check point targeting, or boosting the immune system in patient are the approaches being implemented in cancer immunotherapy. Present review discusses the various immunotherapy options for cancer and explains importance of considering the treatment/prevention with natural compounds.

Keywords: cancer, immunotherapy, PD1, CTLA4, vitamins, antibodies

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Abbreviations: CAR, chimeric antigen receptor; TAMs, tumor associated macrophages; TNF- α , tumor necrosis factor- α ; VCAM-1, vascular cell adhesion molecule 1; MDSCs, myeloid derived suppressor cells; NK, natural killer; HER₂, human epidermal growth factor receptor 2; HLA, human leukocyte antigen; GM-CSF, granulocyte-macrophage colony stimulating factor; MHC, APCs, antigen presenting cells; PBMCs, peripheral blood mononuclear cells; CTLA₄, cytotoxic T lymphocyte-associated antigen 4

Introduction

Immune system in the human body comprises of various types of cells, organs, and antibodies including lymphocytes, leukocytes, thymus, lymph nodes, spleen etc. The major function of the immune system is to defend the body against bacteria, virus, antigens and cancer cells.^{1,2} However, cancer cells are a real challenge as they are able to escape immune attack and further immune system favours the tumor progression by altering tumor microenvironment.³ Initial research was concentrated on identifying cancer cell gene abnormalities, their transformation, gain/loss of functional mutations, stromal differences and dominant oncogenes. Therapies were developed accordingly which led to partial success in cancer treatment.⁴⁻⁶ In many cases, disease free state is being achieved in very few cases and is transient in many patients as the treatment is ineffective or not adequate.^{7,8} There is increasing evidence to suggest that cancer cells also alter and restrict the surrounding normal cells, immune cells and extra cellular components in favour of them.^{9,10} Infiltrated immune cells and tumor associated macrophages (TAMs) can trigger sustained proliferative signals to support cancer cell survival and evolution even in adverse conditions.¹¹ Myeloid derived cells and lymphoid cells are complex in nature depending upon the organ they are present in. After infiltrating into the tumours, they can provide growth factors such as tumor necrosis factor- α (TNF- α), fibroblast growth factor, interleukins, and chemokines to support growth/survival of cancer cells and neighbouring stromal cells in direct and indirect pathways.¹² Normal tissue cells maintain tissue integrity by their organized cell-to-cell

contacts and this function is lost in cancer cells. In this case, tumor cells bind to the immune cells from their surroundings and survive in adverse conditions by promoting growth signals and inhibiting death signals. This type of binding is evident in metastatic breast cancer cells where the α_4 -integrin/VCAM-1 interaction between the tumor associated macrophages and cancer cells respectively induces PI3K/Akt pathway to in favour of cell survival.^{13,14} Moreover, immune cells secrete regulatory molecules such as vascular endothelial growth factor, TNF- α , platelet derived growth factors, matrix metalloproteinases and several factors to stimulate vascular cell proliferation and further favour the tumor by remodeling the microenvironment.¹⁵ Tumor cells alter the functional properties of regulatory T cells, myeloid derived suppressor cells (MDSCs), TAMs, and natural killer (NK) cells in order to protect themselves from cytotoxic T cells responses. All these interactions lead to clonal differences in tumor itself. Hence, it is important to study about all the neighbouring cells in tumor region and investigate how the interactions and further actions are being manipulated. Immune check point blockade, cancer vaccines, T cell based therapies, understanding the micro-biome in regulating cancer therapy, identification of tumor specific and systemic biomarkers are some of the latest strategies in oncoimmunotherapy.¹⁶⁻¹⁸

Because of increased cancer occurrence worldwide and lack of complete treatment for various cancer types with no adverse effects, it is the time to look into an alternative way to prevent or treat cancer. In an effort, since many years researchers are working on natural compounds in identifying their potent anticancer activities.¹⁹ several compounds from plant and animal origins are showing promising results in mice and human studies. These natural compounds have an advantage of low or no treatment associated toxicities and can be taken in form of diet on regular basis for prevention of disease occurrence.²⁰⁻²² Some of the natural compounds also have immune modulating activity.^{23,24} Current review explains various options available for cancer immunotherapy along with a brief account of natural compounds tested so far for the same.

Cancer vaccines

Vaccines are preparations consisting of a specific antigen and provide altered protective response against a disease. Antigens are prepared to resemble tumor associated antigens or biomarkers and administered to individual with or without adjuvants before the strike of the particular tumor. This helps to boost host immune system to fight against the cancer cells at very early stages of cancer occurrence and further prevents its establishment and growth.²⁵ For example, many of the breast cancers show increased levels of HER₂ expression on cancer cells. Treating this with HER₂ antibodies is promising in control of the cancer but is associated with significant side effects, tumor relapse or metastasis in majority of the patients. Hence it is advisable to prevent the occurrence by immunizing an individual with antigens designed to resemble HER₂.²⁶ This particular antigen containing vaccines enhance adaptive immunity in most breast cancer patients. E₇₅ (nelipepimut-S) is a peptide derived from HER₂ and is immunogenic in human leukocyte antigen (HLA)-A₂/A₃ manner. It was tested in phase I/II clinical trials in breast cancer patients to test its ability to prevent tumor recurrence.²⁷ Granulocyte-macrophage colony stimulating factor (GM-CSF) was used as the adjuvant in vaccine preparation from E₇₅. The experiment was conducted in node-positive and high-risk node-negative patients with varying expression levels of HER₂. Results indicate 89.7% disease free survival in vaccinated group of patients while the percentage is 80.2% in control group of patients. Further, vaccination does not also have significant local or systemic toxicities.²⁷ Similarly, AE₃₆ is a HER₂ derived peptide that can stimulate CD₄⁺ T cell responses in cancer patients by interacting with MHC class II molecules. In order to increase AE₃₆ binding efficiency with MHC class II receptor, Ii-key peptide was added to it and together denoted as AE₃₇. Administration of AE₃₇ peptide containing vaccine increases peptide specific proliferation of CD₄⁺ T cells and IFN γ release for cytotoxic T cell activity.²⁸ In Phase I clinical trial in breast cancer patients, AE₃₇ was mixed with GM-CSF adjuvant and administered to patients in a series of intradermal injections. Grade 1 local toxicities were observed in 40% of patients and grade 2 levels of toxicities were observed in 60% of patients. However, adjusting the dose of GM-CSF decreased grade 2 level toxicity. From phase II trials it was proven that AE₃₇ vaccination associated toxicities were well tolerated and safe in patients and induces strong CD₄⁺ T cell response specific to the peptide. AE₃₇ vaccination also reduced recurrence.²⁸

In an alternative way, vaccines are given by loading into cells. Dendritic cells (Antigen presenting cells-APCs) are mainly used to load tumor associated antigens and administration of the same directly presents antigens to immune system in the tumor microenvironment or body for powerful immune response against cancer.^{29,30} Lapuleucel-T is the antigen prepared by loading into peripheral blood mononuclear cells (PBMCs). It consists of HER₂ similar sequence attached to GM-CSF. Lapuleucel-T administration in breast cancer patients was associated with HER₂ specific T cell responses with lower levels of adverse events.³¹⁻³³ Other than HER₂ vaccines, P₅₃ specific antigens were also developed to load into dendritic cells. Because P₅₃ is tumor suppressor gene and the mutations in P₅₃ leads to aggressive forms of cancer.^{34,35}

PD1/CTLA4 targeted therapy

Whenever the immune system is activated in the body, check points are also activated after the immune response reached to certain level to inhibit or subdue the immune response in order to prevent any

possible organ damage. Programmed death-1 (PD-1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA₄) are the surface check point molecules.³⁶⁻³⁸ T cells activation requires the binding of B₇ with CD₂₈ on cell surface after the antigen recognition by T cell receptor.³⁶ However, being the homologue of CD₂₈, CTLA₄ bind to B₇ and prevents activation signals. PD₁ and/or CTLA₄ targeted therapy is termed as check point blockade therapy where the antibodies against PD₁ and CTLA₄ are used to block their inhibitory action and further robust immune responses are carried out for durable period of time.³⁹ In many cancers up regulation of PD₁ and CTLA₄ was observed in tumor infiltration lymphocytes along with higher PD-L₁ expression on cancer cells which serve to shield the cancer cells against immune attack by keeping T cell activity at basal levels.³⁹ Especially, the triple negative breast cancer needs significant interactions with the microenvironment including stroma, tumor infiltrated lymphocytes, fibroblasts and macrophages as it is not hormonal dependent. These multiple interactions reflected in the tumor as mutations and clonal differences making the overall tumor resistant to treatment.⁴⁰ Hence PD₁/CTLA₄ targeted therapy is highly advisable in cancer treatment. PD₁ directed antibodies including brolizumab and nivolumab and CTLA₄ targeted antibodies such as dacarbazine are already tested rigorously in against cancers for their efficacy.⁴¹

Combination treatment of ipilimumab and dacarbazine in phase 3 studies in previously untreated metastatic melanoma patients was conducted to see overall survival rate.⁴² Significant increase in overall survival was observed in patients receiving combination treatment when compared to dacarbazine and place treated group. 3 year overall survival was observed in 20.8% of patients while the control group has only 12.2% of overall survival rate. Moreover, the check point blockade antibodies can be combined with chemotherapeutic agents for improved efficacy. In another study, tremelimumab (CTLA₄ specific monoclonal antibody) was combined with exemestane (steroidal aromatase inhibitor) to test in hormone responsive breast cancer patients to check the maximum tolerance dose, safety and assess tumor response.⁴³ The treatment resulted in mild to moderate levels of adverse events and increased peripheral CD₄⁺ and CD₈⁺ T cells expressing inducible co-stimulator (ICOS). There was also an increased ratio of ICOS⁺ T cells to T regulatory cells. This type of response can activate immune signals along with CTLA₄ blockade.

Vitamins in cancer immunotherapy

In a clinical trial, vitamin A was administered alone or in combination with chemotherapy or radiotherapy tested in clinical trial by administering alone or in combination with chemotherapy and radiotherapy in unresectable bronchogenic cancer patients.⁴⁴ Metastatic unresectable squamous cell carcinoma of lung was treated in 9 patients with Vitamins A in a 60 weeks study. In addition, vitamin A was found to boost the patient immune system evident by increased lymphocyte blastogenesis response.⁴⁴ This shows powerful anticancer activity of Vitamin A and its parallel immune boosting effect. Vitamin E is widely studied natural molecule in cancer treatment. Vitamin E is divided into tocopherols and tocotrienols.⁴⁵ while the tocopherols exert mainly antioxidant properties, tocotrienols were proven for their potent anticancer activity against various cancer types in animal studies. The anticancer activities of vitamin E are mediated by apoptosis, autophagy, cell cycle inhibition, and metastasis inhibition pathways.⁴⁵ Suppression of inflammatory pathway by inhibition of transcription factor NF- κ B, and further slower the tumor growth, and inhibition of HMG-CoA reductase enzyme responsible for protein prenylation,

targeting DNA polymerases and protein tyrosine kinases are the few mechanisms mediated by tocotrienols.⁴⁵ Besides, vitamin E was also proved for its immune boosting functions in recent studies. Vitamin E supplementation at a daily dose of 750mg for 2 weeks in patients with colorectal cancer resulted in increased CD₄:CD₈ ratio and enhanced T cell capacity to produce T helper 1 cytokine interleukin 2 and IFN γ .⁴⁶ In a separate study, anti-oxidant vitamin E supplementation at daily dose of 750mg for 2 weeks increased NK cells' cytolytic activity in colorectal cancer patients. Vitamin E containing self-emulsifying nano-emulsion systems is used for drug delivery.⁴⁷ When vitamin E nano emulsion was loaded with paclitaxel (PTX), it showed increased cytotoxicity against MCF-7 breast cancer cells compared to the PTX treatment alone.⁴⁸ Vitamin E combination with PTX in the form of nano-emulsion not only aiding drug release at controlled rate but also has its own pharmacological activity by inducing apoptosis and growth arrest at G₁-S stage of cell cycle progression. When PTX was loaded into the emulsion, growth arrest was induced in MCF-7 cells at G₂-M phase, and increased IL-12 secretion from macrophages and down regulated IL-4 and IL-10 cytokine secretion were observed. Moreover, the PTX nano-emulsion has benefits with increased *in-vivo* anticancer activity, and associated with lower *in vivo* toxicity and altered pharmacokinetic profile AUC and MRT were extended.^{48,49} In sum, this shows the importance vitamin E in boosting the pharmacological and immunological responses when combined with PTX in breast cancer.

Conclusion

In sum, it is the time to develop immunotherapies against cancer to boost anticancer immunity. It is a challenge to study each and every patient's tumor type and further tumor microenvironment interactions. However, treatments can be developed to inhibit tumor infiltration of immune cells or inhibit their functionalization to support therapy and favour regression. As there is high clonal differences in immune cells, development of resistance against a specific treatment should also be considered. Understanding tumor cell antigen specific priming of T cells is one of the ideas to target. It is strongly advisable to prevent the cancer occurrence through food habits if possible.

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Conflict of interest

The author declares no conflict of interest.

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