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Immunotherapy for Cancer: A Newer Dimension in Chemoprevention

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Abstract

Cancer is multi factorial disease in which the own normal cells of body transformed to malignant cells. The cause of cancer may be chemical, biological or radiation. All etiological factors caused mutation in DNA or activation of some abnormal biological pathways. The altered genetic makeup of transformed cell give order for abnormal protein synthesis and disrupting the normal cellular homeostasis. The available therapy for cancer like Chemotherapy, Radiation and Hormonal therapy have its own limitation and toxicities. In Chemotherapy, the principle of targeting cancer cells is based on rapidly dividing property of malignant cells. But because of similar mitotic index, many time unintentionally normal cells of the body which also have same rapidly dividing property also killed and that responsible for toxicities associated with Chemotherapy. The Radiation and Hormonal therapy also linked with much toxicity due to improper targeting of normal body cells. In Immunotherapy, bodies own immune system trained in such way that it identify abnormal cancer cells based on antigen presentation on surface and killing them specifically with out harming normal cells. The available evidences also show strong correlation between dysfunction of Immune system and arising of cancer. Immunotherapy has been tried in many cancers with promising result.

Keywords: Cancer, Immunotherapy, Chemotherapy, Helper T cell, Cytotoxic T cells, PD-1 receptor, Treg cell.

Abbreviations:
AIDS- Acquired immune deficiency syndrome
BCG - Bacille Calmette-Guérin
CD- Cluster of differentiation
CEA - Carcinoembryonic antigen
CTL- Cytotoxic T lymphocyte
CTLA4- Cytotoxic T-Lymphocyte Antigen 4
Fc- Fragment crystallizable
FDA - Food and Drug Administration
GM-CSF - Granulocyte-macrophage colony-stimulating factor
HER2- Human epidermal growth factor receptor 2 protein
IARC - International Agency for Research on Cancer IARC
Ig- Immunoglobulin
IL- Interleukin
MHC- Major histocompatibility factor
NK- Natural killer
PD- Programme death receptor
RANKL- Receptor activator of nuclear factor kappa-B ligand
RBC- Red blood cell
TGFβ- Transforming growth factor beta
VEGF - Vascular endothelial growth factor
WBC- White blood cell

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INTRODUCTION

Cancer may be define as madness of cell due to altered genetic makeup and showing characteristic of uncontrolled proliferation, lack of differentiation, immortality and worthless if consider normal physiological function of cell and interfere with normal function of cells. Cancer is tilted balance between cell proliferation and cell death. Cancer is representation of altered genetic constitution or mutation which may be occur as normal consequence in which proof reading and editing capacity of DNA polymerase become defected or induced by many carcinogens which may be radiation hazard, biological virus and chemicals like environmental pollutants. The above said factors may responsible for creating break in DNA and when it will recombine it may abnormal or mutated. In this process the proto oncogene may be transformed to oncogene and switch off tumor suppressant gene and culminating as cancer or neoplasia.

Cancer is world's second most deadly disease with mortality rate up to 5, 56,400 people across the India in 2010 (1). Neoplasm classified as carcinoma, sarcoma, adenoma, melanoma, lymphoma, leukemia based on tissue involvement. Major therapy includes chemotherapy, radiation, hormonal therapy and surgical ablation.

Based on ability to invade and spreading to distant tissue cancer can be divided into two category. In case of benign tumor it is remain to confine at one space and not spreading by the process of metastasis but in case of malignant tumor, neoplasia not remain confine to one place and invade to distance tissue by metastasis. Compared to benign tumor, malignant tumor is much more dangerous and stubborn in treatment and prognosis.

Commonly available therapies for cancer are chemotherapy, radiation, hormonal, surgical ablation and miscellaneous drugs which target some more specific characteristic of tumor cells for example inhibitors of angiogenesis, telomerase inhibitors, asparaginase inhibitors (2, 3).

Recently a new dimension arises that is immunotherapy and mostly it is promoting more natural way of immunocompetence for cancer elimination. Normally immune cells can recognize and destroyed cancerous cells at subclinical level that is so called immunoediting. But after some deregulation the, mechanism not helping for eradicating tumor cells and arising at clinical level as cancer disease (4).

Looking back into the history of immunotherapy, the pioneer work has been done by Dr. Coley in 1800. He was observed that after surgery getting infection shown beneficial infection in cancer patient and understood that immune system have crucial role in eradication of cancer cells. The incidence took place before well developed branch of immunology and basic understanding of immune system.

Immunotherapy includes boosting immune system against cancer cells and train immune cells in such way that they target only cancer cell without harming normal cells which is main reason behind toxicity of Chemotherapy and radiation.

Role of Immune System in Eradicating Cancer Cells

Immune system of the body may responsible for identification and destruction of foreign substance. The foreign substance includes antigen from the micro organism or it may be part of cancer cells like abnormal protein secreted by cancer cells and thus giving protection against many disease and infection. The immune cells recognize germs and infectious agent better than cancer cells. It may be due to cancer cells have few similarity to normal cells and that give way to escape out from immune attack. Many evidence showing poor ability of immune system against cancer cells because person although have good health also showing development of cancer.

The immune system of the body categorized in to Innate and Adaptive Immunity. Innate immunity responsible for early phase response while late phase that is more specific and vigorous against foreign microorganism due to activation of Adaptive Immunity. The components of Innate Immunity involved Barrier spread over body surface both internally and externally, Glycoprotein like various cytokines, inflammatory mediators and phagocyte cells like macrophage and Monocyte. The initial defense of innate immunity usually is non specific and can not differentiate between wide diversity of microorganism. This is first line defense and without any kind of memory.

The more specific and potent response of immunity is given by Adaptive Immunity. This immunity show increase in its strength with further and future infection and develop as result of adaptively to infection so called as Adaptive Immunity. The memory of event is main strength of Adaptive Immunity and utilized as principle for various vaccine action. Although Adaptive immunity develops slowly it is more specific to particular pathogens. The Adaptive immunity consisting of B cells which responsible for secretion of Immunoglobulin and T cells which again classify into Helper T cell and Cytotoxic cell.

Naturally human body possesses many fighters who are responsible for protection against cancer. It includes Lymphocyte, Natural killer cell, Macrophage, Dendritic cells, Interferon gamma, Interleukin 12, Chemokines, Apoptosis, Reactive oxygen and nitrogen intermediate, Helper and killer T cells ($CD4^+$and $CD8^+$).

Tumor is complex of cancer cells, stroma components tumor responses are dependent on time and space. The major obstacle of effective anti tumor therapy are lacking of antigen presenting cells like dendritic cells, deficiency of danger signal form immune cells and down regulation of co stimulatory molecules on tumor cells, inadequate recruitment of activated effector T cells at site of tumor, expression of inhibitory molecules the inhibitory receptors PD-1 and CTLA-4 on immune cells, rise in inhibitory cytokines like IL-10, TGF-β, presence of arginase enzyme, increase in number of suppressive cells regulatory T cells, myeloid derived suppressor cells.

Normally cancer cells possess antigen called as tumor specific antigen. The antigen and cancer cells are undergoes process of Phagocytosis by antigen presenting cell. Antigen presenting cells (APC) include macrophage, dendritic cells and B lymphocyte cells. The peptides of antigen presented on the surface of APC along with MHC. The antigen recognized initially by helper T cell ($CD4^+$) and followed by cytotoxic cell ($CD8^+$). The helper T cells also released many cytokines like Tumor necrosis factor □ which promote activation and differentiation of cytotoxic T lymphocyte (CTL) from $CD8^+$ cell. The CTL found to be responsible for lyses of tumor cell.

The overall immune system activation against cancer is indicated by increase in peripheral and tissue infiltrate of lymphocyte, Interferon-γ producing antigen specific cells in spleen, dendritic cells, peripheral blood mononuclear cells, cytotoxic T lymphocyte and decrease in myeloid derived suppressor cell, treg cells both in peripheral and tumor micro environment. Both treg cells and myeloid derived suppressor cell have immune response inhibitory activity and any effective immunotherapy must be able to show decline in the number of these two populations of cells.

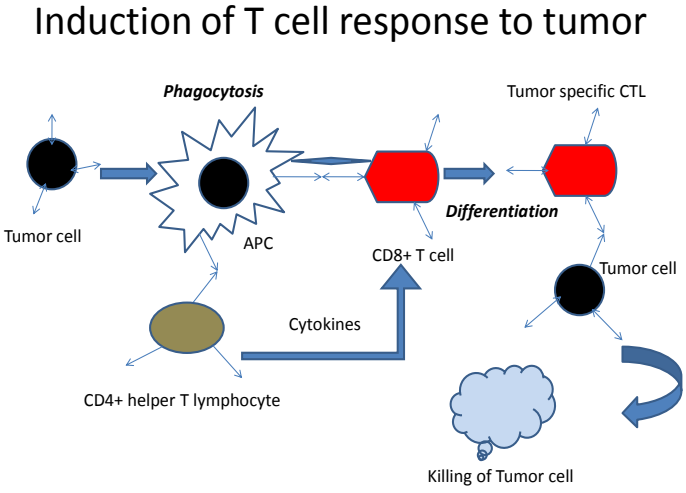

Figure: 1. Mechanism of tumor cell destruction by immune cell

(fibroblast) and many inflammatory cells. The anti During this natural immune war against cancer cell, many memory cells are generated. The memory cell (nearly 10%) has two important roles to play; first one is decrease in metastasis spread and prevention of relapse of tumor and another one is suppression of arising new tumor in body.

Mechanism of Evasion from Immune Response by Tumor Cells

Many malignant tumors develop mechanism which is helpful for escaping from the sight of immune system. The process of evasion called tumor escape. The tumor escape may be due to one of the following mechanism:

- Down regulation of MHC expression on cancer cells.
- Apoptosis of T cell when come upon cancer cell (5).
- Programmed death receptor -1 interaction with PD-L1 and PD-L2 ligand (6).
- Tumor cells may lose the expression of antigens on the surface.
- The tumor cells may suppress anti tumor immune response by producing immune suppressive protein (7).
- Mutation in MHC gene or gene required for antigen processing.
- Failure to produce tumor antigen by tumor cells.
- The antigen surface may be hiding by glycocalyx cover.

The goal of immunotherapist is finding the way for abnormal immune response to cancer cells and promote anti cancer effect. The immune system has three key responsibilities when it comes to preventing cancer:

- Prevention and treatment of viral infections, which when unchecked cause certain kinds of tumors
- Elimination of pathogens for reducing the course of inflammation, which often promotes tumor progress
- Finding strategy for Immunosurveillance, in which transformed cells are identified and destroyed before they can establish malignancy at early stage.

Cancer immunotherapy is interaction between body's defense system and neoplasia which may be benign or malignant. The significance of immunotherapy was observed in colorectal cancer in which cancer tissue shown infiltration of inflammatory lymphocyte cells which indicate some degree of defense and anti tumor activity (8).

According to immunosurveillance theory (9) lymphocyte always keeping watch over and based on need, eliminating nascent transformed cells which

helpful in preventing carcinogenesis, keeping normal cellular homeostasis and immunoediting (4). Tumor cells possessing antigen which is called as tumor associated antigen which self antigen and poorly recognized by immune system so it will become easy to escape from immune attack (10). Sometime the tumor specific receptor also present on the tumor cells which is recognize as foreign antigen and immune system mount response against this.

If we can able to make antigenic determinant more prominent, then it might be possible by immune system to target it and eliminate the same.

Immunotherapy is way of boosting immune system and giving training to immune cells so they will target only cancer cells but not giving harm to normal cells which occurring during auto immune disorders.

Evidence for Relationship between Immunosuppression and Evolution of Cancer

- Even before the proper development of immune system in past, William Coley who established mile stone in the field of immunotherapy first noted that getting an infection after surgery seemed to help some cancer patients. In the 18 century, he begun treatment of cancer patients by infecting them with certain kinds of bacterial toxin, which late popularized by the name of *Coley toxin.*
- Low level of natural killer (NK) cells activity has been reported in familial breast cancer patients.
- Cancer families have lower levels of natural cytotoxic activity than same age individuals without cancer in their close relatives.
- Organ transplant recipient treated with immunosuppressive agents and patients with malignancy treated with anti cancer drugs having high chances of developing malignancy in future (4).
- Ataxia-telangiectasia is a disease of childhood which involved immunologic deficiency consists of low IgA levels and varying defects of cell mediated immunity. At least 10% of the patients died with malignancy (4).
- Immunoglobulin **A** is the predominant one and is believed to be produced mainly in the small bowel. Its high concentration in this area may be one of the factors accounting for the rarity of tumors of the small intestine (11).

Individuals who are older, who have been on immunosuppressive medications over prolonged periods of time or have underlying immune abnormalities, such as an autoimmune disease or a chronic infection (e.g., AIDS) are particularly at risk of malignancy (10).

TYPES OF IMMUNOTHERAPY

The immunotherapy may be stimulate or boosting body immune system in general way to target cancer cells or train immune cells for particularly targeting cancer cells. The immunotherapy are generally classified into three types (12)

1. Monoclonal antibody: In this therapy, antibody specifically designed in the lab for certain antigen of cancer cells. Monoclonal antibody has very specific action and showing rare kind of toxicity. For the preparation of Monoclonal antibody first thing is to identify the nature of antigen on the surface of cancer cells. After proper decoding the nature of antigen of many types, the scientist developing Monoclonal antibody and proving it's efficacy against other kind of therapy of cancer. Antibody may target cancer indirectly by blocking the synthesis pathway of certain protein that is responsible for growth of tumor. As result of this action, cancer cell may die or stop further growth. Many times this kind of antibody action also called as "targeted therapy"

At present two kinds of monoclonal antibody available for cancer treatment:

A. Naked Monoclonal antibody:

This kind of antibody not attached to any other drug molecule, radioactive substance but working themselves as cancer treatment. Antibody work by binding to antigen of cancer cell or non cancer cells and may be to some floating protein. Few antibodies after attaching cancer cells it act as biomarker for easy identification by immune cells and subsequent destruction by cancer cells. Naked Monoclonal antibodies include Alemtuzumab, trastuzumab

B. Conjugated Monoclonal antibody:

The word itself defines its meaning that the antibody attached to chemotherapy drugs (Chemolabeled antibodies), radio labeled substance (radioimmunotherapy) and poison (immunotoxins). The antibodies locate these entire things into the cancer cells because it has similar code of antigen and it can easily target it, so antibody takes all the content inside of cancer cells and lead to its death. The advantage linked to this therapy is less toxicity to normal cells so many side effect can be avoided. Conjugated Monoclonal antibody include Ibritumomab tiuxetan, Brentuximab vedotin, tositumomab, Denileukin diftitox

The side effects of monoclonal antibodies are usually allergic in nature and not that much harassing compare to side effect of Chemotherapy. Most common are rashes, fever, diarrhea, vomiting, weakness, chills and some other like elevation of blood pressure, internal bleeding, and blood clotting that is concerned when some drug targeting tumor blood vessel growth like bevacizumab.

Normally vaccine consist of fragment of micro organism or it's whole dead body which may be act as virulence factor for stimulation of immunity but does not act as pathogenicity. The cancer vaccine used for prophylaxis or preventive and for preventing relapse of cancer once it has been treated. Many cancer are caused by virus which are after inhabitation inside the body, interfering many biological process, changing the genetic make up or creating phenomena of mutation or producing some abnormal protein which may suppress immune system and direct the body cell to behave in abnormal way which lead to cancer. Vaccine if able to prevent virus infection it may able to block cancer that is subsequently arising due to viral infection. Vaccine prevents growth and proliferation of virus but not affecting tumor cell proliferation. So the application of vaccine is limited to certain cancer that is caused by virus infection. Many reports indicate that approximately 25% of cancers are due to infection with microbes and higher cases found in developing countries than developed country (13). For example Human Papilloma virus (some strain) responsible for arising of anal, cervical (nearly 70%) and throat cancer in human so vaccine against this virus may able to prevent these cancer. Similar example can be given for Hepatitis virus in case of liver cancer. Helicopylori bacteria responsible for cases of stomach cancer and prevention of infection with that bacterium with vaccine may able to prevent stomach cancer.

According to International Agency for Research on Cancer (IARC) many micro organisms are comes under category of carcinogen (14). It includes Epstein barr virus (cause Burkitt lymphoma), human herpes virus (cause Kaposi sarcoma), and human T- cell lymphotropic virus type-1 (cause adult T cell leukemia or lymphoma).

Vaccine for cancer work in different way compare to vaccine for any infection. Cancer vaccine can not prevent the diseases (as prophylaxis) but give protection against already exist disease. Vaccine used part of cancer cell like antigen for initiating immune response against cancer. Antigen is special characteristic for specific cancer so immune cells specifically target only those cell who having same kind of antigen. So, instead of general immune response more specific immune response taking place.

FDA approved Sipuleucel-T**,** a vaccine for treatment of advanced prostate cancer. For this purpose the patient's blood collected from that immune cells are isolated. The isolated cells are undergoing chemical treatment for transform to dendritic cell that is very helpful for mounting immune response against cancer. The dendritic cells are exposed to antigen called 'prostatic acid phosphatase'. After this kind of training, dendritic cells are administered in to body by intravenous route. The dendritic cell along with other immune cell mount response against tumor for it eradication.

2. Cancer vaccine:

Many types of vaccine are under development which may promise the future of immunotherapy of cancer. The tumor cell vaccine that is prepared from patient's tumor cell. During surgery the tumor cell harvested and later treated with chemicals or radiation and makes it less malignant so it can not further spread cancer when reintroduce in body. The changes made after treatment make cancer cell more prominent to immune system for attack. The vaccine may be autologus or allogeneic type. Autologus means the donor and acceptor are same but in allogeneic type the donor and acceptor are different. The next class of vaccine is antigen vaccine in that instead of whole cell few antigens are utilized for boosting immunity. Another one is dendritic cell (antigen presenting cell) vaccine that involved in recognition of cancer cell by immune system. The example of this kind vaccine is Sipuleucel-T. Few other types of vaccines are DNA vaccine and vector based vaccine.

Many adjuvant substances are added to enhance effectiveness of vaccine like Bacillus calmette Guerin (15), emulsified oil montanide ISA–51 and cytokines like IL-2, Interferon alpha and Granulocyte macrophage colony stimulating factor.

The common side effects of vaccine are inflammation at site of injection, allergic response like rash, itching, redness, pain, and swelling, disturbance in blood pressure, fever and chills.

3. Non specific immunotherapy:

This therapy result in stimulation of immunity in general way without any specificity and result in killing of cancer cells. This therapy not based on targeting cancer cell by recognition of specific tumor antigen or stimulating specific population of immune cells. The therapy can be used as either adjunctive therapy or as main therapy.

The non specific immunotherapy divided into two major groups. First one is natural body component and second is synthetic drug which stimulating body immunity.

The cytokines are group of protein with structurally diverse molecules and almost all concerned with immune response. Cytokines are involved in cell trafficking and development of various tissue and organs of immune system. Based on nature of synthesized cytokines during immune response there may be allergy, cytotoxic, cellular or humoral mediated immune response taking place. Cytokines are pleiotropic molecules so along with immune function

also concerned with apoptosis, cell activation and communication. Leukocytes and antigen presenting cell like dendritic cells are mainly responsible for production of leukocyte but many other cells under certain condition also synthesize cytokines (16). Synthetic cytokines can be synthesized in lab and utilized for adjunctive therapy and for combating toxicities of chemotherapy. Chemotherapy targeting rapidly dividing cells of blood like RBC, WBC, platelets so by maintaining their normal level cytokines help to maintain homeostasis of body. The various cytokines like interleukins (IL), interferon, Granulocyte-macrophage colony-stimulating factor (GM-CSF) all plays very crucial role in cancer pathogenesis and in response to cancer treatment. The wider category of interleukin involved IL-2, IL-7, IL-12, and IL-21are concerned with chemoprevention.

Among other types of Interferon, alpha type related with boosting immune cells against cancer cell. It also has anti angiogenesis property. The FDA gave approval against kidney cancer, Kaposi sarcoma (in AIDS patient), and chronic myelogenous leukemia. The next candidate is GM-CSF responsible for increase in number of blood cells and specific immune cells from bone marrow.

Few synthetic drugs like thalidomide, Bacille Calmette-Guérin (BCG) vaccine, Lenalidomide have non specific stimulating activity on immune cells similar to cytokines.

MECHANISM OF CANCER IMMUNOTHERAPY

The mechanism for monoclonal antibody involves activation of Fc receptor on Natural killer cell by Fc portion of antibody which is further promoting Antigen dependent cytotoxicity. This event may responsible for lyses of targeted cancer cells. The complement dependent cytotoxicity mediated by stimulating complement receptor on target cancer cells also responsible for cell destruction mediated by many monoclonal antibodies (11).

Some antibody has been shown to targeting HER2 (Immunotherapy of breast cancer), transmembrane soluble protein which is up regulated in solid tumor. In case of colorectal cancer, targeting carcinoembryonic antigen (CEA) protein has been shown good immune response. In prostate cancer, vaccine specifically target prostate-specific antigen and prostate-specific membrane antigen. Lymphokine activated killer cells that are T cells isolated from patient and treated with IL-2 in lab has more potent cancer fighting activity. Tumor-infiltrating lymphocytes are cells that found inside of tumor also treated similar to lymphokine activated killer cells and reenter in patient for immunotherapy.

migration, hematopoiesis, proliferation, cellular

ADVANCES IN IMMUNOTHERAPY

- Immunotherapy for cancer treatment has been concluded as most important scientific break through of 2013, according to the journal of Science.
- Merck declared that, it has started a rolling submission to the U.S. Food and Drug Administration (FDA) of a Biologics License Application for MK-3475 molecule, the company's investigational anti-PD-1 immunotherapy in the treatment of advanced melanoma.
- Juno Therapeutics, a new biotechnology company focused on bringing forward novel immunotherapy for cancer.
- Advaxis, a clinical stage biotechnology based company developing the next generation of cancer immunotherapy drugs. The Company is preparing to submit an IND for ADXS-cHER2 in breast cancer in 2014.
- Kumari et al shown the way of epigenetic modulation that utilized sub lethal dose of radiation on colorectal tumor cells and enhancement of immune response by cytotoxic T cells (17).

RECENTLY APPROVED IMMUNOTHERAPY DRUGS FOR CANCER (18)

FDA gave permission for many drugs that working based on principle of immunotherapy. In 2009, FDA approved bevacizumab, a humanized antibody against vascular endothelial growth factor (VEGF). Combination of Bevacizumab and Interferon-α has been used in treatment of metastatic renal cell carcinoma. Bevacizumab prevents interaction of VEGF to its receptor that is present on the surface of endothelial cells by making complex with it. The consequence of this process is inhibition of angiogenesis which is crucial for progression of tumor.

In 2010, FDA approved Denosumab, a Human IgG2 monoclonal antibody. Denosumab bind to transmembrane protein called as human RANKL that is required for normal functioning and survival of osteoclast. In solid tumors with osseous metastases the activity of osteoclast increased that is due to RANKL activity. Denosumab prevent binding of RANKL to its receptor which is located on osteoclast and thus prevent bone pathology or skeletal events in solid tumor.

Another drug was Trastuzumab or Herceptin is a human IgG1 kappa monoclonal antibody. Trastuzumab selectively target human epidermal growth factor receptor 2 protein (HER2) that is responsible for cell growth, proliferation and differentiation. In patient with tumor of digestive system, HER2 expression has

been increased and Trastuzumab along with fluorouracil, cisplatin or capecitabine employed as therapy.

In 2011, FDA approved Ipilimumab that is recombinant human monoclonal antibody. Ipilimumab binds and block cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), present on T cells and responsible for suppression of the immune function or immunosuppression. When CTLA molecules are blocked, it leads to activation and proliferation of T cells, which is mechanism of anti tumor immune response mediated through Ipilimumab. The drug approved for the treatment of metastatic melanoma.

In the last year 2013, FDA approved humanized anti-CD20 monoclonal antibody named by Obinutuzumab belongs to subclass of IgG1. It target CD-20 molecule present on B cells. The drug used in untreated cases of chronic lymphocytic leukemia in combination with chlorambucil. The drug causes B cell lysis by activating intracellular death signaling pathway and activation of complement cascade leads to antibody dependent cytotoxicity and Phagocytosis and cell death.

Another drug approved was Ado-trastuzumab emtansine, a HER2 targeted antibody which is drug conjugate. Stimulation of HER2 receptor lead to release to intracellular cytotoxic metabolite called as DM1, a small molecule cytotoxin. The DM1 binds to tubulin causes disruption of microtubule network and subsequent cell cycle arrest and cell death by the process of Apoptosis. The drug has special application in case of metastatic breast cancer patient with HER2 positive.

The drug was Denosumab,a human IgG2 monoclonal antibody. Denosumab binds to human RANKL transmembrane soluble protein. As described previously, RANKL involved in higher osteoclast activity in solid tumor with osseous metastases and responsible for arising bone pathology. The solid tumors are composed of malignant cells and different non-malignant cells. Non malignant tumor called stroma, a structural part like fibroblasts, endothelial cells, inflammatory cells and many other abnormal tissue substances. The inhibitor of stroma may become one therapeutic strategy in cancer.

CONCLUSION

It will be possible in the coming year to find out specific antigen that is located on surface of various tumor cells and target it with immunotherapy specifically. Immunotherapy treatment already approved to treat a number of cancers like cancers of the lungs, colon, multiple myeloma, breast, kidney, prostate, leukemia, lymphoma, and melanoma.

Many mechanism exist for immune surveillance but most of become fail during advance stage of cancer. Immunity suppression also occurs due to chemotherapy. Tumors also secrete inhibitory molecules which are target subpopulation of immune system towards apoptosis and anergy. The program death receptor interaction with its ligand dampen T cells receptor signaling, decrease secretion of few important cytokines responsible for stimulation of immunity that result into decrease in production, proliferation and apoptosis of immune cells (18). Immunotherapy may work by various mechanisms like increase the frequency of tumor antigen-specific T cells in the systemic circulation, blocking of immune suppressive cascade within the tumor microenvironment, and way to induce immune inflammation within the tumor microenvironment from beginning (19).

Tumors expressing PD-L1 serve as protective weapon and suppressing infiltration of lymphocyte in tumor micro environment that lead to escape of tumor cell from immune surveillance (20). The same mechanism of PD-1/PD-L1 interaction play crucial role in prevention of auto immune disorder. Research is underway for development of imagine technology for observing interaction between cancer cells and immune cytotoxic T cells inside body as part of cancer biology (21).

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