

Immunotherapy for Cancer

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Abstract: *Cancer is the most threatening disorder with increasing sufferers globally. The statistics of International Agency for Research on Cancer (IARC) indicate the arousal of 18.1 million new cancer cases causing 9.6 million deaths worldwide in the year 2018. Human body possesses a set of defensive processes carried out by the immune system whenever cancer is detected by its specialized cells. But when cancer escapes these processes, an anticancer therapy becomes the need. Three routes of treatment used widely today are Chemotherapy, Radiation therapy and Surgery. A new era in anticancer therapy is immunotherapy. It involves modification of patient's own immune cells using biotechnology for treating cancer. There are various types of immunotherapies depending on the cells or cellular components modified and the molecules targeted in cancer cells. They include T cells, macrophages, specific receptors, proteins, chemical mediators and enzymes involved in immune response towards neoplasm. Hence immunotherapy is a much more specific and targeted therapy for cancer. A high therapeutic potential with minimum adverse effects and tumor specificity with no harm to normal body cells makes this therapy different than the pre existing ones. Immunotherapy will thus prove to be a major tool to combat all types of cancer.*

Keywords: Cancer, immunotherapy, targeted, protein, receptors

1. Immune Response to Cancer

The immune system defends body against newly proliferating tumor cells by a special process carried out by the immune cells. They include dendritic cells [1], NK cells [2], CD - 8 cells [3], CD - 4 cells [4] and other macrophages. The process involves sampling of tissues and fluids in the body to identify and locate the tumor cells and then initiate appropriate immune response to ward off those tumor cells. This is known as immunosurveillance [5]. It is broadly divided in to three phases.

1.1 Elimination

1) Detection of tumor cells

In this first phase, the dendritic cells analyze different tissues and fluids in the body for presence of tumor or cancer cells. During proliferation, the tumor cells cause injury to the surrounding tissue and enable the dendritic cells to locate the tumor. Dendritic cells bind to tumor specific antigens on the plasma membrane of tumor cells. This allows identification of tumor cells as 'foreign' or 'non - self' cells.

2) Antigen presentation

The DCs initiate an immune response that attracts macrophages to destroy tumor cells. The resulting dead cell debris is ingested and processed by DCs and combined with MHC - II molecules. The Ag + MHC II complex is displayed on the surface of plasma membrane of dendritic cells. Such DCs then migrate to the lymph nodes where they present the Ag - MHC II [6] complex indicating presence of tumor in body. They promote chemotaxis and activate other immune cells like T cells and NK cells.

3) Role of Natural Killer (NK) cells

NK cells bind to tumor cells and release perforins and granzymes [7]. The CD - 8 cells (cytotoxic T cells) formed by DC induced differentiation of un differentiated helper T cells also destroy tumor cells by secreting granzymes, NK

cells, CD - 8 cells, macrophages and DCs also secrete INF - γ [8]. INF - γ prevents development of normal cells into tumor cells, induces Ab production in B cells and agonizes chemokine [9] production. Chemokines induce chemotaxis and inhibit angiogenesis in tumor. Hence tumor cells die due to starvation. NK cells activate macrophages by production of INF - γ and macrophages in turn activate other NK cells by production of IL - 2 [10]. Both of them together destroy even more tumor cells by production of toxic oxygen and nitrogen intermediates that induce tumor cell apoptosis. The dead tumor cell debris resulting from action of all these immune cells is again processed by DCs and presented in lymph nodes to activate more and more immune cells. This cascade of reactions goes on until all the tumor cells are destroyed.

1.2 Equilibrium

Many tumor cells are able to rescue themselves from attack of immune cells, cytokines and enzymes in first phase. This is possible due to certain modifications by tumor cells in their tumor - specific antigens through mutation because of which DCs fail to identify them as foreign cells. This process is called immunoediting [11]. Some tumor cells also present PDL -1 molecule on their surface, which on binding to the PD-1 receptors on CD - 8 cells, inactivate them. Tumor cell as also attract immunosuppressive cells i.e. certain myeloid macrophages and regulatory T cells which inhibit the attacking immune cells, thus promoting tumor growth. Decrease in NK cells in body can also promotes tumor growth. Such resistant tumor cells are called tumor variants. The lymphocytes and INF - γ exert a selection pressure [12] on unstable and rapidly proliferating tumor variants. As a result, the tumor cells either continue to proliferate without being affected in this phase, or become dormant. Dormant tumors don't proliferate but survive in body. They proliferate on obtaining favorable conditions in body, i.e. weakening of immune system. Such dormancy is responsible for metastasis and relapse of cancer even after treatment.

Volume 8 Issue 3, March 2019

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1.3 Escape

The resistant tumor variants escaping equilibrium phase enter third and last phase. These tumors remain unaffected even after repeated immune responses or attacks. Finally, the body becomes deficient of immune cells and is incapable of producing any immune response further. Hence, tumor cells continue proliferating and damaging the body tissues. Such a condition gives rise to the need of administration of external agents to kill tumor cells. This is accomplished by an anticancer therapy.

2. Currently Used Therapies to Cure Cancer

2.1 Radiation Therapy

Radiation therapy or Irradiation uses X rays, Gamma rays or other charged particles to destroy cancer cells. It is aimed at creating maximum effect on cancer cells and minimum effect on other body parts and organs. It can be used for following purposes:

- 1) To alleviate cancer from the body
- 2) To limit spread of malignant tumors
- 3) As a supplementary treatment to increase the effectiveness of other treatments.
- 4) To reduce the symptoms of cancer

This therapy can be used to shrink tumors so that their removal by surgery becomes easy and chances of their recurring decreases. It is then called Neoadjuvant therapy. If given during surgery, it is called Intra operative radiation therapy (IORT).

Mechanism of action

Cancer cells proliferate very rapidly as compared to normal cells. But unlike normal cells, they have very less capacity to repair and that depends on the extent of DNA damage. Radiation therapy directly damages DNA of cancer cells by making cuts or leads to production of toxic free radicals that damage their DNA. When DNA is completely destroyed, cancer cells are unable to repair it. They fail to divide and die. They are then eliminated by phagocytosis.

Types of Radiation Therapy

1) External beam radiation therapy

In this method radiations are delivered from outside the body using a special device. Machines/devices used are-

- a) **Linear accelerator –LINAC** produces highly energetic X rays or electron beam using electricity [13].
- b) **3-dimensional conformal radiation therapy (3D-CRT)** - It uses advanced machines and software techniques to deliver radiations [14].
- c) **Intensity-modulated radiation therapy (IMRT)** – It delivers a single dose a combination of multiple small beams by a device called collimator [15].
- d) **Tomotherapy** – It is a combination of CT scanning and external beam radiation therapy [16].
- e) **Stereotactic radiosurgery** - It can be used to heal small brain tumors requiring high doses [17].
- f) **Stereotactic body radiation therapy** – Tumors outside brain and spinal cord can be treated by this technique [18].

g) **Proton beam therapy** – It uses positively charged protons to kill cancer cells [19].

2) Internal radiation therapy

When the radiation source is implanted inside the body, it is called internal radiation therapy or Brachytherapy [20]. It may be given as temporary therapy or as permanent implants. Types of brachytherapy are-

Type of Therapy	Location of Radiation Source
Interstitial brachytherapy	Within tumor tissue (e.g. prostate cancer)
Intracavitary brachytherapy	Surgical/body cavity near tumor (e.g. chest cavity)
Episcleral brachytherapy	Eye (e.g. melanoma of eye)

3) Systemic radiation therapy

In this therapy, the radiation source travels through systemic circulation, locates tumor and destroys it. The radiation source is mostly monoclonal antibody [21] bound radioactive element. E.g. radioactive iodine to treat thyroid cancer. Certain chemical agents which are currently under study are Radiosensitizers and Radioprotectors. Radiosensitizers are the agents which increase the sensitivity of cancer cells towards radiations, thereby increasing the effectiveness of radiation therapy. Examples are Cisplatin and 5-Fluorouracil. Radioprotectors are the agents which shield the normal cells surrounding cancer cells from these radiations. Amifostine is an example of radioprotector.

2.2 Chemotherapy

Chemotherapy involves use of drugs to treat cancer. These drugs are called anticancer agents. They generally classified as:

Class of anticancer drugs	Mechanism of action
Alkylating agents e.g. Nitrogen mustard, Cyclophosphamide	Addition of alkyl (e.g. methyl) groups on bases in DNA (where they are not usually present) leading to miscoding of DNA strands. They also inhibit strand separation by cross linking bases in opposite strands.
Antimetabolites e.g. Folate antimetabolite- Methotrexate Purine antimetabolite- Mercaptopurine Pyrimidine antimetabolite- 5- fluorouracil	Being similar in structure to important metabolites in DNA synthesis, get themselves incorporated in the process and inhibit DNA synthesis.
Antitumour antibiotics e.g. Doxorubicin, Daunorubicin	Disrupt the structure of DNA by intercalating between two strands or prevent strand separation by forming covalent bond between two strands.
Antimitotics 1) Microtubule polymerization inhibitors e.g. Vincristine 2) Microtubule depolymerization inhibitors e.g. Taxol	Prevent mitosis by- 1) Blocking formation of microtubules so that mitotic spindle won't attach to chromatids. Blocking division of parent cell into daughter cells.
Molecular targeted agents e.g. HER2 for breast cancer Topoisomerase inhibitors I & II	Targets signaling pathways and specific proteins in cancer cells. Inhibits DNA ligation step in

e.g. Etoposide, Doxorubicin	introduction of negative supercoiling.
Hormonal antagonists e.g. Tamoxifen	Block secretion of steroidal hormones which facilitate cancer growth.
Telomerase blockers e.g. Imetelstat	Inhibit enzyme Telomerase which protects the ends of cancer cell chromosomes from degradation.
Biologic response modifiers e.g. Interferons, Interleukins-2	These are immune response enhancers.

Chemotherapy can be major treatment or supplementary to other therapy. These agents are given mostly in combination intravenously, intramuscularly or orally. Route of administration depends on cause, location, type and severity of cancer as well as age and condition of patient. However, chemotherapy may cause injury to normal healthy cells of body leading to side effects like hairfall (keratin damage), GI problems, dry mouth, appetite loss, effects on reproductive system and many other problems.

2.3 Surgery

Non malignant tumors can be removed from the body by surgery. The doctor may remove the entire tumor or a part of tumor if complete removal may damage the organ involved. This procedure is not possible for malignant forms of cancer like leukemia. Other methods of surgery are:

a) Cryosurgery

In Cryosurgery or Cryotherapy, cancer cells are killed using extreme freezing conditions. Liquid nitrogen or Argon gases are used to create such low temperatures. Early stages of cancer can be eliminated by this method [22].

b) Laser

Laser is a fine beam of high energy light waves which can be used to target cancer cells. It is used to cut, contract or kill cancer cells on or inside the lining of body organs [23].

c) Hyperthermia

Cancer cells are killed or sensitized by treatment with radiofrequency waves that generate large amount of heat. This is rarely used method [24].

d) Photodynamic therapy

In this method, the external source, i.e. a special type of light, is not targeted directly onto cancer cells, but on certain drugs. The drugs on exposure to this light get converted into active form and kill the neighboring cancer cells [25].

3. Introduction to Immunotherapy

Immunotherapy has led to the beginning of new era in cancer treatment. As per the term, it is therapy using immune cells. The basis for this idea is the fact that immune cells can be the best way to fight cancer. Strengthening and targeting them can also result in anticancer activity. This is done using two types of processes:

- 1) Modification or intensification to direct the body's own immune cells against target cancer cells in the body
- 2) Introduction of synthetic immune proteins into the body that can be used by the immune system to potentiate the attacks against cancer cells.

Since this therapy uses biological system to fight against cancer, it is also known as Biotherapy or Biotherapy.

Types of Cancer Immunotherapies

Immunotherapeutic treatment includes:

1) Monoclonal antibodies

Hybridization of myeloma cells and specific immune cells (e.g. spleen cells) leads to production of a clone of hybridomas that produce antibodies against target cancer cells [21]. These antibodies selectively bind to receptors on cancer cells or with proteins attached to their MHC complexes called as cancer antigens. This is a passive therapy which can result in a targeted attack. Monoclonal antibodies (MAbs) labelled by radioactive substances or isotopes can aid in diagnosis of cancer. Binding of such MAbs to cancer antigens help to locate the cancer/ tumor in body when screened for radioactive property [26]. e.g.: Bevacizumab, Cetuximab.

2) Immune checkpoint inhibitors

Immune check points are specific receptors on T cells and normal body cells that help T cells to distinguish between self and non-self cells. T cells contain PD-1 protein which performs checking of body cells to ensure that no foreign cell is present. PD-L1 protein is usually present on the surface of normal cells. It acts like a license that a normal cell shows to a T cell guaranteeing that it is body's own (self) cell. But certain cancer cells also display the same PD-L1 protein on their surface. Binding of PD-1 protein of T cell and PD-L1 protein on cancer cell enables the T cell to recognize the cancer cell as self-cell. This promotes cancer growth. Immune checkpoint inhibitors bind to any one of these proteins. This allows the T cell to bind to cancer antigen, recognize it as non-self and initiate an immune response [27].

e.g.:- PD-1 inhibitors: Pembrolizumab, Nivolumab

PD-L1 inhibitors: Atezolizumab, Avelumab, Durvalumab.

3) Cancer vaccines

Vaccination is introduction of an immunogenic substance into the body in order to evoke an immune response. Cancer vaccines are proteins isolated from cancer cells after exposure to whom a targeted immune response occurs against cancer cells. Preventive cancer vaccines prevent occurrence or growth of cancer and Treatment cancer vaccines help to initiate immune response to kill the cancer cells.

e.g.:- Gardasil against Human Pappiloma Virus [28]

Bacillus Calmette Guerin (BCG) against bladder cancer

Oncophage against kidney cancer

4) Nonspecific immunotherapies

This therapy does not target any cancer cell. It is often used complementary to chemotherapy or any other immunotherapy. It empowers the immune system to increase the production of antibodies, T cells, macrophages and other immune cells to carry out a powerful immune response. This includes administration of cytokines. Cytokines are the proteins which mediate the immune responses in the body. The therapy involves following cytokines:

a) Interleukins(IL)

Interleukins [29] are the proteins which stimulate production of more lymphocytes, activation of B cells, Cytotoxic and Helper T cells and are also involved in costimulation of certain lymphocytes. Natural and synthetic ILs like IL-2 can be very useful to fight cancer.

b) Interferons(INFs)

Interferons are naturally occurring antiviral protein which can also act as anticancer agents. Among three types of interferons, i.e., INF-alpha, INF-beta and INF-gamma, only INF-alfa can act as anticancer agent. These proteins arrest the growth of cancer cells, may induce transformation of a cancer cell into a normal cell and stimulate NK cells, macrophages, etc to destroy cancer cells [30].

5) Colony Stimulating Factors(CSFs)

CSFs are proteins which stimulate stem cells in red bone marrow to differentiate and produce more amounts of lymphocytes, erythrocytes and platelets. This is useful in the condition where bone marrow suppression due to chemotherapeutic drugs lead to decrease in ability of the body to produce sufficient immune cells. This enables patient's body to support or withstand further therapies for cancer treatment [31].

6) Macrophages

Macrophages are large phagocytic cells which help to clear off cancer cells. Administration of laboratory modified macrophages can boost immune responses in body. Here, liposomes are used to deliver macrophages to the site of action. Liposomes are tiny globules whose composition is similar to lipoidal membranes in the body. Hence, they easily cross all lipid barriers and deliver macrophages or other immunotherapeutic agents to the cancer site [32].

7) Histone deacetylase(HDAC) inhibitors

HDAC [33] is an enzyme involved in coiling of DNA strands. It removes acetyl group from histone proteins that participate in winding of DNA strands. This allows high affinity coiling of DNA strands. Gene coding for this enzyme promotes cell proliferation and controls many cell functions. HDAC inhibitors arrest growth of tumor cells and interfere in their cell cycle by altering expression of gene coding for HDAC. Hence, they play an important role in cancer treatment.

8) T cell Therapy

This is the most modern technique that uses genetically engineered T cells for targeting cancer cells. T cells are the major defenders of our body. Hence, genetic modifications in these cells can be a very efficient way to fight cancer. Also, use of patient's own T cells in the therapy makes it unique as compared to other therapies.

Chimeric Antigen Receptor (CAR) Engineered T cells [34] are the T cells of the patient that are designed in order to make them act specifically against the cancer cells. Blood of a cancer patient is collected and T cells are separated. CAR gene is inserted into the DNA of T cells and they are cultured. Expression of this gene leads to insertion of Chimeric Antigen Receptors into plasma membrane of these T cells. The receptor consists of 3 parts:

- i) Antibody fragment – binds to antigen on the surface of cancer cells
- ii) Costimulatory Domain – responsible for second signal
- iii) Essential activating Domain CD3 – responsible for first signal and activation of T cell

These CAR T cells are transferred back to the patient's body to attack cancer cells. When this receptor binds to cancer antigen, synergistic effect of both stimulating domains leads to release of chemicals inducing apoptosis of the cancer cells.

9) Oncolytic virus therapy

Oncolytic viruses [35] are cancer killing viruses. When administered intramuscularly, the virus rapidly locates cancer cells and infects them. Inside the cancer cell, virus multiplies in such a large number that the cell becomes unable to accommodate so many virion particles and hence bursts. Released virion particles affect other cancer cells. Bursting cancer cell releases many cancer antigens that alert lymphocytes by recognition as 'non-self' particles. Oncolytic viruses do not harm normal body cells. They stimulate the immune system to initiate an immune response against cancer cells. e.g.: T-VEC for melanoma, RIGVIR for lung cancer.

10) CTLA-4 inhibitors

Cytotoxic T Lymphocyte Associated protein 4 (CTLA-4) [36] is a protein present on the surface of cytotoxic T cells. It suppresses activation of cytotoxic T cell and prevents further immune response. CTLA-4 inhibitors like Ipilimumab target this protein and inhibit its action. This causes normal immune response of cytotoxic T cell against cancer cell.

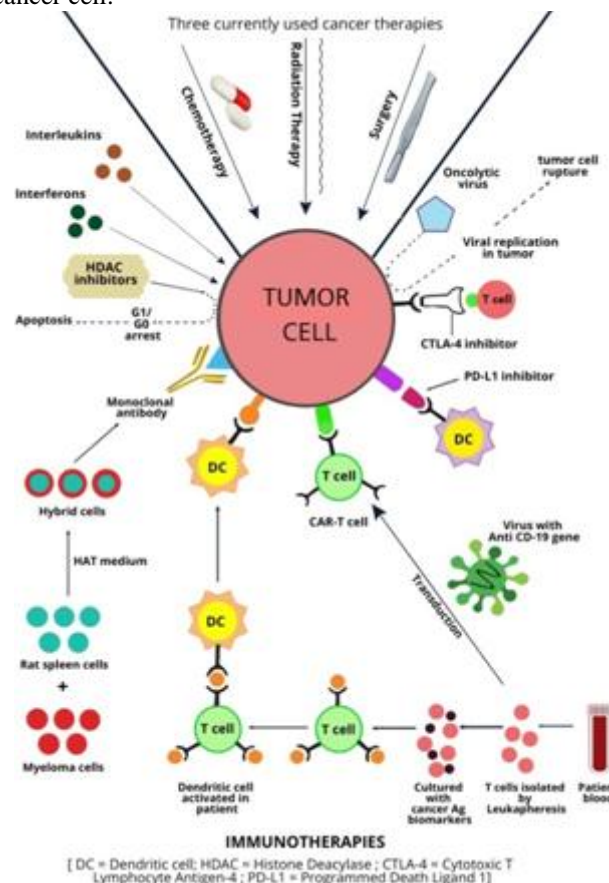


Figure 1: Summary of Cancer therapies

4. Advantages of Immunotherapy

Immunotherapy is the best way to treat cancer when traditional methods are ineffective or if tumor becomes resistant to these treatments. In immunotherapy, the modified immune cells are target-specific and so they are very less likely to harm the normal body cells. This eliminates the occurrence of side effects like hair fall, GI problems, loss of appetite and many other effects. Along with negligible side effects, immunotherapy has been proved to show maximum efficiency in warding off cancer from the body even at end stages. It can treat almost all types of cancer if planned accordingly. Also, immunotherapy can supplement chemotherapy in many cases. Another significant aspect of our immune system is its 'memory'. Immunotherapy trains immune cells against cancer, imparting an 'immunomemory'. This can give a long term protection from cancer and prevent its rebound.

5. Discussion

Immunotherapy is benefiting increasing number of patients worldwide. Special efficacy is observed in case of multiple myeloma, cervical cancer and lung cancer. Recent findings reveal increased survival rates of metastatic brain cancer patients. Checkpoint blockade immunotherapy has increased the survival of patients from 5.2 months to 12.4 months according to a latest study [37]. CAR-T cell therapy has also contributed a lot to the cancer treatment.

Constant research is being held in this field to explore newer and better ways to defeat cancer. Scientists are working on increasing the specificity of immune cells which will help in improving the treatment. Also, use of newer biomarkers in immunotherapy will greatly broaden the spectrum of immunotherapy.

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