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IMMUNOTHERAPY: THE EMERGING ARM OF ONCOLOGIC MANAGEMENT

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Abstract

Oncology, the study of malignant tumors, has been a field of extensive research in all aspects of management including primary prevention which automatically evolved the concept of early diagnosis and better results in many cases. As research boomed, so evolved chemotherapy and the effort to reduce side effects succeeded however etiology and nutritional side effects needed more studies and efforts. The past decade has witnessed monumental progress in the treatment of malignancies with more specific and targeted therapies emerging, many holding a promise for providing a cure for cancer. At the forefront of these therapies is immunotherapy, which is fast changing the landscape of cancer medicine. It has joined ranks with chemotherapy, radiotherapy and surgery as the fourth arm of cancer treatment. Parallelly RNA and DNA analyses has contributed to familial tumours workup and therapeutic interventions. Very rapid strides have been put in place and immunotherapy as a modality of treatment is becoming a primary therapeutic choice for patients. Globally immunotherapy has been accepted and is evolving to make a difference in therapeutic outcomes in very many mitotic lesions. In this review we provide a brief history of the advent of immunotherapy and a detailed description of the different immunotherapeutic strategies that have emerged as key players in cancer treatment.

Keywords: Immunotherapy, Role in Surgery

INTRODUCTION

Cancer can be described as a disease caused when cells divide in an uncontrolled manner and spread to surrounding tissues and the rest of the body. These cells become roguish and start playing havoc in the host, proliferating aberrantly largely due to acquired or inherited genetic changes[1].

Cancer is the leading cause of death worldwide, accounting for nearly 10 million deaths every year and it is increasing. In India there were 14.6 lakh cases in 2022 and by 2025 it is projected to reach 15.7 lakh cases.

Cancer is a disease of the genome, and it is characterized by a genomic instability in which numerous point mutations accumulate and structural alterations occur in the process of tumor progression.

Conventional cancer treatment includes surgery, radiotherapy, chemotherapy with low specificity and significant side effects[2]. Other modalities of treatment are targeted therapy, hormonal therapy, stem cell and bone marrow transplant and immunotherapy. There was always an aspect of failure of the immune system, but one was not able to point exactly. The past decade witnessed the birth of immunotherapy, an important arm of malignancy management.

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The foundation for immunotherapy was laid when unequivocal evidence proved immune cells, specifically the T cell's ability to fight the spreading of cancer cells. Fundamentally, immunotherapy harnesses and boosts the body's own immune cells to target and kill the tumor cells[3].

Immune system is very complex and is spread all over the human body and functions tirelessly knowing when to respond and how much[4]. Immunotherapy has emerged as the first strategy and there is a relatively high level of success against advanced malignancies and integrating it with other modalities of cancer treatment. Advances in immunotherapeutic strategies have gained approval as a standard care of treatment for different conditions, specifically various cancers.

Adoptive T cell therapy[3,5,6] involves isolation of T lymphocytes, synthetically modifying them followed by re-infusion into the patient's body which enhances the tumor driven responses of the immune system[7]. Immunotherapy has emerged as the first strategy that has demonstrated a relatively high level of success against advanced malignancies[8]. It is almost getting approved as a standard care of treatment for various conditions. A remarkable result and a great promise for treating malignancies include administration of tumor directed antibodies, cancer vaccines, immune checkpoint blockade therapy and adoptive T cell therapy.

Cancer Immunotherapy – The journey so far

Immunotherapy leverages the power of the immune system for treating different types of life threatening and debilitating conditions. In 1893, William Bradley Coley injected a mix of bacterial lysates, comprising *Streptococcus pyogenes* and *Bacillus prodigiosus* also called as Coley's Toxins for treating tumors. Coley was the first to channelize the power of immune systems and hence is considered the Father of Cancer Immunotherapy. In 1909, Paul Ehrlich postulated immune surveillance which said that the neoplastic cells can develop spontaneously inside the human system and immune cells continuously monitor and kill aberrant cells. The advent of radiation therapy and chemotherapy dampened the advancements made in cancer immunotherapy and it was a few decades before the focus shifted to immunotherapy again (Fig.1).

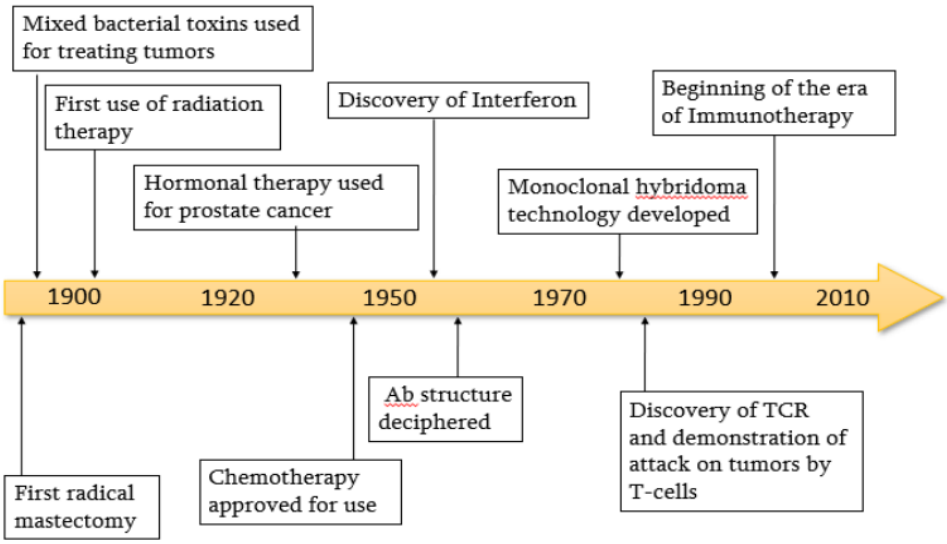

Figure 1: Timeline with key milestones in cancer treatment

The administration of interleukins and interferons for treating cancers in the 70's and 80's brought back life into the field of cancer immunotherapy. Immunotherapeutic strategies have emerged for treating different diseases in the past few years and majority of these are approved by the FDA (Food and Drug Administration). These have been approved to be administered as first line treatment in different types of cancers and autoimmune disorders. Of the many immunotherapeutic strategies, performance of CAR-T cell (chimeric antigen receptor - T cell) therapy has been exceptional in treating hematologic malignancies. The other immunotherapeutic strategies that have produced very exceptional results in the treatment of cancers include –

- Tumor Directed Antibodies
- Cancer Vaccines
- Immune Checkpoint Blockade (ICB therapy)[3,9]
- CAR T cell therapy

Tumor Directed Antibodies

Monoclonal Antibodies(mAbs) have emerged as one of the biggest classes of drugs for treating cancer in the past decade. The massive progress achieved is because of developing the hybridoma technology, one of the most commonly used techniques for producing mAbs. Hybridoma technology has been used to produce a number of mAbs over time[55]. Tumor directed antibodies and their conjugates have been developed against a plethora of antigens expressed on malignant cells.

FDA approval has been gained for the combination therapies in treating different types of cancers. First monoclonal antibody that was approved for human use is Rituximab (Anti CD20 mAb) for treating NHL (Non-Hodgkin's Lymphoma) and diffuse large B lymphoma. Other mAbs which are in use are Trastuzumab targeting Her-2 neu expressed in breast cancer, Cetuximab targeting Epidermal Growth Factor expressed in colorectal cancer. Bevacizumab targeting Vascular Endothelial Growth Factor again expressed in colorectal, breast and lung cancer[10]. mAbs use a multifaceted approach for targeting the tumor cells where they either act directly or trigger the adaptive immune system eliciting a long-term immune response.

In the direct mechanism, mAbs bind to their target receptors and disrupt their signaling by blocking its ligand binding or altering its activation state. Other mechanisms involving different components of the immune system include Complement Dependent Cytotoxicity (CDC), Antibody Dependent Cell Mediated Cytotoxicity (ADCC) and Antibody Dependent Cell Mediated Phagocytosis (ADCP). The target cells get lysed by activated complement pathway or through phagocytic or non-phagocytic lysis. Administration of mAbs for cancer treatment has been started recently, however, in the short span it has been proved to be extremely successful.

Resistance developing against mAbs in a subset of patients is proving to be a major challenge which is being addressed[11,12]. One of the causes for resistance include mutations. Mutations in the target antigen can lead to loss or decrease in expression or alteration in structure of the target in a way that efficacy of the mAb gets hampered. New approaches need to be identified for improving the efficacy of mAbs to overcome these challenges.

Cancer Vaccines

Cancer vaccines primarily aim to broaden the breadth of endogenous responses to elicit adaptive immune responses against the tumor cells[13]. Cancer vaccines being developed can be derived from different components of the tumor antigens like the DNA, RNA, tumor proteins, tumor lysates, synthetic peptides etc. They are delivered by employing different platforms such as dendritic cells, viral particles, nanoparticles etc[14].

Cancer vaccines can be broadly classified as either prophylactic (preventive) or therapeutic (curative). Sipuleucel-T, an FDA approved dendritic cell based therapeutic cancer vaccine is administered in patients with metastatic prostate cancer. It elicits an immune response against prostatic acid phosphatase, expressed in most prostate cancers.

BCG, originally administered against tuberculosis, has also been repurposed as a therapeutic vaccine against bladder cancer. HPV vaccine and HBV vaccines are FDA approved prophylactic vaccines that have been instrumental in reducing the incidence of cervical cancer and hepatocellular carcinoma[15]. The goal of cancer vaccines is to provide humoral and cellular immunity mediated by B-cells and T-cells for specifically killing cancerous cells and generating a lasting immune response.

An innovative approach to increase the efficacy and specificity of cancer vaccines is fast evolving that entails development of personalized cancer vaccines using high-throughput genomics which involves identifying immunogenic patient specific antigens and incorporating it in existing vaccine platforms[16].

Personalized cancer vaccines are proving to be a potent strategy and a number of clinical studies involving patients with various tumor types are ongoing[16]. Cancer vaccines till date have only been moderately successful in eliminating cancer when administered alone but they could greatly help in augmenting immune responses when used in combination with other therapies. Cancer vaccines have immense scope for developing individualized treatment plans for patients and with the right combinatorial therapies can become standard anti-cancer therapies.

Immune Checkpoint Blockade (ICB therapy)

Immune checkpoint receptors are negative regulators that keep tight checks on the proliferation of T cells by suppressing their function (Fig.2). They fine tune the immune responses and prevent exacerbated reactions. The up-regulation of these inhibitory receptors by neoplastic cells is one of the primary reasons resulting in an immunosuppressive tumor microenvironment[72]. Immune Checkpoint Blockade (ICB) has received a lot of attention this past decade and involves ‘releasing the breaks’ on T-cell activation. ICB therapy has been extensively used for treatment of several types of cancers and has proven to be a therapeutic milestone in the field of cancer treatment. Presently, a number of inhibitory receptors are being targeted for ICB therapy such as TIGIT/ CD155, T-cell immunoglobulin and mucin domain containing protein-3 (Tim-3), lymphocyte activation gene-3 (LAG-3) etc. But two receptors that have received maximum attention for ICB therapy are cytotoxic T-lymphocyte associated protein-4 (CTLA-4) and Programmed Cell Death (PD-1)[74]. Ipilimumab is the first FDA approved antibody targeting CTLA-4 which is effective for patients with advanced stage-3, stage-4 melanoma. CTLA-4 block A has been effective in treating tumors. However, further studies of the gene profile of tumor cells before and after

antibody treatment and a vigorous analysis of the T-cell subsets involved will further increase the efficacy of treatment. Programmed Cell Death-1 (PD-1), an immunomodulatory receptor, inhibiting the proliferation of T-cells and its loss leading to peripheral tolerance breakdown.

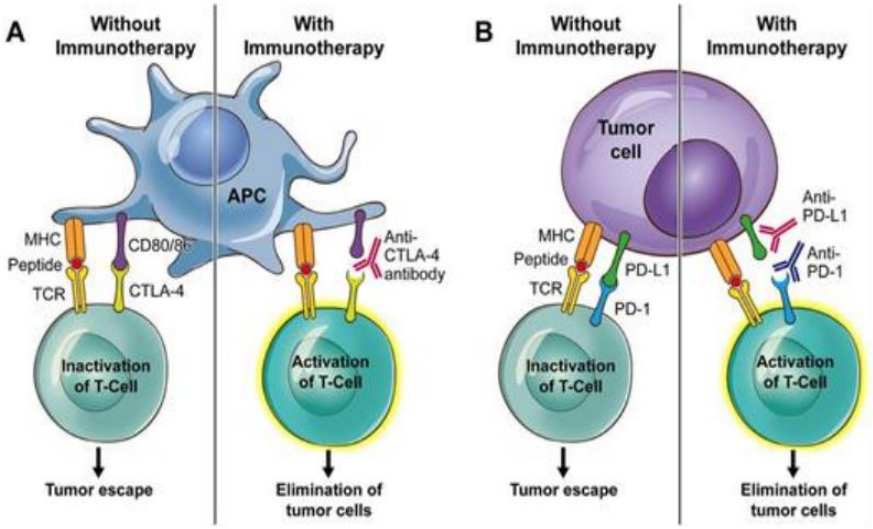

Figure 2: Mechanism of action of ICB therapy [43]

Chimeric Antigen Receptors

Chimeric Antigen Receptors (CARs) are an amalgamation of B-cell and T-cell receptors (BCR and TCR) where the Antigen binding region is from BCR and signaling domain is from a TCR (Fig.3). The first CAR developed were expressed on T-cells leading to the generation of CAR-T cells. Due to the ground-breaking research in CAR-T cell therapy and successfully treated patients with advanced leukemia by administering anti-CD-19 CAR-T cells[17,18]. The engineered cells have produced breakthrough results in treating hematological malignancies like ALL (Acute Lymphoblastic Leukemia), Chronic Lymphocytic Leukemia (CLL), Non-Hodgkin's Leukemia (NHL)[96-102]. Unlike T-lymphocytes, CAR-T cells are not limited by MHC presentations getting activated directly upon binding to its target antigens.

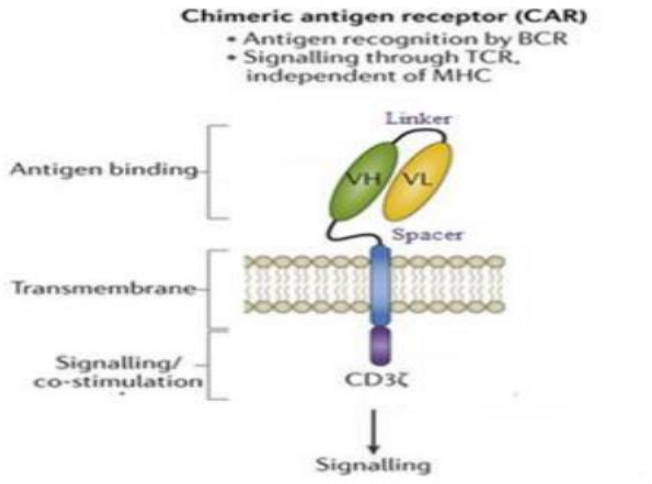

Figure 3: Structure of CAR construct [44]

CAR-T cell therapy has been immensely successful in treating hematologic malignancy and has produced durable responses in the cases of adult and pediatric groups. In this technology, T-cells are isolated from a patient; *ex vivo* activated, expanded and genetically modified to express CARs recognizing a selected antigen and finally re-infused into the donor's body (Fig.4). Though CAR-T cell therapy has paved the way towards the era of cancer treatment, there are several challenges limiting its therapeutic efficiency which needs to be addressed. These primarily include CAR-T cell therapy associated toxicities, resistance in B-cell malignancies and poor efficacy against solid tumors. The most commonly observed toxicity in patients being administered with CAR-T cells is the occurrence of cytokine release syndrome (CRS) that results in extensive activation of CAR-T cells leading to a surge in the release of pro-inflammatory cytokines that triggers monocyte and macrophage activation with further release of massive amounts of cytokines. The severity of CRS varies between patients ranging from minor to moderate to high. Primary management of strategy of CRS involves administering tocilizumab, a monoclonal antibody that blocks IL6 receptors. Despite numerous challenges hindering the advancement of CAR-T cell therapy, novel approaches are constantly being developed by researchers to expand its therapeutic efficiency. To make it a more durable and efficient therapeutic approach in the near future.

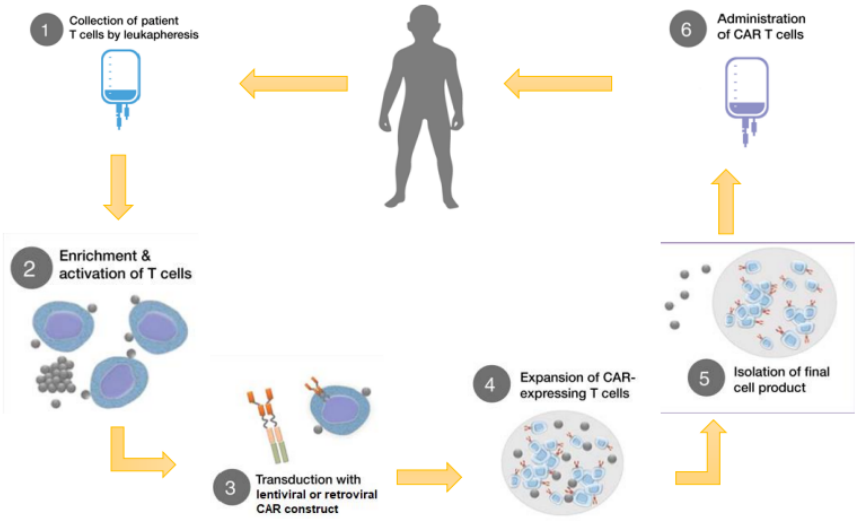

Figure 4: CAR T cell therapy [45]

Tumor-Infiltrating Immune Cells and their associations with Immunotherapies

Immunotherapies such as Adoptive Cellular Therapy (ACT) and Immune Check-Point Inhibitors (ICI) have obtained high success rates and have demonstrated that immune cells, particularly T-cells, can be used to eliminate tumor cells. Despite the proven clinical efficiency, only a small number of cancer patients have benefited from them[19].

As a major component of the TME, immune infiltrates have been proven to contribute to tumor progression and immunotherapy response.

For deciphering the mechanisms of immunotherapy, we therefore need a better understanding of both innate and adaptive immune cells in the tumor microenvironment.

T-Cells

T-cells have gained a major focus in tumor immunology due to their potent tumor-killing capability[21,22]. The T cell functionality is initiated when there is an engagement of T-Cell Receptors (TCRs) with short peptides of tumor antigens presented by major histocompatibility complex (MHC) molecules or human leukocyte antigen. Tumor Infiltrating Lymphocytes play a critical role in effective antitumor immunity, and different types of T cells, including cytotoxic T cells, T helper (TH) cells, and regulatory T cells (Tregs), are involved in T cell-mediated immune responses within the tumor environment[23].

As such Tregs are indispensable for maintaining homeostasis [24], they demonstrate antitumor immunity by directly undermining T-cell function via immunosuppressive soluble factors, as well as by indirectly impeding T-cell activation via CTLA-4-mediated inhibition of costimulatory signals of APCs[25,26].

B Cells

B cells are immune cells that function through the humoral immunity of the adaptive immune system[27]. As a response to infected cells or tumor cells, B cells separate into either memory B cells or plasma cells, the latter secretes immunoglobulins (Igs), also known as antibodies, which can bind and neutralize target antigens[28].

The process of B-cell activation involves an interaction of the Antigen with a B-cell Receptor (BCR) which is a membrane bound of Ig (mIg), providing B-cell with Antigen specificity.

B cells have a crucial role in antitumor immune regulation and indicate that B cells and TLSs have substantial applications for cancer treatment, although we will need further investigations to showcase the mechanisms of B-cell-mediated responses to immunotherapies.

NK Cells

NK cells, also called Natural Killer cells or larger granular lymphocytes (LGL) are critical to the innate immune system. They are unique lymphoid cells that exert cytotoxic functions without the presence of an antibody or MHC specificity. NK cells directly eradicate tumor cells through cytolytic granules and cooperate with other immune cells through proinflammatory cytokines and chemokines[29-31]. Importantly, the activation of NK cells is mediated by the combined action of activating and inhibitory receptors expressed on the NK cell surface.

Till date, several NK-based immunotherapies have been explored, this includes the adoptive transfer of autologous NK cells, which involves the transfusion of ex vivo activated and expanded NK cells into patients;[32]. In the CAR-NK cell therapies, engineered NK cells expressing CARs are transfused against a specific tumor antigen;[33] cytokine therapies, which involve the infusion of specific cytokines to augment NK cell activity;[34] and mAb-based therapies, referring to the delivery of antibodies to block inhibitory receptors on NK cells[35].

Myeloid cells

Myeloid or myelogenous cells are blood cells that arise from a progenitor cell for granulocytes, monocytes, erythrocytes, or platelets[36,37] and have been shown to play critical roles in tumor immunity[38].

Neutrophils, which are the most common subtype of granulocytes, are typically responsible for the functionality of innate protection against bacterial and fungal infections, their roles in tumor immunity remain controversial[39].

Macrophages are phagocytic cells, which engulf and digest pathogens which do not have proteins specific to healthy body cells on their surface, such as cancer cells, microbes, cellular debris, and foreign substances[40,41].

Macrophages can eliminate malignant cells through phagocytosis or through producing soluble factors to induce tumor cell apoptosis[42]. In addition to the direct tumor-killing capability, macrophages play important roles in modulating tumor progression through mechanisms such as angiogenesis, fibrosis, and immunosurveillance.

Tumor-associated macrophages (TAMs) have profound effects on the TME and may offer new opportunities for cancer immunotherapy.

CONCLUSION

Immunotherapy has completely altered the face of cancer medicine. The past decade has witnessed a massive development in immunotherapy with the introduction of different strategies for targeting tumor cells. One of the many immunotherapeutic strategies that has led to a paradigm shift specially for treating hematological malignancies is CAR-T cell therapy, which is a form of adoptive T-cell transfer that involves isolating T-cell from a patient and reprogramming it to the target tumor antigens, overexpressed in cancerous cells and infusing the cells back into the donor systems.

CAR-T cell therapy holds immense promise for treating cancers and there is a need to develop more methodologies for increasing the overall performance of CAR-T cells against different malignancies specially the solid tumors.

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