Overview of T-Cell Therapy: An Enormous Breakthrough in the Fight against Cancer

ABSTRACT

Background: Cancer cells are cells which have relinquished their capacity to adhere to typical regulatory controls. As cancer progresses, it can spread to adjacent tissues, posing significant risk to one's survival. Current approach towards cancer management involves; Surgery, Radiotherapy, Chemotherapy and Cyber-knife. These produce immunosuppression, which could last from 6 weeks to several years. Current dogma of cancer progression is linked to the immune status of the patient; important to balance the immune markers for cancer patients. Efforts to reset the body's immune system clock can lead to improved disease outcomes and prognosis. Key Facts: T cells serve as the defenders of the immune system and defend the body from cancer. Non-specific activation of T-cells leads to increased T-cell numbers, discharge of pro-inflammatory and anti-tumor cytokines. Cells that are not specific to antigens can identify tumor cells by recognizing stress signals, causing them to destroy the tumor cells and release hidden tumor antigens. Cytokines produced by different cells attract immune cells, such as antigen-presenting cells (APCs) that ingest tumor antigens, triggering the activation of CD4+ and CD8+ T cells specific to those antigens. Cells, whether specific to antigens or not, demonstrate the ability to fight against tumor cells by selectively attacking tumor antigens and stress signals. The secretion of cytokines by antigen-specific cells serves to sustain and perpetually attract cells that are not specific to antigens within the tumor microenvironment. Conclusion: Non-specific T-cells could help reset the immunological deficiencies in body, which could translate to reduced incidence of tumor load.

Keywords: Neoplasm, T-Lymphocytes, Non-Specific, Immunotherapy, Antitumor Cytokines

1. INTRODUCTION

It is a reality that approximately one out of every two men and one out of every three women will face a cancer diagnosis at some point in their lives. Yet, despite these alarming figures, many individuals remain unaware of the true implications behind them. Cancer is complex, an abnormal proliferation of cells resulting from numerous alterations in gene, disrupting the homeostasis between cell division and apoptosis. This aberrant growth transforms into a cell population with the ability to infiltrate tissues and spread to distant locations, leading to substantial morbidity [1]. Every year, India sees 8 lakh new cancer cases, and of 5.5 lakh are cases of Solid cancer as per the ICMR data. Around the world, cancer seriously threatens public health, accounting for one-sixth of all deaths. An estimated 19.3 million new cases of cancer occurred in 2020, and approximately 10 million people died of the disease around the world [2]. During the development of cancer, tumours go through many changes. The result is a high level of heterogeneity within the cell population. These differences take spatial and temporal forms. The cells possess different molecular characteristics, and reactions to therapeutic interventions differ from cell to cell as well [3].

When we call a tumour as benign, it means it's not much of a concern. It won't spread to nearby or distant areas, is easily treatable with surgery, and doesn't pose a significant risk to the patient's life. Malignant tumours, collectively known as cancers, derive their name from the Latin word for crab. This is because their behaviour is reminiscent of a crab, involving the tissues in a crab-like manner. These tumours can invade and destroy neighbouring structures and have the potential to metastasize, resulting in life-threatening consequences [4].

2. DEVELOPMENT OF CANCER

Cancer is mostly caused by genetic mutations, which means that changes to the genes controlling cell behavior, particularly growth and division, are the underlying cause of the illness [5].

The following can result in genetic alterations that lead to cancer:

- Errors which occurs during cell division.

- DNA damage brought on by toxic agents. Examples include harmful substances found in cigarette smoke and exposure to ultraviolet radiation from the sun.

- Genetic inheritance from parents.

Normally, the body gets rid of cells that have damaged DNA prior to becoming cancerous. However, as we get older, the capacity of body to do so decreases. This contributes to a higher likelihood of developing cancer in older age.

Each person's cancer is triggered by a unique Integration of genetic changes. More alterations will take place when the malignancy spreads. Different cells within the same tumour may have different genetic alterations.

On the contrary, the development of cancer involves a series of gradual changes that lead to malignancy, indicating it as a multistep process. One clear sign of this is the tendency for most cancers to appear later in life.On a cellular level, cancer progresses through a series of steps involving mutations and the selection of cells that become progressively better at growing, surviving, invading, and spreading. The first stage, known as **tumor initiation**, is thought to occur due to a genetic change that causes one cell to start dividing uncontrollably. This leads to the formation of a group of tumor cells, all originating from that one mutated cell. **Tumor progression** involves ongoing mutations in the cells within the tumor. Some of these mutations provide certain cells with advantages, such as quicker growth. As a result, these advantaged cells and their descendants become more prominent in the tumor. This process, called **clonal selection**, leads to the evolution of a new clone of tumor cells that have superior growth rates or other advantageous properties like improved survival, invasion, or metastasis. Throughout the development of a tumor, clonal selection continues, leading to progressively faster growth and increased malignancy [6].

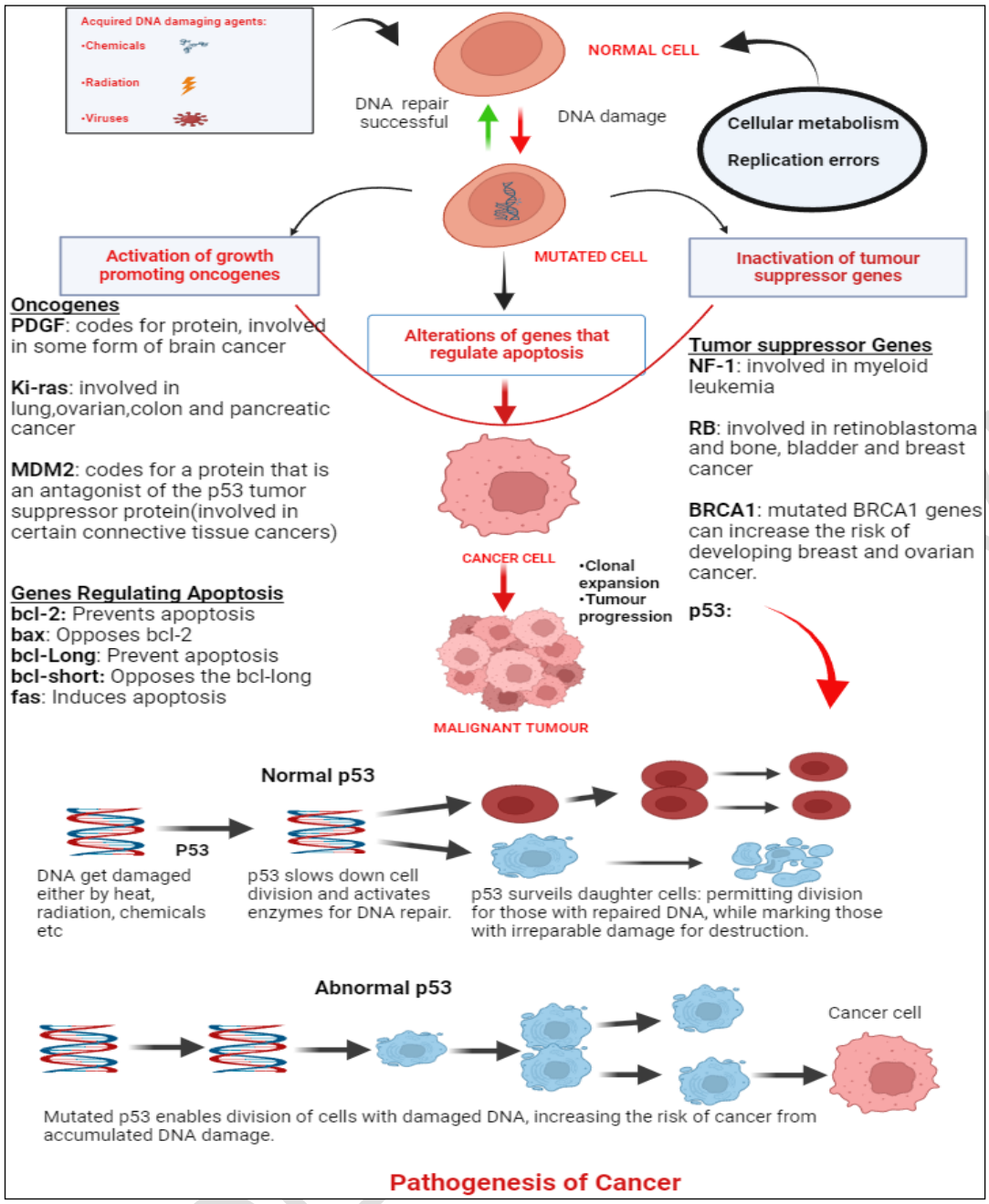

Figure 1. Pathogenesis of cancer: The formation of malignant tumors is driven by a series of detrimental changes within the genetic framework of cells. These changes involve the impairment of tumor suppressor genes, the activation of oncogenes that stimulate cell growth, and modifications to genes responsible for regulating programmed cell death (apoptosis). Collectively, these genetic alterations culminate in the development of malignant tumors. Source: Created with BioRender.com

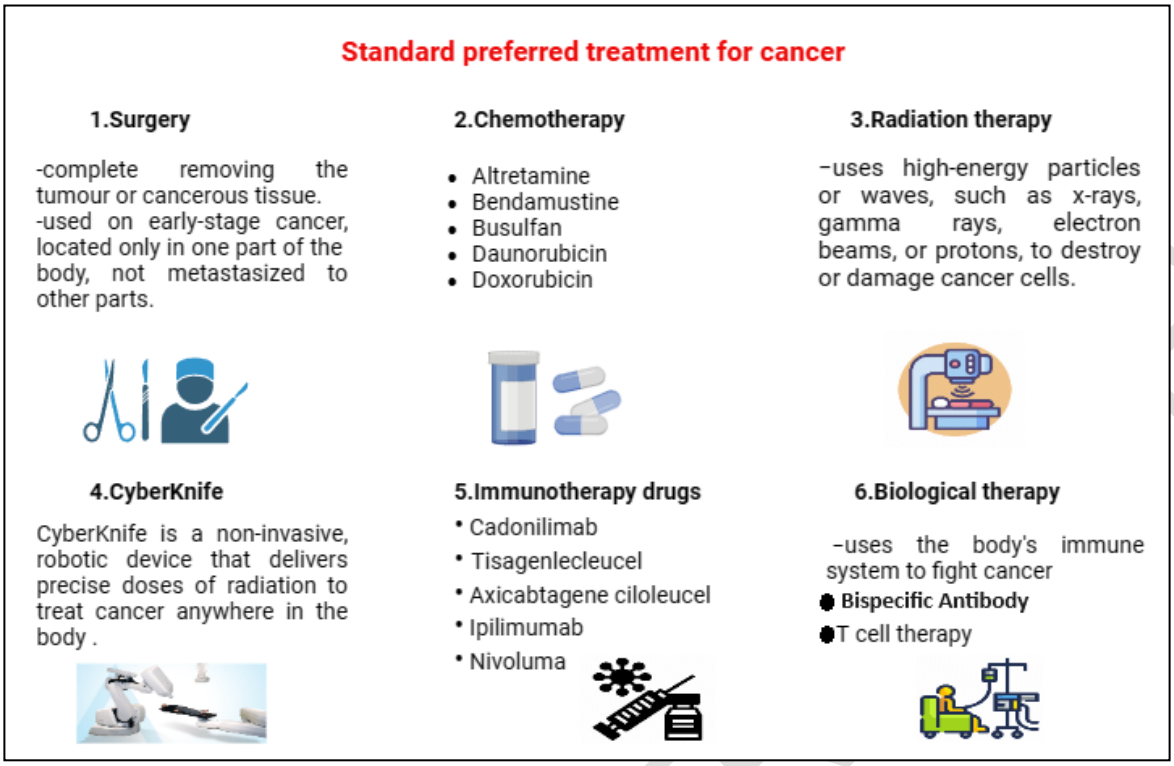

Figure 2. Standard preferred treatment for cancer; Surgery, Chemotherapy, Radiation therapy, Cyber knife, Immunotherapy drugs and biological therapy [7, 8, 9].

Several studies have indicated depression of the immune system post-surgery, RT/CT. Immuno-suppression leads to predisposition of the body to secondary complications and opens a window of opportunity for invasion of cancer cells into other organs in the body [10].This also indicates increase in relapse rates.

A strong body of evidence points to the shortcomings of the current approach towards cancer treatment is the immune system and current review have to keep in mind the immune system when subjecting a patient to surgery, CT/RT. A sure shot method of overcoming this immune suppression is to bolster the immune system prior to surgery/RT/CT by immune modulators (cellular immunotherapy) which would help reset the immunological deficiencies in the body, which could translate to reduced incidence of relapse.

There are 2 issues here to consider:

- Methods of immune modulation.
- Time intervals at which one could intersperse with the standard care.

Several studies indicate the following methods: (mainly)

- Herbal immune modulators
- Non-specific T cell stimulation
- Adoptive T cell

- Dendritic cells
- NK cells

3. NOVEL APPROACH OF CELLULAR THERAPY IN CANCER

The idea of utilizing the immune system of the body for treating cancer first emerged in the 19th century. The first person to establish an epidemiological correlation between cancer and immune status are Wilhelm Busch and Friedrich Fehleisen [11]. Immuno-oncology has revolutionized cancer care. William B Coley – the father of immunotherapy, explored cancer treatment by utilizing the immune system in late 19th century. 1891 marked the start of Coley's clinical experiments, wherein over a thousand patients were given live and inactivated bacteria concoction to trigger potent immune antitumor reactions. This cocktail of bacteria, called "Coley's toxin," was the first recorded cancer immunotherapy intervention that involved active action. Coley produced lasting complete remissions in various forms of malignancies such as sarcoma, lymphoma and testicular carcinoma [12].

Some of the most promising cancer immunotherapies are: immune checkpoint inhibitors (ICIS), ICIs block the action of immune checkpoint proteins, which possess the ability to suppress the immune response towards cancer cells. Several malignancies, including melanoma, lung, kidney, and bladder tumors, have been effectively treated with ICIs [13]. T cell therapy, involving introduction tumor-fighting T cells within the body, along with cancer vaccines, can be devised with intentions for either preventive or therapeutic objectives [14].

3.1 Potential synergy between T cells and Immune markers

T lymphocytes are crucial in building immunity against cancer. T cells perceive cancer as extraneous cells that are not native to the body. T cells actively target and attempt to eliminate the cancerous cells. T cell-mediated tumor rejection involves several processes, including the actuation of the effector T cells and antigen specific T cell migration to sites where tumors are formed as well as targeting them along with destruction. The various class of T cells include regulatory, helper and cytotoxic T lymphocytes. Cytotoxic T cells are the most potent effectors in the anticancer immune response. Though regulatory T cells suppress the immune responses to prevent autoimmune reactions, helper T cells provide signals which direct other immune cells on how best fight off infection [14, 15].

3.2 Production of T Cells

T lymphocytes have their origin from hematopoietic stem cells inside the bone marrow. A subset of these multi-potent cells transformed into lymphoid progenitor cells which exit the bone marrow and traverse through the bloodstream to reach the thymus. T lymphocytes within the thymus, known as thymocytes undertake a crucial selection process where the majority do not survive. This elimination is accomplished through the reception of negative signals by thymocytes possessing receptors for self-antigens. T cell receptor (TCR) is present on each T lymphocyte with the ability to recognize a specific antigen. Those T lymphocytes that successfully pass through thymic selection will undergo maturation and become mature and then exit the thymus. Once in circulation within peripheral lymphoid organs, they stand prepared to encounter their respective antigens and undergo activation. As humans age, the thymus undergoes atrophy, resulting in a reduced production of naïve T lymphocytes over time [16].

3.3 Role of T cells in cancer

DCs (dendritic cells) continuously check the immune clock of human body, constantly searching for threats or pathogenic antigens. In face of secreted tumor-specific antigens, DCs engulf them by phagocytosis and insert on the MHC class II molecules. Upon movement into secondary lymph nodes, T cells including naïve cytotoxic T lymphocytes (CTLs) identify and react to peptides presented by MHC class II molecules [17].After maturation and activation, T cells develop an effector status where they are poised to hunt down target cancer cells. When activated, these T cells circulate through the system performing their duties [18].Naïve CD4+ T cells have the ability to transform into different T helper cell types like Th1, Th2, and Th9.The identification of Th1 or Th2 CD4+ cells is based on the type of cytokines which are released by these cells. However, the imbalance between Th1 and Th2 cells causes' impaired immune system causing development of autoimmune diseases [17].CD4+ T cells hold a pivotal role in the rejection of human tumors, actively participating in the process. They contribute to the elimination of tumors by supporting the activation and priming of cytotoxic CD8+ T cells. Notably, a specific subdivision of CD4+ T cells engage in the elimination of tumor cells, further enhancing the immune response hostile to cancer. CD4+ T cells, in reaction to MHC class II molecules produce IFN-γ that leading host cells to eliminate cancer cells. IFN-γ promotes the release of two CXC chemokines and interferon gamma-inducible protein of 10 kilodaltons (IP-10). These

chemokines disrupt the tumor vascular structure and produce anti-angiogenic effects through inhibition of angiogenesis that causes growth arrest and tumor necrosis [17].
CD25, the interleukin-2 receptor alpha chain, is a key marker for regulatory T cells (Tregs) and is pivotal in cancer research. Tregs, which express the transcription factor FOXP3, suppress effector T cells that attack cancer cells, thus maintaining immune tolerance and preventing autoimmunity. However, in cancer, this creates a paradox: the suppressive function of Tregs fosters an immunosuppressive tumor microenvironment (TME), hindering effective anti-tumor responses. High intratumoral CD25 expression, indicating increased Treg infiltration, is correlated with poorer patient outcomes in various cancers [19].

3.4 Impact of T-Cells in Cancer cells

By the process of TCR recognition and antigen presentation, T cells recognize the cancer cells. Antigen-presenting cells (APCs) through the major histocompatibility complex (MHC), show digested antigens to T cells, so that they can recognize the antigen as harmful. In order to communicate with and confuse other immune cells, tum or cells can produce cytokines which interfere with the capability of T cells to pinpoint and fight against cancer cells [20].

T cells identify short antigenic peptides attached to MHC-I and -II outwardly cancer cells via their TCRs [21]. In the immune response opposed to cancer, T cell recognition of tumor-associated and tumor-specific antigens is an important step. Neoantigens, or mutated proteins found in cancer cells, may be detected by T cells because they differ from self-antigens [4].The cancer immunotherapy focuses on the T cell recognition of cancer cells leading to numerous strategies such as adoptive cellular therapies, checkpoint blockade and a wide range of tumor vaccines. The main objective is to increase the T cell responses against cancer [22].

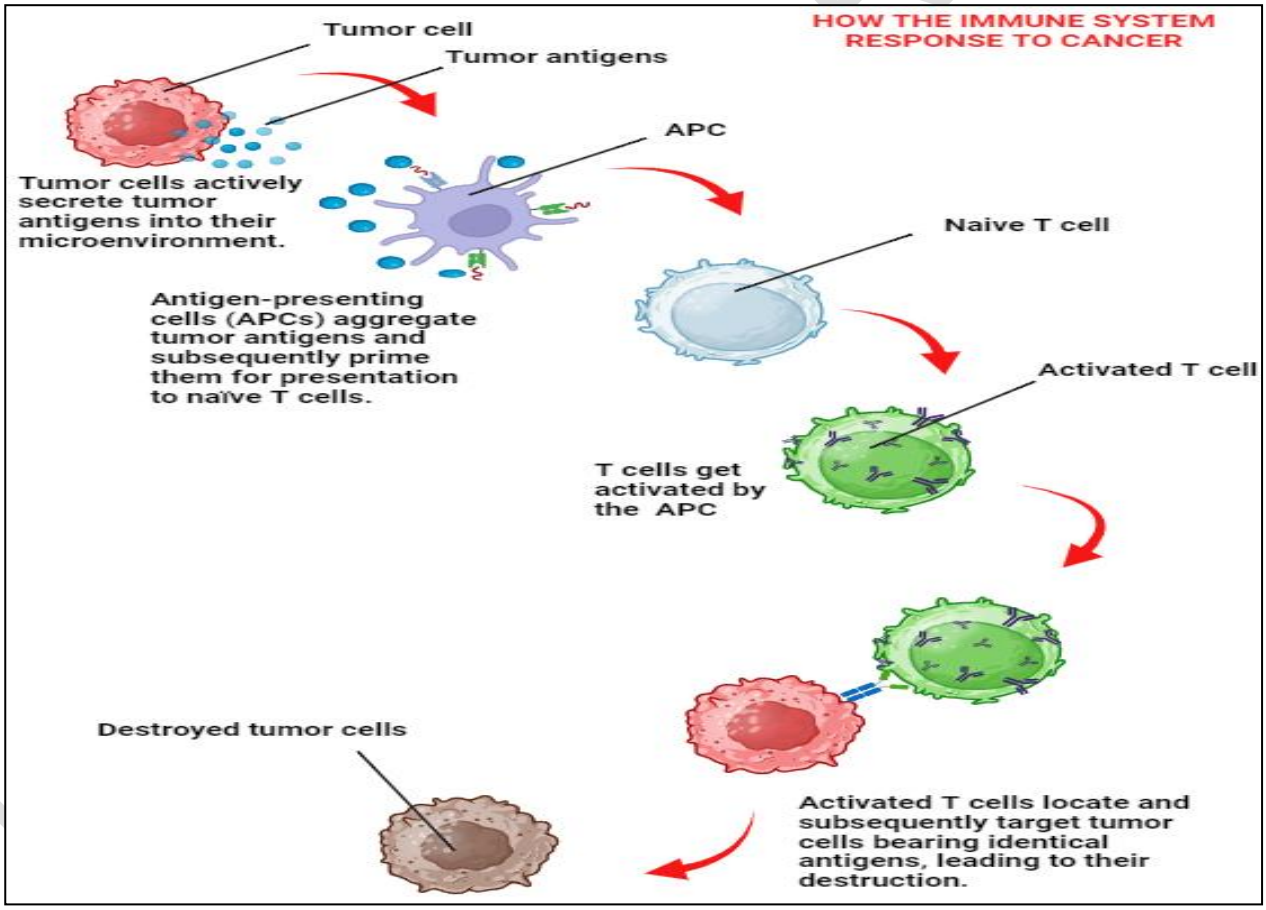

Figure 3. How the immune system deals with cancer: Tumor cells release tumor antigens, which are gathered by antigen-presenting cells (APCs) and presented to activate naive T cells. Once activated, these T cells identify and abolish tumor cells that carry corresponding antigens. Source: Created with BioRender.com

4. T CELL BASED CANCER IMMUNOTHERAPY

T cells are a specialized subset of blood cells within our immune system. These shapeless entities move swiftly, extending their leading edge and exploring their surroundings as they navigate. When a cytotoxic T cell encounters a cancer cell, it swiftly extends membrane protrusions to scan the cell's surface, searching for characteristic indicators of cancer. They eliminate their targets through the utilization of proteins. These cytotoxic granules travel along specific pathways within the cell known as microtubules, reaching the interface between the T cell and the cancer cell. The T cell breaches the surface of the cancer cell and releases its potent cytotoxins, minimizing harm to neighboring cells. Once the fate of the cancer cell is sealed, the T cell continues its quest, driven by the urge to locate another target. Immunotherapy for cancer utilizing T cells mainly includes the following approaches: bi-specific T cell engagers (TCEs), immune checkpoint blockade (ICB) and co-stimulation, adoptive cell therapy (ACT).

4.1 Immune checkpoint blockade

In the regulation of activation of T cell, several evolutionarily conserved negative regulators, acting as 'checkpoint molecules, intricately regulate the immune response to avoid over activation. Two prominent examples are programmed cell death 1 (PD1) and cytotoxic T lymphocyte antigen 4 (CTLA4), each playing a crucial role at specific locations and stages throughout the lifespan of T cells. Their complementary functions work in harmony to maintain self-tolerance and safeguard the body against pathogens and neoplasms. Tasuku Honjo and James P. Allison were bestowed the Nobel Prize in Physiology or Medicine in 2018 for research on CTLA4 and PD1 as treatments for various types of recalcitrant cancers [14].The first checkpoint inhibitor approved by US FDA is Ipimumab, a monoclonal antibody(mAb) which targets the CTLA4 [22].

4.2 Bi-specific T cell engagers (TCEs)

Recent findings clearly show that the dual targeting of two or more immunoremodulatory molecules possess strong anti-tumor activity at reduced toxicity levels. This transformation has led to unprecedented innovations, such as the emergence of bi-specific antibodies (bsAbs) and in some instances tri-specific antibodies (TsAbs) [23, 24]. Bi-specific T cell engagers (TCEs) represent a targeted immunotherapeutic approach designed to reroute effector T cells towards tumor cells for the purpose of inducing cytotoxicity. These entities comprise a bi-specific adaptor protein that facilitates the connection between any T cell within the systemic milieu and specific cells, affording a level of control over dosage and scheduling. This precision in administration aims to minimize possible adverse effects associated with broader systemic T cell activation. Moreover, the application of TCEs is characterized by a simplified manufacturing process in comparison to cell-based therapies. This innovative strategy holds promise in achieving efficacious tumor cell elimination while concurrently addressing concerns related to therapeutic complexity and adverse effects [25, 26]. In contrast to the combination of two monoclonal antibodies (mAbs), bi-specific antibodies (bsAbs) exhibit a unique capacity to either engage with two molecules conveyed on a single cell (in-cis binding) or act as bridges between two divergent cells (in-trans binding). This distinctive feature enhances the therapeutic efficacy of bsAbs, setting them apart from traditional dual mAb approaches [22]. The Chinese National Medical Products Administration (NMPA) approved cadonilimab as the first bispecific antibody (bsAb) for treating cervical cancer that has relapsed or metastasized [27].

4.3 Adoptive cell therapy (ACT)

Adoptive T cell (ATC) therapy, that concerns the administration of either autologous or allogeneic T cells within cancer patients, has shown the significant promise in recent years. It involves withdrawing of donor's or patient's T cells, that are grown and/or modified inside the laboratory and then the cells are reintroduced back into the patient [28].In adoptive cell therapy (ACT), there are primarily three types: tumor-infiltrating lymphocyte (TIL) therapy, chimeric antigen receptor (CAR)-T cells, and T cell receptor (TCR)-T cells [29].

4.3.1 Tumor-Infiltrating Lymphocyte (TIL) Therapy

The strategy behind TIL therapy incorporates harnessing the potential of tumor-infiltrating lymphocytes, situated in the proximity of the tumor. The underlying idea is that these lymphocytes have already demonstrated an aptitude for identifying and attacking tumor cells. Yet, their numbers may be insufficient to effectively combat the tumor or override the immune-suppressive signals emanating from it. Administering a significant quantity of the lymphocytes exhibiting the most robust response to the tumor is intended to surmount these obstacles [30].Tumour-infiltrating lymphocytes (TILs) are harvested from the tumor biopsy of patient and cultured in the laboratory with interleukin-2 (IL-2) for expansion. These expanded TILs are subsequently administered to patients who have undergone lymphodepletion, creating a favorable environment for the implanted TILs to grow, act as effective cells, and create immune memory. Given their derivation from the tumor, it is assumed that an abundant proportion of these T cells can identify tumor-associated antigens (TAAs) or neoantigens [14].Figure 4

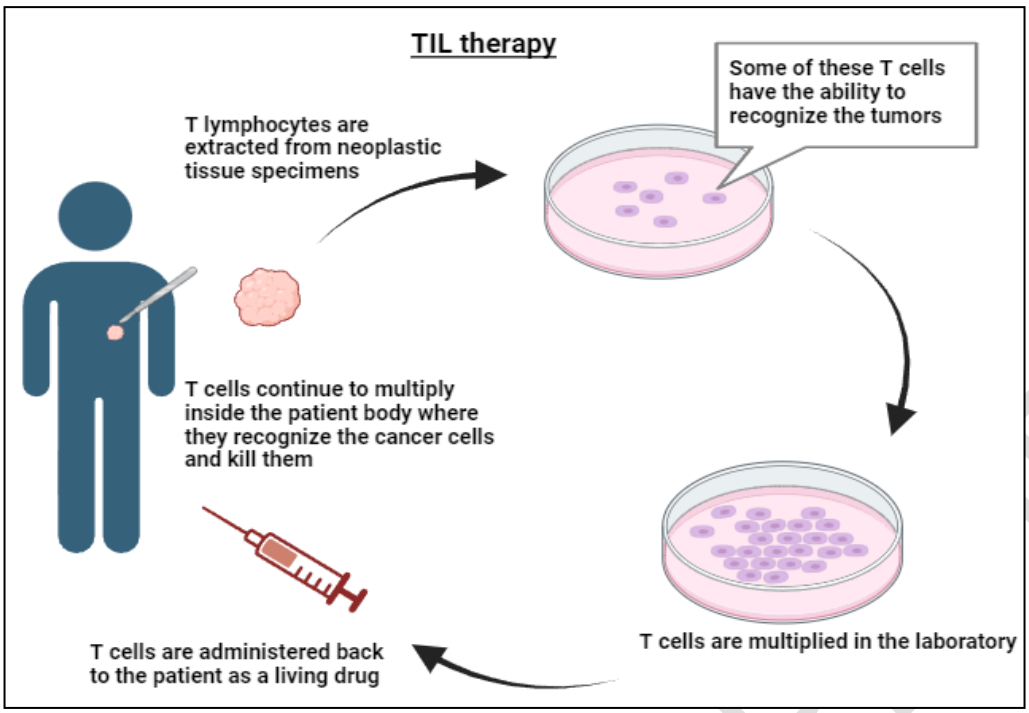

Figure 4. TIL therapy: T lymphocytes extracted from tumor tissue are selected for their tumor recognition capabilities, multiplied in the laboratory, and then reintroduced into the patient's bloodstream. These engineered T cells expand in vivo, identifying and eliminating cancer cells. Source: Created with BioRender.com

4.3.2 T cell receptor-engineered T cell (TCR-T) therapy

In T cell receptor-engineered T cell (TCR-T) therapy, T cells are taken from patients, and the sequences of their TCR genes are identified before being integrated into peripheral T cells. Advances in this therapy involve refining the affinity of TCRs and creating highly specific cell therapies, resulting in improved tumor response and enhanced patient safety. Although TCR-T therapy holds great potential, it has its difficulties which are presented by its intricate nature, inter-individual variabilities, and the potential for adverse effects like cytokine storms or T cell tolerance, influencing both safety and antitumor efficacy. However, with the development of TCR-T therapy in treating solid tumors also come several challenges including dependence on human leukocyte antigen (HLA) and susceptibility to HLA down regulation [31,32].

4.3.3 CAR (Chimeric antigen receptor) T-cell therapy

CAR T-cell therapy shares similarities with TIL therapy, but it involves modifying the body's T cells in the laboratory so that they make a type of called CAR (chimeric antigen receptor) before being grown and reintroduced into the patient. CARs are engineered to enhance T cells capacity to bind to specific proteins found on the surface of cancer cells, boosting their capability to identify and eradicate these malignant cells [30]. Figure 5

4.3.3.1 Development of Car T Cells

To produce CAR T cells, the procedure begins with gathering cells from a patient through leukapheresis. Subsequent steps include elutriation for myeloid cell removal, T lymphocyte enrichment, transgene delivery, and cell expansion outside the body. A pivotal challenge in cellular manufacturing is the effective extraction of the samples of T leukapheresis. The products Leukapheresis obtained from cancer patients comprise diverse groups of cells encompassing T cells, erythroid cells, natural killer cells, myeloid cells (like monocytes, dendritic cells and neutrophils) and malignant cells. A patient's cells are extracted by leukapheresis and then T cell selection and monocyte elutriation is done. Subsequently, the selected product is activated by employing paramagnetic beads coated with anti-CD28 and anti-CD3 agonistic antibodies. Next, a viral vector carrying the CAR transgene is introduced into it. The last step in creating the CAR T-cell infusion product involves cultivating and harvesting T cells after gene delivery [33].

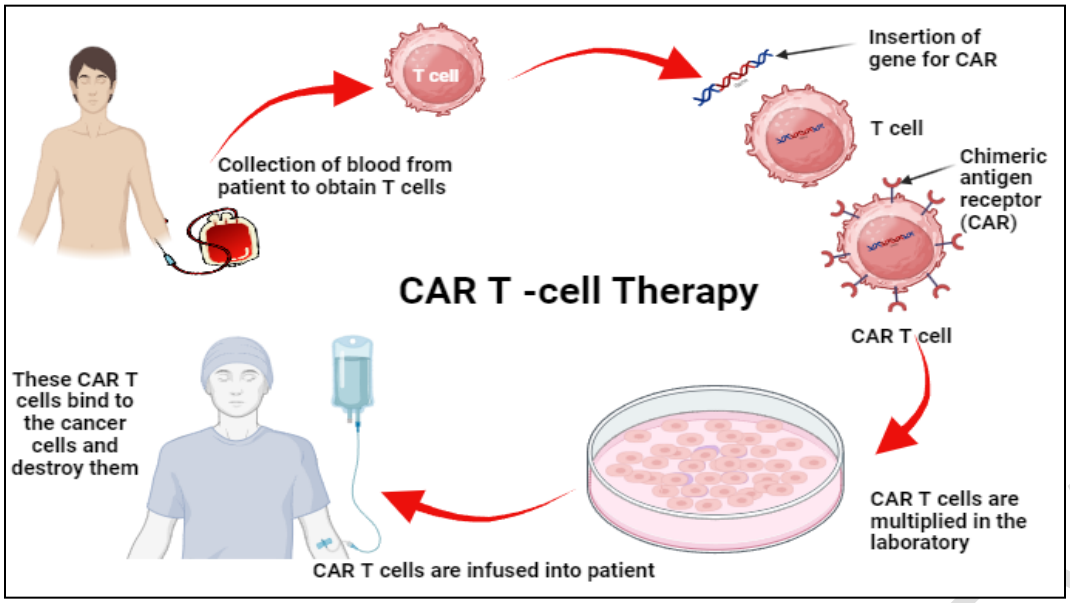

Figure 5. CAR T –cell therapy: Blood is drawn off the patient to isolate T cells, which are subsequently genetically engineered to produce CARs. Following expansion in the laboratory, CAR T cells are given to the patient. Once infused, these CAR T cells identify and eradicate cancer cells. Source: Created with BioRender.com

Table 1. T lymphocyte-based immunotherapy in various cancer types

Cell Therapy	Cancer type	Key points	Reference
CAR-T	Chronic Lymphocytic Leukemia (CLL)	Scientists has investigated the potential of employing CAR T-cell therapy for the treatment of B-cell malignancies in individuals who have undergone allogeneic hematopoietic stem cell transplantation. However, in this instance, one of the main side effects is graft-versus-host disease where transplanted cells target and damage recipient tissues.	[34]
CAR-T	Acute Lymphoblastic Leukemia (ALL)	CD19-targeted CAR therapy shows promising results in treating acute lymphoblastic leukaemia (ALL), with an 88% complete remission rate in one clinical trial and a 70% rate in another encompassing paediatric and adult patients.	[34,35]

		The choice to focus on CD19 as the primary target for CAR therapy in patients with ALL is based on its proven effectiveness.	
CAR-T	Multiple Myeloma (mm)	CAR T-cell therapy has transformed the landscape of multiple myeloma (MM) treatment, significantly enhancing patient survival. Challenges associated with CAR T-cell therapy in multiple myeloma include treatment resistance, limited patient accessibility, lengthy manufacturing times, and associated toxicities. Despite facing obstacles, CAR T-cell therapy guided towards B-cell maturation antigen (BCMA) has demonstrated exceptional clinical efficacy in multiple myeloma, leading to FDA-approved treatments with encouraging outcomes. Ongoing research aims to improve therapy efficacy, including earlier treatment phases and dealing with relapse following treatment with anti-BCMA CAR T-cell therapy.	[36,37,38,39,40]
TIL	Liver cancer	Tumour-infiltrating lymphocytes (TILs), including subsets like Foxp3+, CD8+, and CD4+ T cells, greatly influence prognosis and response to immunotherapy in hepatocellular carcinoma (HCC). Higher densities of CD8+ and CD4+ TILs, particularly within the tumour or perivascular regions, correlate with improved overall survival and recurrence-free survival, indicating their potential as prognostic markers and predictors of treatment outcomes in HCC.	[41]

TIL	Melanoma	Dafni et al. reported that between 1988 and 2016, the combination treatment of TIL-ACT with IL-2 disbursed an objective response rate (ORR) of 41% among individuals with advanced cutaneous melanoma. Furthermore, they noted an overall complete response rate (CRR) of 12%.	[42]
TIL	Breast cancer	In a study with 42 female metastatic breast cancer patients, tumour-infiltrating lymphocyte (TIL) therapy showed promising efficacy, with 67% of participants displaying a notable immune reaction against their cancer, indicating a favourable response to the treatment.	[43]
TCR T-cell	Leukemia	TCR T-cells show promise for leukaemia therapy, targeting antigens like WT1, FMNL1, human TERT, AURKA, MDM2, BOB1, and HMMRRhamm, particularly in treatment-resistant cases. Further research is crucial to enhance their clinical effectiveness in leukaemia immunotherapy.	[44]
TCR T-cell	Non-small cell lung cancer (NSCLC)	Progress in TCR-T cell therapy for NSCLC focuses on targeting NY-ESO-1 antigens, showing promising potential. Clinical trials with NY-ESO-1 TCR-T cells reported responses in 50% of NSCLC patients without severe toxicity. Ongoing trials, like NCT03709706, explore safety and efficacy of NY-ESO-1/LAGE-1a TCR-T cells alone or with pembrolizumab, providing insights into TCR-T cell therapy for NSCLC.	[45]

5. FUTURE CLINICAL APPLICATION

Cytotoxic T cells are unique members of the WBC. They monitor the body, identify and then destroy virally infected and cancer cells and they do so with exceptional precision and efficacy. Several studies have indicated the suppression of immune cells post-surgery or, chemo-radiation. Non-specific T-cell therapy involves utilizing the body's natural immune system to combat cancer and it leads to increased t-cell numbers, pro-inflammatory and anti-tumor cytokines, which may inhibit or slow the growth of cancer cells and the immune system operates more effectively in eliminating cancerous cells. A sure shot method of overcoming this immune suppression is to bolster the immune system prior to surgery/RT/CT by immune modulators (cellular immunotherapy) which would help reset the immunological deficiencies in the body.

6. CONCLUSION

It has been found that from the review, Activated cytotoxic T-lymphocyte cellular therapy is effective for cancer cells. Activation of T-cells via tumor antigen recognition leads to increased T-cell numbers, release of pro-inflammatory and anti-tumor cytokines can significantly improve therapeutic efficacy of cellular immunotherapy for cancer. Hence, if the primary treatment fails or incomplete due to the immunodeficiency's or/and limited treatment option for disease condition, T-cells therapy might be an effective or adjuvant therapy for cancer patients to reset the immuno markers deficiencies.

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