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Advancement in Immunotherapy; A Study Targeted for Treatment of Cancer

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ABSTRACT

Promising novel immunotherapies have emerged in the recent past and have greatly impacted the field of oncology and treatment of malignancies. The present paper aims at describing the case, its development, and the existing position of the cancer immunotherapy that includes the checkpoint inhibitors, adoptive cell therapies, and cancer vaccines. It also looks at the innovative targets like antibody-drug conjugates, immune cell engage, cytokines as well as oncolytic viruses. Special attention is paid to the combination approaches intended for the suppression of the resistance and strengthening of response persistance. The review emphasizes on the application of biomarkers for decision-making in treatment and appliance of the strategies where important issues, such as immune-related adverse events, tumor microenvironmental factors, and resistance to treatment, lie. Finally, the economic and global availably options are also discussed in order to look at the wider perspective of immunotherapy. Lastly, the review provides insights into future perspectives such as; neoadjuvant immunotherapy, innate immune, and adjuvant approaches, and future innovation technologies in the area of AI and spatial omics. As the basis of this article is the advancement of science and clinical perspectives, researchers, clinicians, and policymakers could find the information provided in this article helpful for the enhancement of reachable and fair immunotherapy in cancer treatment

Keywords: *Cancer Immunotherapy, Checkpoint Inhibitors, Adoptive Cell Therapy, Tumour Microenvironment, Personalized Medicine*

1. INTRODUCTION

Immunotherapy's origin as a cancer treatment can be dated back to the 19th century when William Coley observed that the tumour of cancerous patients reduced when they acquired bacterial infections. They are all known to have used inactivated bacteria or toxins in some of the initial immunotherapeutic forms of treatment that his subsequent development of "Coley's toxins" also exemplifies". Before this, in the 17th and the 18th centuries, basic procedures included actions of purposefully inflicting a wound to develop infection or applying infected matter with to tumours; many of these practices were not based on scientific knowledge.

Nevertheless, it was not for those early observations that it took several decades to develop a sound scientific foundation for immunotherapy, which came only during the second half of the twentieth century as the science of immunology as well as tumour biology progressed. The 1980s was strategically turning point when scholars and researchers at The National Cancer Institute carried out more cancer research studies that enhanced discovery, for instance, BCG Vaccine for Bladder Cancer, Interleukin-2 for Metastatic Cancers, or Rituximab for the B-Cell Lymphomas.

Immunotherapy is currently regarded as the fourth modality of treating cancer besides surgery, radiotherapy, and

chemotherapy. Immunotherapy is different from ordinary treatment methods where cancer cell is directly attacked and destroyed but in this method the body immune system is strengthened to fight cancer. This approach is advantageous for prospective metastatic disease given the ability to deliver a drug to multiple areas throughout the body. Also, immunotherapies are more effective in developing tumour specific immune response having relatively less side effects than conventional treatments.

Immunotherapy has provided better survival in some cancers including advanced melanoma, non-small cell lung carcinoma and some leukemias and lymphomas to mention but a few, in some instances, even leading to remission or cure, something which cannot be said of traditional chemotherapy. But treatment using immunotherapy is not fully successful; for instance, checkpoint inhibitors that have an average efficacy of approximately 12% for numerous types of cancer. It is important to mention that there are some inherent and external factors that affect immunotherapy's effectiveness, such as tumour immunogenicity and tumor microenvironment, as well as genetic and immunological features of patients. Most tumors possess the ability to suppress the immune system's ability to attack the tumor through such measures such as up-regulating negative immune checkpoints, recruiting regulatory T cells and placing hurdles towards immune system cells. Malignant tissues, especially, solid tumors, are known to possess niches within them due to peculiar architecture and physiology including improper vasculature and dense extracellular matrix that hinders the access of immune cells and drugs. Also, it becomes a big problem since cancer cells often evolve and produce a phenomenon known as acquired resistance to effective treatments. However, immunotherapy is associated with immune intolerance with severe side effects involving organs.

This review has been undertaken with a view of giving the current and potential advancement in the field of cancer immunotherapy and a general outlook at the new approaches to cancer treatment. It will discuss the biology of some immunotherapeutic approaches such as, immune checkpoint inhibitors, adoptive cell therapies, including CAR T-cells and TIL, cancer vaccines, ADC and Oncolytic viruses. Emphasis will be made to methods for managing immunotherapy resistance, optimising combined therapies and developing new treatment modalities for the patients.

For enhanced understanding, a review of the present paper will also explore how novel biomarkers including PD-L1, TMB, MSI and ctDNA are used in selection of patients and prognosis. Other topics of further discussion will be the topic and Molecular Profiling, Spatial Omics and AI in personalized therapy.

Some of the issues in implementation include managing immune-related toxicities, evaluation of responses, and expensive treatment regimens in the advanced level. Concerning immunotherapy's limitations, the global availability concerns as well as possible ways of making this treatment cheaper and widely available will be also discussed.

Last, the review will discuss potentials in improving patient benefits through more advanced immunotherapy such as neoadjuvant immunotherapy, approaches involving the components of intrinsic immune system, combination of immunotherapy and other treatments, newer form of antibodies, neoantigens vaccines and bispecific antibody construct.

This kind of analysis should increase the general knowledge of immunotherapy in cancer treatment, demonstrate areas that still need improvement, and discuss the role of the immune system in cancer.

FUNDAMENTALS OF CANCER IMMUNOTHERAPY

The relationship between immune cells and tumors underpins immunotherapy, which aims to enhance immune responses against cancer. Tumors express unique antigens—tumor-associated or tumor-specific—that the immune system can recognize. According to the immune surveillance theory, the body routinely identifies and eliminates emerging cancer cells using various immune cells like dendritic cells, macrophages, and T lymphocytes. The cancer-immunity cycle explains how antigen-presenting cells activate T cells, which then attack tumor cells. However, tumors develop mechanisms to evade immune detection, such as reducing MHC molecule expression, altering antigens, and creating immunosuppressive environments. They manipulate regulatory immune cells and secrete inhibitory cytokines like TGF-β and IL-10. Tumors also express checkpoint molecules like PD-L1 to inhibit T cell activation. Immunotherapy seeks to counter these evasion strategies by restoring or boosting immune activity. Notably, immune checkpoint inhibitors have demonstrated success by reactivating immune responses, offering promising outcomes across multiple cancers, including treating metastases and preventing recurrence.

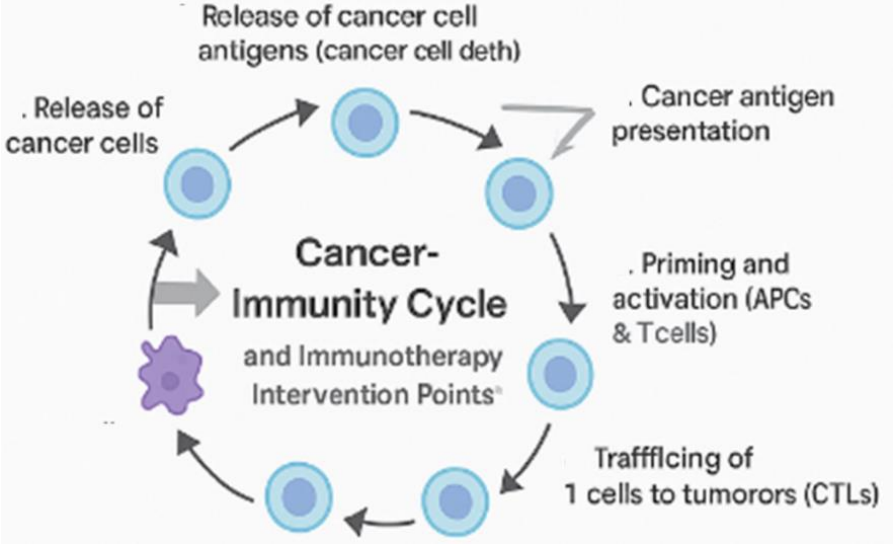

Figure 1: The Cancer-Immunity Cycle and Immunotherapy Intervention Points

Cancer immunotherapy can be employed at any stage of the cancer immunity cycle. Checkpoint inhibitors work on the T cells and increase their efficacy while avoiding the T cell exhaustion through the employment of proteins and receptors such as PD-1/PD-L1 and CTLA-4. Cancer vaccines enhance antigen presentation and T cell activation and proliferation, adoptive T cell therapy involves the transfer of preactivated or engineered T cells to the patient's body. Cytokines can play different roles in different phases of the cycle and can affect factors such as the dendritic cells ability to activate T cells. Also, oncolytic viruses and some chemotherapy procedures promoted immunogenic cell death, thus increasing antigen leakage.

Specifically, a new perspective of specifying an activity and a deficiency of the cancer-immunity cycle is provided which offers a rational approach to formulating a definite therapeutic strategy for cancer immunotherapy.

CHECKPOINT INHIBITOR THERAPIES

Immune checkpoint inhibitors are a novel therapy for cancer that blocks cancer cell signalling that helps them avoid destruction by immune system. At the moment, two primary checkpoint restraints are ventured into clinical practice; these are the PD-1/PD-L1 and CTLA-4.

PD-1 is an inhibitory receptor expressed on the activated T cells that elaborates its action through binding to its ligands PD-L1 or PD -L 2. Tumours can increase the expression of PD-L1 as a part of immune resistance mechanism to the therapies given to them. In this way, checkpoint inhibitors eliminate immunosuppressive signals and allow T cell to regain functionality in the tumour microenvironment. This refers to their ability to proliferate, produce cytokines and their inherent ability to kill tumour cells.

Cytotoxic T-Lymphocyte, Activated or CTLA-4 works differently since it binds to CD 80/86 on Antigen presenting cell it behaves as a negative regulator of immune response by competing with CD 28 molecule. The failure to bind to B7 molecules prevents this competition thereby allowing the CD28 co-stimulation and proper sensitisation and activation of the T cells. In contrast to CTLA-4 that functions predominantly in the lymphoid organs during the initial activation of the first T cell, PD-1 controls ongoing immune response in peripheral tissues, and thus, these two pathways can be targeted concomitantly.

Some of the checkpoint inhibitors are available as follows; The Food and Drug Administration has approved several checkpoint inhibitors in various indications of cancer. They are the PD-1 inhibitors Keytruda and Opdivo and the PD-L1 inhibitors Tecentriq, Imfinzi, and Bavencio. Ctla-4 is only represented by the ipilimumab (Yervoy) although there are other molecules in pipeline. Recent entry is two-in-one check point inhibitors such as nivolumab and relatlimab where the latter is known as Opdualag. The approval of pembrolizumab for renewed tissue-agnostic cancer type, namely MSI-H or dMMR biomarker cancers was a big step forward because this was the first time a cancer cure has been approved based on biomarkers and not the tissue of origin.

The effectiveness and their longevity of checkpoint inhibitors depend on the type of tumor and the patient's characteristics. The response rates vary between about 15 to 20 percent in all patients to over 60 percent in biomarker selected population and /or some specific diseases such as Hodgkin's Lymphoma. Combinations with chemotherapy agents like pembrolizumab and durvalumab have proved useful in the improvement of treatment. Checkpoint inhibitor therapy is characterised by durable response that can last for years despite the short duration of treatment and this is something that cannot be said about conventional therapies. A recent data on trial on using ipilimumab with nivolumab we see that the survival rate in the advanced melanoma rises to more than fifty five percent after five years as compared to less than 10% with historical controls before immunotherapy came into the picture.

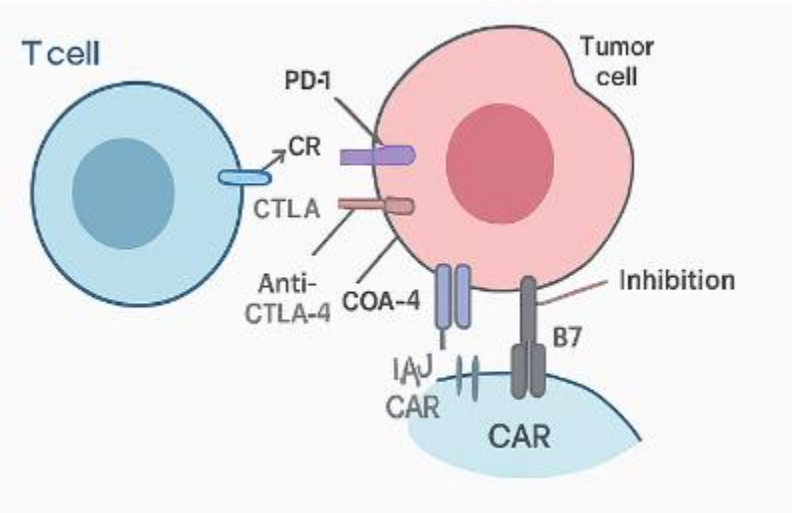

Figure 2: Mechanism of Action of Major Checkpoint Inhibitors

\Nonetheless, primary and acquired resistance still represent a major problem in this regard. Despite the selection biomarkers being used in PD-L1 expression, tumor mutational burden, and immune-related gene expression, none of them are ideal. Other than PD-1/PD-L1 and CTLA-4, newer checkpoint inhibitors include LAG-3 (Lymphocyte Activation Gene-3), TIM-3 (T-cell Immunoglobulin and Mucin-domain containing-3), TIGIT (T cell immunoreceptor with Ig and ITIM domains), B7-H3. These are referred, as "second-generation" immune checkpoints, control T cell activity through various mechanisms. When used in conjunction with other checkpoint inhibitors, these drugs have been identified to bring about promising treatments in patients with refractory disease. Another unique process involves dual-action antibodies to two checks in different receptors potentially being better than distinct combinations.

ADOPTIVE CELL THERAPIES

Adoptive cell therapy can be referred to as personalized immunotherapy that entails the use of patients' cells that may be grown and sometimes genetically modified to target cancer cells. TIL therapy is one of the oldest forms of ACT that has been used in cancer treatment, where T-cells are taken directly from tumour tissues, expanded outside the body, and then returned to the patient after the lymphodepletion. There has been enhancement in the choice of TILs for the following reasons: While the approaches of TIL selection have been enhanced and helps identifying the T cell population, most reactive to tumours. The experimental treatment of TILs with pembrolizumab has been proven quite effective in treating melanoma and other solid tumours where this checkpoint inhibitor allowed the transferred cells not to become exhausted and improve their activity within the tumour microev-environment.

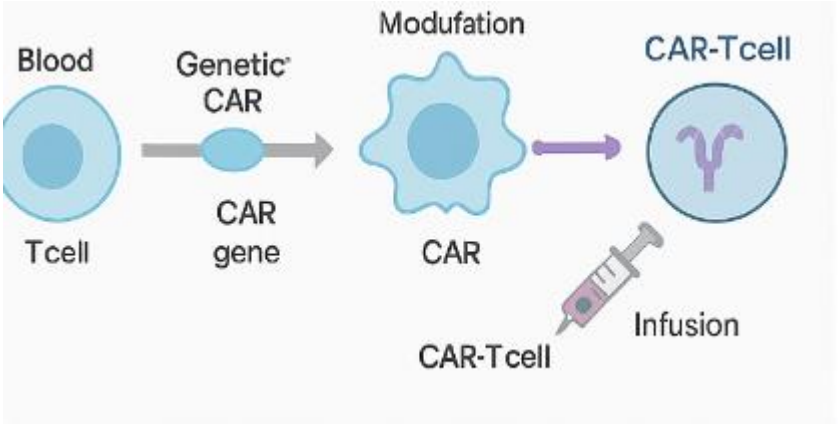

Figure 3.1: Mechanism of CAR-T Cell Therapy

CAR T-cell therapy has revolutionized treatment options for hematologic malignancies since its approval by the FDA. It involves the ability to change the T cells to have artificial receptors that can identify tumour antigens with unique features

that do not require MHC presentation. CAR-T cells directed to CD19 show high efficacy in B cell malignancies, specifically relapsed/refractory B-ALL that demonstrated complete remission over 80% and some Subgroup of B-NHLs 50-70%. Nevertheless, challenges exist as they include antigen escape, transient persistence, and severe toxicities that include CRS and neurotoxicity. Applying CAR-T therapy to solid tumours has been more difficult given factors like differential antigens in the tumour cells, immunosuppressive tumour microenvironment, and the size of tumours which gives physical barriers to the T-cells. These challenges have been managing to be addressed by new controls such as, the multi-Specific CARs, Boolean logic gates that need more than one Antigen to trigger them and the armoured CARs that release cytokines that stimulate the immune system.

Allogeneic cell therapies have a set of advantages over the autologous methodologies, regarding better availability, standardization, and faster manufacturing. These therapies involve the use of genetically compatible BMSC from other persons donor source that has been genetically manipulated to reduce rejection and GvHD. The current strategies include the deliberate disruption of TCR endogenous expression and HLA molecules, in addition to incorporation of suicide genes. Some issues concerning the existence, effectiveness, and safety of allogeneic therapies are still and other problems related to the specifics of allogeneic strategies are still challenging.

Table 1 comparing different adoptive cell therapy approaches:

Aspect	TIL Therapy	CAR-T Cell Therapy	Allogeneic Cell Therapy
Cell Source	Patient's tumor	Patient's blood	Healthy donor
Antigen Recognition	Natural T cell receptor	Engineered chimeric antigen receptor	Engineered receptor (e.g., CAR)
Manufacturing Time	4-8 weeks	2-4 weeks	Off-the-shelf (minimal wait)
Tumor Types	Primarily solid tumors	Primarily hematologic malignancies	Both solid and hematologic (in development)
Antigen Specificity	Polyclonal (multiple antigens)	Typically single antigen	Single or multiple antigens
MHC Dependence	Yes	No	No (for CAR-based approaches)
Persistence	Variable	Can be long-lasting	Generally shorter than autologous
Main Advantages	Broad antigen coverage, potential for solid tumors	Highly effective in B-cell malignancies, engineered for enhanced function	Immediate availability, consistent quality
Main Challenges	Limited by tumor sample quality, long production time	Antigen escape, toxicities (CRS, neurotoxicity)	Potential for rejection, limited persistence
FDA Approvals	Lifileucel (pending for melanoma)	Multiple for B-cell malignancies (e.g., Kymriah, Yescarta)	None yet (as of 2024)

CANCER VACCINES AND EMERGING IMMUNOTHERAPIES: INNOVATIONS IN TARGETED CANCER TREATMENT

Immunotherapy at the current moment can be considered as one of the most effective and promising fields of anti-tumor vaccines where the primary goal is the improvement of the immune system, mostly from the perspective of its ability to recognize tumour cells. Tivantinib is one of the therapeutic cancer vaccines; this is in contrast with preventive vaccines which are used in the prevention of infectious diseases as these are used in treatment of cancers by provoking the corresponding immunities. These vaccines can be of distinct form and in treatment, they can be applied in different methods based on the development of the bacteria that the vaccine targets.

In general, there are cell-based vaccines or the dendritic cell (DC) vaccines that are special forms of cancer vaccines. These are the generation of dendritic cells from a part of the patient’s tissue and then loading it with TAAs followed by reinfusing them in an attempt to activate dT against the tumour. Among them the most widely known is known as Provenge (sipuleucel-

T) for the treatment of prostate cancer. DC vaccines are effective especially for the individual treatments; one is able to demonstrate quite many patient-specific Antigen and neoantigens derived from tumour mutations.

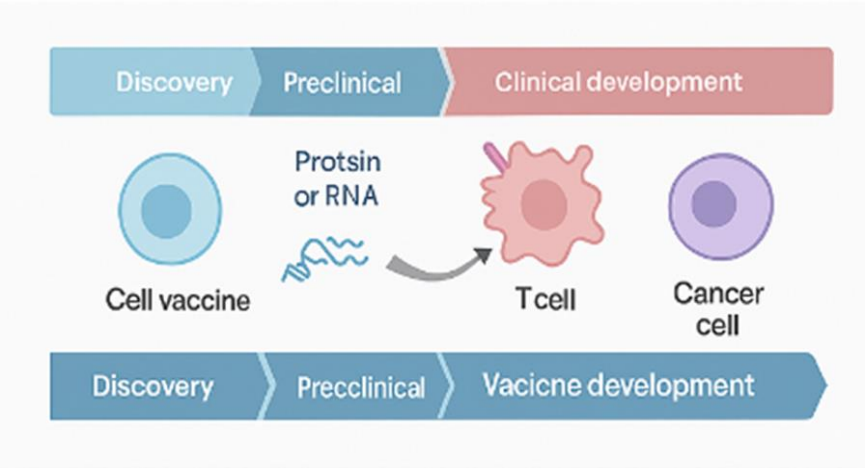

Figure 3.2: Cancer Vaccine Development Pipeline and Mechanisms

Another form of vaccines is the protein or peptide in which the vaccine includes proteins or oligopeptides from cancer cells. These are at times mixed with adjuvants, which enhance the antigenicity of the immunity and the overall response as well. That is the reason they are currently being researched in different types of cancer including breast, lung and melanoma, easily scalable and possess relatively low toxicity. Nonetheless, to exert a strong effect they need to be strengthened through the use of agents that stimulate the immune system.

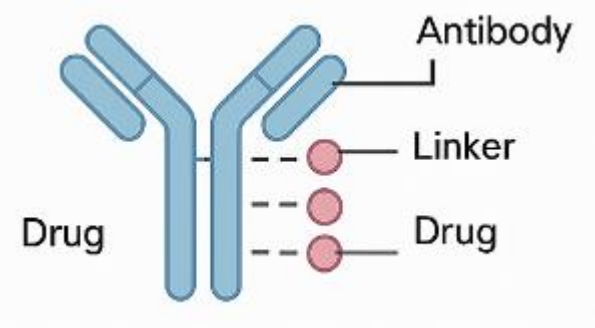

Figure 4: Structure and Mechanism of ADCs in Cancer Treatment

The relatively recent development and upset potency of COVID-19 developed mRNA vaccines have been getting attention in the development of cancer vaccines. These vaccines introduce synthetic mRNA that codes for tumor antigens into the host cells where they make the antigens inside the body, thereby eliciting a strong immune response. The major benefits of mRNA vaccines are that they are flexible and easy to develop and can possibly be tailored to specific patients. Cancer trials involving melanoma, lung and pancreatic cancer are in process, and it has been observed that the immune activation is promising.

In a like manner, DNA vaccines introduce plasmids containing genes that codes for tumor antigens, which are then produced by the host cells. To be more specific, although DNA vaccines share many similarities to mRNA vaccines in terms of mechanism of action, they are harder to deliver efficiently and target the nucleus. Electroporation and nanoparticle carriers are used as a new generation carriers to overcome clinical inefficiency arising from promising preclinical studies.

The most personalized are neoantigen vaccines which target cancer-specific mutations not found in the rest of the body tissue. These mutations form new peptides (neoantigens) in the human body which are considered as foreign by the immune system. Technological progress in sequencing technologies and computational immunology has enabled the fast and efficient classification of neoantigens to be prioritized for vaccination attempts. Such vaccines are beneficial in the minimal residual disease or relapse situation and the cancers with high mutation rates.

To boost its performance, cancer vaccines are currently combined with checkpoint inhibitors or other immunomodulatory agents. Checkpoint blockade when used to reverse immunosuppression can enhance the T cell responses elicited by vaccines. This prompted the use of neoantigen vaccines together with PD-1 and CTLA-4 inhibitors where it has been observed increased T- cell infiltration and tumour shrinkage.

Besides vaccines, Antibody-Drug Conjugates (ADC) is one of the most selective cancer treatments. ADCs are designed as monoclonal antibodies in which specific cytotoxic agents are attached. The antibody part specifically targets antigens that are overexpressed on cancer cells and directs the toxic compound to the source of the disease without detrimentally affecting the surrounding tissues. After internalization, the linker is cleaved, or the antibody is degraded, and the cancer cell is killed by the drug.

A critical issue in ADC design is the choice of targets which should be overexpressed on tumor cells and by the same token, not present or only minimally expressed on healthy cells in order to avoid toxicity to normal cells. Technological progress in proteomics and genomics has provided an increased pool of realistic targets. However, advances in linker chemistry have enhanced the stability of a linker position to control the output of the subsequent drug release. For example, cleavable linkers can be sensitive to intracellular environment (pH, enzymes etc.), while non-cleavable linkers are degraded by lysosomes.

Another advantage of new ADCs is the use of new payloads, such as toxins that are not affected by MDRs. The advances have shifted from universal conjugation approaches that cause variability and poor ADC products' performances in terms of pharmacokinetics and fewer side effects. Currently, trastuzumab emtansine (TDM-1) and enfortumab vedotin are other clinically exploited ADCs that have shown improvement in breast and bladder cancer patients.

Table 2: Major Cytokines in Cancer Immunotherapy and Their Functions

Cytokine	Primary Cellular Targets	Key Functions in Cancer Immunotherapy	Clinical Applications
IL-2	T cells, NK cells	T cell proliferation, NK cell activation	Approved for metastatic melanoma and renal cell carcinoma
IL-15	NK cells, CD8+ T cells	NK cell activation and persistence, memory T cell support	Multiple clinical trials in solid and hematologic malignancies
IFN-α	Multiple immune cells, tumor cells	Enhanced antigen presentation, anti-proliferative effects on tumor cells	Approved for melanoma, renal cell carcinoma, and certain hematologic malignancies
IL-12	T cells, NK cells	Th1 polarization, enhanced cytotoxicity	Early-phase trials in multiple cancer types
GM-CSF	Dendritic cells, macrophages	Dendritic cell maturation, enhanced antigen presentation	Adjuvant in cancer vaccines, component of T-VEC
TNF-α	Tumor vasculature, immune cells	Vascular disruption, direct tumor cytotoxicity	Limited use due to systemic toxicity
IL-10	Multiple immune cells	Immunoregulatory functions, potential anti-tumor effects	Early investigation in combination therapies
TGF-β inhibitors	Multiple immune and stromal cells	Reversal of immunosuppression, enhanced T cell function	Multiple clinical trials in combination with other immunotherapies

Cytokine therapies are anotherstrategy of immune-based treatments, which work through altering cytokines for the purpose of boosting the efficacy against tumor cells. Among them, IL-15 has been promoted to be explored in depth because it can selectively activate the NK cells and memory CD8+ T cells, while it does not activate the T reg cells that inhibit anti-tumor immunity. This has therapeutic advantage over IL-2 since it has higher toxicity levels when used for other indications apart from activation.

Other variants and modified cytokines such as recombinant IL-2 and IL-12 fusion proteins are also under development to have better targeting and minimal systemic side effects. These cytokines are usually co-administered with checkpoint inhibitors to enhance their activity. Such combinations appear to be effective in overcoming resistance to single agents as they stimulate various immune relations at a time.

Other strategies include immune-cell callers, including bispecific antibodies, which also control immune reactions towards the tumor. These agents can engage both with a tumor antigen and with T cell receptor, CD3 participating and bringing immune cells in proximity to tumor cells for killing. This way, ICE are not restricted by the ability of tumor to present antigens through MHC as some tumor cells have defective antigen presentation system.

Recent developments of trispecific and tetraspecific antibodies confer a hope that it will be possible to address several targets at the same time–which may increase specificities, minimize mutation, and improve activity in micro-heterogenous tumor environment. Specific examples of clinical candidates include blinatumomab, an FDA-approved for B-cell acute lymphoblastic leukemia, which has proved the efficacy of this modality, especially in hematologic cancer.

Lastly, oncolytic virus therapies are based on the concepts of virology and oncology with a viral base therapy. It is a type of radical treatment that employs; genetically engineered cells that are selective for cancer cells and cause cancer cell destruction. Apart from directly eliminating malignant cells they liberate tumor specific antigens and stimulate the systemic immunity. Talimogene laherparepvec (T-VEC), a HSV encoding GM-CSF, is used for the treatment of advanced melanoma and show anticancer effect in both direct viral cytolysis and immunomodulation.

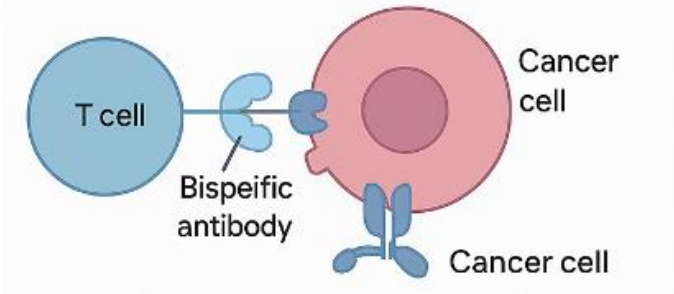

Figure 5: Mechanism of Action of Immune Cell Engagers

Transducing oncolytic viruses with checkpoint inhibitors when given in combination can increase immune infiltration past tumor induced immunosuppression. Live attenuated vaccinia virus, self-complementary adenoviruses of group C, and reovirus are currently the most extensively explored in cancer trials; more trials are expected to involve the application of these therapies in treating a variety of solid tumors. New viral vectors and methods of their application, such as intravenous injection and tissue-specific enhancer sequences, are also being designed.

Table 3: Oncolytic Viruses in Clinical Development

Virus	Genetic Modifications	Mechanism of Action	Cancer Types	Development Stage
T-VEC (HSV-1)	Deletion of ICP34.5 and ICP47, insertion of GM-CSF	Selective replication, immune stimulation	Melanoma	FDA approved
ONCOS-102 (Adenovirus)	GM-CSF expression	Immunogenic cell death, DC activation	Multiple solid tumors	Phase I/II
Pexa-Vec (Vaccinia)	GM-CSF expression, TK deletion	Oncolysis, antivascular effects	Hepatocellular carcinoma	Phase III
Reolysin (Reovirus)	Naturally selective for RAS-transformed cells	Preferential replication in cancer cells	Multiple solid tumors	Phase II/III
CG0070 (Adenovirus)	GM-CSF expression, E2F-1 promoter	Selective replication in Rb-defective cells	Bladder cancer	Phase III
DNX-2401 (Adenovirus)	Deletion in E1A, RGD-4C fiber modification	Enhanced infectivity of cancer cells	Glioblastoma	Phase II
RP1 (HSV-1)	Deletion of ICP34.5 and ICP47, expression of GALV-GP R- and GM-CSF	Enhanced spread, immune stimulation	Multiple solid tumors	Phase II
Vaxinia (Vaccinia)	CD19 expression	Enhanced T cell engagement	Multiple solid tumors	Phase I

ADVANCED CONCEPTS IN CANCER IMMUNOTHERAPY: FROM BIOMARKERS TO FUTURE DIRECTIONS

Both biomarker identification and the choice of patients suitable for immunotherapy are considered significant factors that augment immunotherapy effectiveness. PD-L1 IHC was the first immune checkpoint inhibitor biomarker as well as the first ever approved by the FDA. However, its application is rather restricted by some aspects such as tumor-specific heterogeneity, inter-phase changes, andensch diffusion across experiments. Primary, results indicate that responses have been achieved in patients with negative expression of PD-L1 and more than half of the patients with PD-L1 positive score did not respond to treatment. This has been attributed to the presence of the peripheral environment in the tumor tissue and the various isoforms of PD-L1 that is present the membrane bound, cytoplasmic and the secreted forms. While intracellular PD-L1 may translocate to the membrane as well as being secreted and governing the effects in the PD-L1 negative group, the membrane localized PD-L1 may internalize under antibody stress thus putting into account to the low response rates even in the PD-L1 positive patients.

MSI status is one of the significant predictive biomarkers that have grown more significant especially due to the tissue-agnostic approval of pembrolizumab in treating MSI-H or dMMR cancers. Labeled as MSI-H, the malignant colon tumors have a mutated or otherwise altered mismatch repair gene and protein inactivation capabilities which permits the cells to correct DNA mismatch repair mistakes rarely. This leads to higher mutation frequency and neoantigen generation; thus such tumors are sensitive to immune checkpoint therapy. Whereas, MSS colon cancers have normal levels of mismatch repair gene & protein synthesis, and therefore are capable of 'fixing' any impairment of DNA mismatch repair. MSS colorectal cancers have a higher risk of recurrence, these factors may affect adjuvant treatments.

TMB, which is the amount of mutations in tumour cells, or rather the density of mutations per 1 million nucleotides, has recently become famous as the biomarker for immunotherapy response. Higher TMB provides greater number of neoantigens to be recognized by T-cells and is associated with improved immune checkpoint inhibitors. This has been well illustrated by works in dual immunotherapy wherein immunotherapy has been proven to provide better overall survival and progression-free survival rates compared to chemotherapy in high TMB patients. Thus, TMB remains an imperfect response biomarker, and a comprehensive predictor that would include MHC and T cell receptor repertoire range factors should be used in order to better select patients for treatment.

New spatial technologies and AI applications that are currently on the horizon continue to transform biomarker identification process and patients' selction. concerning biomarkers, AI algorisms are able to process genomical, proteomic, and transcriptomic data in order to find possible immune-related targets for cancer therapy. Specifically, exploring tumor and immunity plus genetic mutation information, AI, can also identify the potential target protein or biomarker for ICI, CAR T cell treatment and cancer vaccines. Moreover, it is possible to apply AI in estimating how a concrete patient would react towards certain immunotherapies, guiding special treatment plans and lessening trials and errors. These technologies are also help in identification of biomarkers by mining cancer genomes and clinical trial data quickly and efficiently.

The ctDNA is rapidly growing as a less-insidious dynamic biomarker in tracking the response to immunotherapy. It has been demonstrated that plasma ctDNA is associated with the other markers of the tumor response to systemic therapy, such as CEA levels and imaging. In particular, ctDNA allows for tumor response prediction also for the CRC tumors with initial absence of CEA. Such changes or clearing of ctDNA have implications with radiographic tumor responses while elevations in plasma ctDNA levels have implications with the radiographic tumor progression. This minimally invasive tool seems to be useful in identifying hyperprogressors or distinguishing between the true progression group and pseudoprogression in a setting of immunotherapy regimens.

The idea of combination strategies in immunotherapy derives from understanding that it is possible to target various phases of the cancer-immunity cycle to overcome immune resistance. Although it has been demonstrated in a number of cancer types, therapy failure can be primary or acquired and up to two thirds of patients, making the development of other more effective treatment regimens important. Conjugation strategies try to win the best result by combining different targets with enhanced and long-term efficiency regarding anti-tumor immunity.

This make it possible to harness the immunomodulatory effects of such conventional treatments like cytotoxic chemotherapy, radiation therapy and targeted therapy over their direct cell kill cancer activities. Chemotherapy drugs and ionizing radiation can cause immunogenic cell death and will thereby release tumor associated antigens and danger signals that may boost immune reaction. Targeted therapies can alter the tumor microenvironment in a manner conducive to immune cells . Such combinations have demonstrated efficacy in different cancer forms some of which have been approved for use in combination therapy.

Opportunistic combinations of both PD-1/PD-L1 and CTLA-4 inhibitors have shown a promising clinical outcome. Immunotherapy when combined appears to be more effective when it comes to mean overall survival as well as the progression-free survival regardless of the level of PD-L1 expression. This is specifically seen in the subgroup of patients with high TMB and or Sq cell histology. However, the combination of the immune checkpoint inhibitors is more effective in terms of OS and ORR as a second-line treatment versus single agent with PFS benefit only in patients with < 25% PD-L1 expression. The disadvantage is the higher risk of treatment-emergent adverse events with compared to mono therapy.

Immunotherapy is another brand of an anticancer treatment that is being developed in various combination with other therapies to improve its efficiency. These are combinations with anti-angiogenic agents, PARPi and other targeted agents that can alter the tumor microenvironment and improve tumor immunogenicity. This means that the outcome of these combinations will only hinge on employing strategies as supported by reasonable preclinical research and enhanced knowledge of the mechanisms of resistance to these drugs.

Primary and acquired resistance are the main factors of therapeutic failure in immunotherapy approaches. Primary or de novo resistance refers to a situation in which a cancer cannot be treated by an immunotherapeutic approach at all. HPDs have been considered to be a primarily resistant type with proficiencies that belong to HPD comprising of MDM2/4 gene amplification, alteration of chromosome 11 region 13 and the EGFR gene. Some changes related to tumor microenvironment, for example, some types of macrophages may also contribute to HPD. Thus, acquired resistance is a clinical situation where the tumors initially undergo significant regressions, but progress and/or stop responding to the immunotherapy. It is a well-known fact that 30-35% of patients with metastatic melanoma experience a disease relapse after initial treatment, making this problem relevant from the clinical perspective.

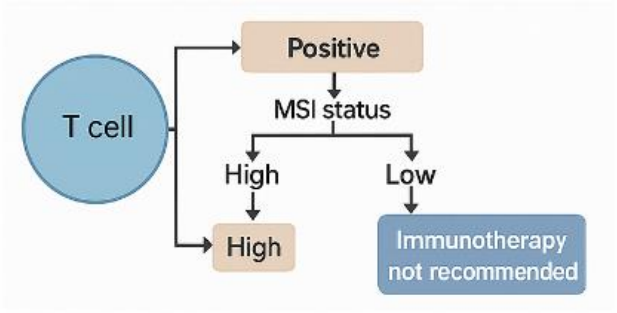

Figure 6: Decision Tree for Immunotherapy Selection Based on Biomarkers

Morbidity and Mortality associated with irAEs is however a challenge that is peculiar to immunotherapy. These autoimmune diseases may involve any organ in the body, and their natural histories differ from other autoimmune diseases that exist in the general population. irAEs may arise at any moment in treatment, but are most frequent within the first 3 months of treatment or even years after all treatment has ended. Standard treatment for most immune-related adverse events involves glucocorticoids and most of the symptoms subside within several weeks of treatment with glucocorticoids. However, some of the symptoms persist and the patient may need a lifetime treatment such as hormone replacement therapy or immunosuppressive agents.

Tumor microenvironment constrains such as hyaluronic acid, collagen, and fibroblast structures hinder the penetrations of drug molecules and immune cells to the tumors making the therapeutic remedies to be less effective. Moreover, Tregs, MDSC and TAMs residing within the tumor can overcome tumor specific immunity and dampen the immune response towards tumor cells. For progress to be made in immunotherapy, all these barriers should be eliminated.

New approaches for modulating the innate immunity in cancer therapy have been developed as potential means of boosting the anti-tumour immune response. These are Toll like receptors, cGAS/STING DNA sensing pathway, NOD like receptors and Receptors for Retinoic acid inducible gene-I like receptors. Further, to optimize the anti-tumor immunity there are attempts to therapeutically target specific innate immune system component like macrophage and natural killer cells.

The immunomodulatory therapy to target complement system which is part of innate immunity is seen as a promising avenue in the treatment of cancer today. Despite the shortcomings of the knowledge on the complement activation in cancer, available preclinical and clinical information suggest that the process takes place due to the engagement of the classical pathway. Like any other signaling systems, complement activation can lead to the either pro-survival or pro-apoptotic cascades of the tumor cells; as such the complement pathway can be exploited in the treatment of cancer. Complement regulation is intricate both in terms of general regulation and localized/intracellular complement activation thus, it could be regarded as beneficial to research approaches that could selectively target pro-tumorigenic outcomes while promoting the anti-tumorigenic ones.

Neoadjuvant immunotherapy involves using immunotherapy before surgery to eliminate the micrometastases since both the tumor and its micro-environment are intact at this stage. This approach offers a chance to initiate antitumor immune response when there is a possibility of low variation of tumor antigens. Hence, immune checkpoint blockade in neoadjuvant melanoma treatment have shown promising results with patients developing pathologic responses having good relapse-free survival. Such strategies are also being implemented in other cancers, with similar success.

Table 4: Synergistic Immunotherapy Combinations and Their Mechanisms

Combination Type	Examples	Mechanism of Synergy	Clinical Benefits
Dual Checkpoint Inhibition	Anti-PD-1/PD-L1 + Anti-CTLA-4	Complementary targeting of different immune checkpoints; CTLA-4 blockade enhances T cell priming while PD-1 blockade reinvigorates exhausted T cells	Improved OS and PFS across PD-L1 expression levels; particularly effective in high TMB and squamous histology
Immunotherapy + Chemotherapy	Pembrolizumab + Platinum/Pemetrexed	Chemotherapy induces immunogenic cell death, releases tumor antigens, and depletes immunosuppressive cells	Improved survival in multiple cancer types; standard of care in NSCLC
Immunotherapy + Radiotherapy	Pembrolizumab + SBRT	Radiation induces immunogenic cell death and abscopal effects; enhances antigen presentation and T cell priming	Improved local and distant tumor control; potential to convert "cold" tumors to "hot"
Immunotherapy + Targeted Therapy	Pembrolizumab + Lenvatinib	Targeted therapy modulates tumor microenvironment; reduces VEGF-mediated immunosuppression	Improved response rates in multiple tumor types; addresses resistance mechanisms
Immunotherapy + Oncolytic Viruses	T-VEC + Pembrolizumab	Oncolytic viruses induce immunogenic cell death and enhance T cell infiltration	Improved response rates in melanoma; potential to enhance systemic immunity
Immunotherapy + Cancer Vaccines	Neoantigen vaccines + Checkpoint inhibitors	Vaccines prime T cell responses; checkpoint inhibitors prevent T cell exhaustion	Enhanced T cell responses; potential for durable responses

The targeted immunotherapy that incorporates artificial intelligence and biomarkers of the patients might be considered the primary thing in the future of cancer immunotherapy. A prospective use of AI is to facilitate identification of combination therapies, interactions between all the drugs and identification of synergistic drug combinations which yields maximal therapeutic benefit with minimal toxicity. Also, AI is being used in CAR-T cell therapies by enhancing the T cell receptor engineering, estimating the efficiency of T cells in regard to specific cancer cells, and minimizing side consequences. They include the favorable approaches that seek to target cancer immunotherapy strategies on the basis of a patient-specific tumor and immune signature.

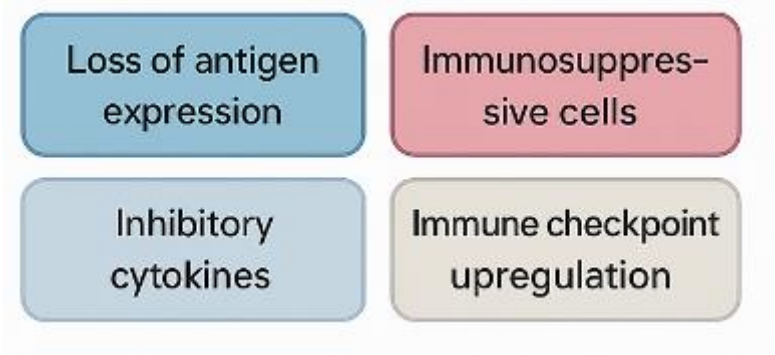

Figure 7: Major Resistance Mechanisms to Immunotherapy

Instead of using only PD-L1 as a selection criterion, current strategies have incorporated several predictors that include TMB, MSI, gene expression profiles, and immune infiltration. , the ability to define objective criteria to identify patients who may benefit from immunotherapy has proven to be difficult but the efforts are being made to incorporate numerous biomarkers along with enhanced analytics.

Toxicity has its management involving a team of physicians, with identification of the presence of toxicity and its treatment as soon as possible being vital. There are some issues regarding the response assessment in immunotherapy, including the

pseudoprogression and hyperprogression factors. Acceptable quality of life is now considered as the essential parameter, which indirectly indicates the effectiveness of immunotherapy owing to the patients' higher quality of life compared to treatments without immunotherapy.

Table 5: Emerging Immunotherapy Approaches in Early Clinical Development

Approach	Target/Mechanism	Potential Applications	Development Stage
STING Agonists	cGAS/STING pathway activation	"Cold" tumors with low T cell infiltration	Phase I/II
TLR Agonists	TLR7/8/9 activation	Enhancement of antigen presentation	Phase I/II
NK Cell Engagers	CD16 x tumor antigen bispecific antibodies	Tumors with low MHC expression	Phase I
Macrophage Reprogramming	CD47-SIRPα blockade; CSF1R inhibition	Tumors with high macrophage infiltration	Phase I/II
Metabolic Modulators	IDO/TDO inhibitors; Adenosine pathway inhibitors	Tumors with immunosuppressive metabolism	Phase I/II
Microbiome Modulators	Fecal microbiota transplant; Bacterial consortia	Enhancement of immunotherapy response	Phase I
Epigenetic Modifiers	HDAC inhibitors; DNA methyltransferase inhibitors	Enhancement of tumor antigen expression	Phase I/II
Cytokine Therapies	Engineered IL-2, IL-15, IL-12	Enhancement of T cell and NK cell function	Phase I/II
Complement Inhibitors	C3a/C5a receptor antagonists	Reduction of immunosuppressive myeloid cells	Preclinical/Phase I
Neoadjuvant Combinations	Checkpoint inhibitors + chemotherapy pre-surgery	Early-stage cancers with high recurrence risk	Phase II/III

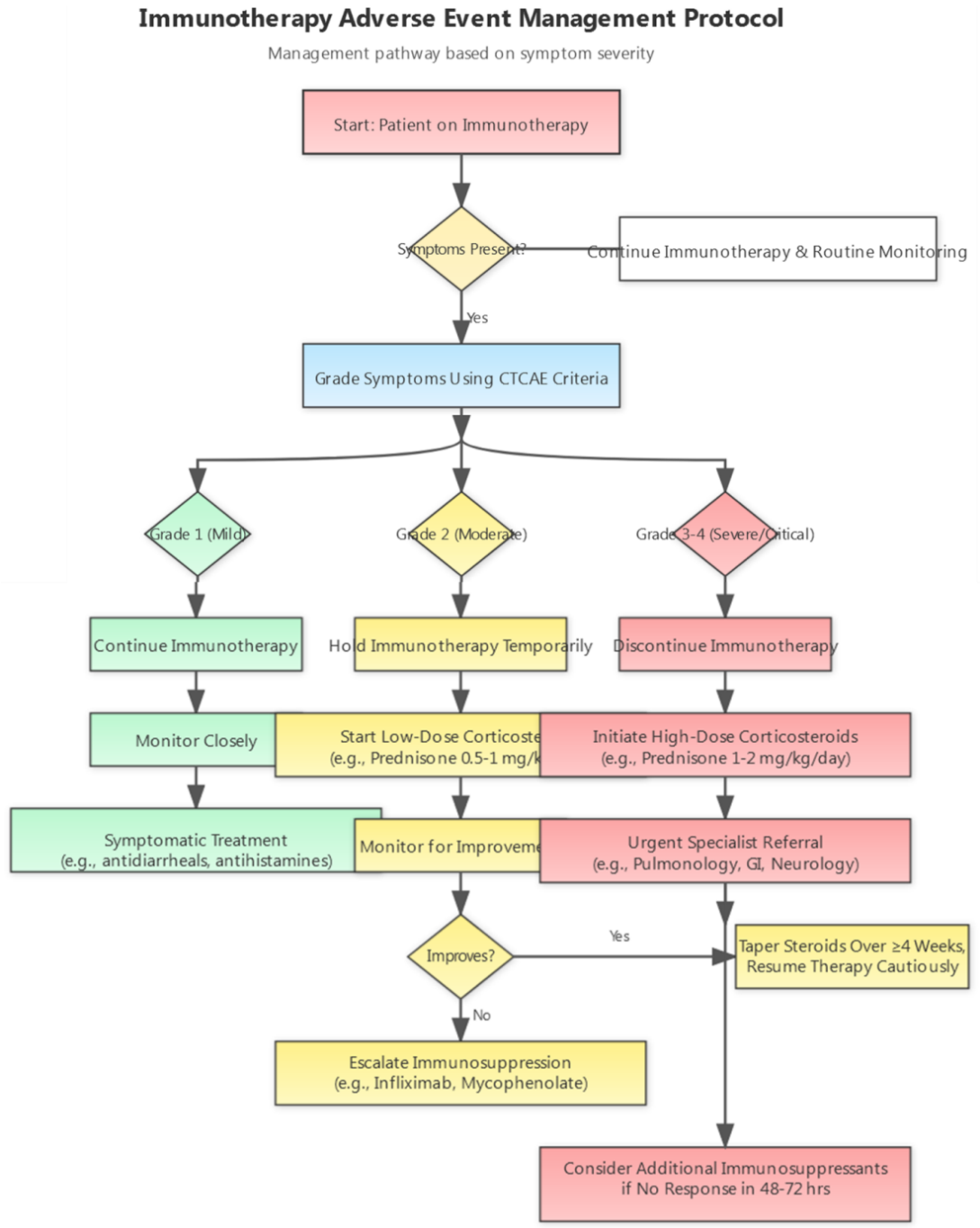

Figure 8: Algorithm for Managing Immune-Related Adverse Events

ECONOMIC AND ACCESSIBILITY CONSIDERATIONS

Cancer immune therapy is a breakthrough in the treatment of cancer with astonishing clinical values; however, it poses significant economic consequences to the healthcare systems globally. This is because innovative but costly treatments are common in these establishments; hence, CEA has turned out to be a vital resource in determining its value. Investigations into Immune Checkpoint Inhibitors: An Economic Complexity In light of the recent findings, it is necessary to determine how Immune Checkpoint Inhibitors impact patients and the economic structure. For example, tislelizumab with platinum and etoposide for extensive-stage SCLC had an ICER of $19,881.48 / QALY from the Chinese perspective and was within China's willingness to pay for $39,855.79. Nevertheless, the economic perspective is different depending on the type of immunotherapy and the type of cancer. When applying durvalumab to the combination with chemotherapy with or without olaparib maintenance therapy in advanced endometrial cancer, the ICERs ranged from 219,601.20 to 584,140.94 per QALY, exceeding the threshold of $ 150,000 per QALY in the United States. Under similar reasoning, the use of pembrolizumab with chemoradiotherapy generated an ICER of $183,400 per QALY which makes it only cost effective if the monthly cost of pembrolizumab is reduced by $16,990 to $9,190; or the duration of the course of treatment was reduced from 24 to 10

months.

Accessibility issues of cancer immunotherapy remain global issues that are a potential threat of significantly deepening the existing gap between HIC and LMICs areas. International Cancer Bank's curve predicted cancer incidence to reach 28.4 million people by 2040, the major increase of which are predicted to occur in LMICs. Still, it must be noted that basic access to these innovative immunotherapies is still largely unavailable to patients in developing countries due to the expensive nature of the treatment. The following are possible reasons for these disparities. There are stains of restriction due to available funding; these LMICs often spend a lesser percentage of the gross domestic product on health more so as compared to the HICs. Constraints on infrastructure also add to the problem, poor facility, lack of skilled professionals, coupled with relatively a poor research angle for immunotherapeutic regimens. There are also regulatory and administrative challenges towards the approval and subsequent use of new immunotherapies in most LMICs. Most worrying is that pharmaceutical companies conduct trials and their marketing strategies for drugs mainly target those countries with reimbursement models and higher income levels hence, they end up creating a cycle of perpetuating the same problem.

Here specific actions that can make cancer immunotherapy more accessible to more patients can be discussed and they are going to involve multiple categories and actors. At the global level, a proposal of including effective immunotherapies on the WHO Model List of Essential Medicines will trigger market competition, generic manufacturing and could help to put down the prices. Government and its policies about health insurance, cost constrain, and financial aid programs are the measures for insured affordability. This means that political processes of price negotiation with countries and legal measures to address the issue of 'evergreening' of patents should assist in that aim. Exempting these pharmaceutical firms from taxes or providing them with direct grants or fast track approvals may encourage them to extend their trials to the LMICs as well as helping to grow research capabilities. There is a need to invest in the development of health care structures in those areas, personnel education, and providing the centers necessary for effective immunotherapy implementation. Governments, non-governmental organizations, healthcare providers, pharmaceutical companies, and patient advocacy groups are instrumental in catering the needs of the patient due to the complexities involved in geographic and financial requirements which cannot be effectively handled by individual organizations. Moreover, it is suggested that there is a need to come up with new payment modalities like outcome-based and installment payment systems to enable health-care systems deal with the challenges posed by high costs of immunotherapy to the patients as they access potentially life-saving treatments.

Table 6: Cost Comparison of Major Immunotherapy Approaches

Immunotherapy Approach	Average Cost (USD)	Cost per QALY (USD)	Accessibility Challenges
Checkpoint Inhibitors	50,000	20,000	High cost, limited to high-income countries
CAR-T Cell Therapy	373,000	183,400	Complex manufacturing, limited availability
Cancer Vaccines	20,000	10,000	Limited efficacy data, high development costs
Oncolytic Virus Therapy	150,000	58,400	Limited approvals, high production costs

2. CONCLUSION

Cancer immunotherapy is one of the promising therapeutic strategies that have evolved in the past decade and are now applied for the treatment of many malignancies. Previously, immune checkpoint inhibitors changed the landscape of treatment for melanoma, non-small cell lung cancer, and several other types of tumors, some patients can survive for years or achieve cure. CAR-T cells in particular have realized unprecedented resonance in specific hematological malignancy diseases, which gives the patient a new life-sustaining treatment option. Antibody-drug conjugates mean that the targeted cytotoxic agents could be delivered to cancer cells with little effect to the rest of the body. Oncolytic viruses are quite a different approach that can directly kill cancer cells and at the same time elicit antitumor immunity. Thus, we have seen one of the most important aspects – the development of the multifaceted relationship between tumours and the immune system, which contributes to more reasonable combinatorial tactics and better selection of patients.

Nonetheless, great progress has been made, but various needs and research gaps have yet to be addressed. The mechanisms of primary and acquired resistance to immunotherapy are known to impact a large group of patients, and research into optimistic approaches to avoid them is needed. Thus, the expansion of immunotherapy advantages to ''cold'' tumors with minimum infiltration of immune cells is yet another big challenge in the field that needs new modalities for the promotion of tumor immunogenicity and elimination of immunosuppressive activity. Thus, biomarker development for selecting the

most appropriate patients and/or predicting their response remains inadequate with markers such as PD-L1 expressivity and TMB being rather imprecise. This is especially in handling immune-related adverse effects that can cause damage to several organs and systems and can sometimes be life threatening. The factors such as cost, which result in relatively expensive immunotherapies, and availability and geographical distribution of immunotherapies remain concerns as not everyone around the world has equal access to such treatment. Furthermore, the aspects like performing the optimal schedule and duration of the treatment, and identifying the methods for the treatment of MRD and new targets apart from the conventional pathways should be explored in future.

The prospects of the cancer immunotherapy are looking bright in the coming years with many trends on the horizon. It will be standard practice to fight cancer based on molecular and immune profiles that will help match a particular patient with the best immunotherapeutic regimen. Targeting strategies that act in different phases of the cancer-immunity cycle for concurrent use may sustain the evolution that can lay aside the existing resistance mechanisms and implement implication for more populace of patients. Immunotherapy designed for the innate immunity component consisting of Natural killer cells, Macrophages, and the complement system, is another area that has not been so explored but has corresponding potential and can be permitted to work in conjunction with T cell therapy. Based on immune conditions, the use of immunotherapy before the surgical resection of the tumor when the tumor microenvironment remains unaltered appears to improve curative efficacy in early-stage diseases. AI biomarkers, and biomarkers for treatment optimization, technological improvement will enhance the biomarker's rate of advancement. New innovations in delivering systems and engineering practices may help in improving safety and effectiveness of cellular therapies while at the same time have simplicity of manufacturing and affordable price. As knowledge in cancer immunology advances as well as as these novel strategies evolves, immuno-oncology is poised to become one of the main pillars of cancer treatment aiming at enhancing the quality of life or patients with cancer around the world

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