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Biological Basis of Cancer

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Abstract: ***Cancer is a multifaceted disease characterized by uncontrolled cell proliferation, genetic mutations, and the ability to evade immune surveillance, making its treatment increasingly challenging. Over the years, significant advances have improved therapeutic strategies to control disease progression and maintain patient well-being. This review examines the biological basis of tumor evolution and explores the principles of two major treatment modalities: chemotherapy and immunotherapy. It discusses how these therapies act against cancer cells, their classifications, clinical applications, and the advantages and limitations of each. The review presents a comparative analysis of chemotherapy and immunotherapy to highlight key differences in their characteristics, effectiveness, and challenges. In addition, the review explores emerging therapeutic approaches developed to bridge gaps between existing treatment modalities, providing more personalized and accurate cancer treatment for every patient. By synthesizing current knowledge from published literature, this paper provides an overview of the ongoing evolution of cancer treatment and emphasizes the importance of continued scientific research in advancing more effective, patient-specific therapeutic strategies.***

Keywords: Cancer treatment, Tumour evolution, Immunotherapy, Chemotherapy, Immune evasion, Combination therapy, Personalised Cancer therapy.

1. Introduction

Cancer is a genetic disease that occurs when information in cellular DNA is corrupted, leading to abnormal patterns of gene expression. [1]Consequently, the effects of normal genes that support cellular functions such as growth, survival, and motility are accentuated, while genes that suppress these effects are repressed. The main mechanism of alteration is mutation accumulation; however, non-mutational (epigenetic) changes driven by processes like DNA methylation are also a leading cause of cancer. Most common cancers are caused by acquired mutations that happen in your somatic cells after birth (90-95%). Hereditary mutations (inherent mutations in specific genes) occur in the germline (5-10%). Familial cancer can also happen where there is a constant interplay of genetic and environmental factors, including similar lifestyles or exposure in a family, and doesn't necessarily stem from inherited mutations. (multiple genetic variations with smaller individual effects). Aberrant gene expression fundamentally alters the biological processes within a cell, leading to the appearance of the so-called 'Hallmarks of cancer' in the cell.

The Hallmarks of Cancer were proposed as a set of functional capabilities acquired by human cells as they make their way from normalcy to neoplastic growth states, more specifically, capabilities that are crucial for their ability to form malignant tumors. [2,3] This idea was coined by Douglas Hanahan and Robert Weinberg in their paper "The Hallmarks of Cancer". Cancer cells have defects in the control mechanisms that regulate how often they divide, and in the feedback systems that regulate these controls. Normal cells grow and divide but have many controls on their growth. They only grow when stimulated by growth factors. If they get damaged, the molecular brakes stop them from dividing until they are repaired. If they cannot be repaired, they commit programmed cell death called apoptosis. They can only divide a limited number of times. They are a part of the tissue culture, remain where they belong, and need a blood supply to grow. All these mechanisms must be overcome for a cell to develop into a cancerous one. Each mechanism in the body is controlled by several proteins. A critical protein must malfunction in each mechanism. These proteins become nonfunctional or malfunction when acquired or somatic mutations damage their gene sequence. This occurs in a series of steps that Hanahan and Weinberg refer to as the Hallmarks: self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue evasion and metastasis.

The continual genetic and epigenetic evolution of cancer cells enables them to adapt to various kinds of pressures. [3] Subclones with advantageous mutations or epigenetic alterations that allow them to survive treatment driven therapeutic resistance. Clonal evolution also facilitates metastasis by supporting the development of the cell populations because of the ability to invade local tissues, enter and survive in circulation and colonize distant organs.

Cancers are typically fuelled by sequential accumulation of driver mutations in a previous healthy cell. Some of these mutations such as inactivation of the first copy of the tumor suppressor gene can be neutral and some, like those resulting in activation of oncogene, may provide cells with a selective growth advantage. Clonal selection is the process by which cancer cells acquire random genetic mutations, generating diverse subclones. Cells with advantageous mutations that promote rapid growth or survival outcompete others, leading to a dominant tumour mass that drives progression and treatment resistance. The reiterative process unfolds as follows:

1) Genetic Diversification: Tumour cells exhibit high genetic instability, causing them to constantly spawn new variants via mutations, copy number variations and epigenetic alteration.
2) Selective Pressure: The diverse cells compete for space, oxygen and nutrients within the tissue microenvironment. External stressors such as chemotherapy, radiation or immunotherapy eliminate vulnerable cells.
3) Clonal expansion: Rare mutant cells possessing a driver mutation (which confers a resistance or a growth edge) survive and proliferate, establishing a new dominant subclone.
4) Intra-tumour Heterogeneity: This continuous evolutionary cycle creates mosaic or distinct cell populations within a single tumour, which directly complicates targeted treatment.

Tumour evolution explains how cancers mutate, adapt and diversify over time. It makes the tumours more invasive, metastatic and resistant to therapy.

The immune system is essential for recognizing and destroying abnormal cells, maintaining cellular homeostasis, and protecting against malignant changes. [4] However, cancer cells are using various complex mechanisms to evade immune surveillance enabling them to grow uncontrollably and ultimately form life-threatening tumours. The immune evasion phenomenon in cancer involves a complex interplay among tumour cells, tumour microenvironment and immune cells. Tumour cells evade immune detection and destruction through various strategies, including altering antigen presentation, creating an immunosuppressive microenvironment and inhibiting immune cell function. These tactics enable cancer cells to persist and grow despite the immune system's effort to eradicate them. Recent immunology and oncology advances reveal mechanisms of immune evasion, providing new insights into how cancer cells manage to subvert immune responses. New findings have led to treatments targeting immune evasion, including immune checkpoint inhibitors, CAR-T cell therapy and cancer vaccines.

Tumour cells stimulate significant molecular, cellular and physical changes within their host tissues. [5] The emerging tumour microenvironment (TME) is a complex and continuously evolving entity. The composition of the TME varies between tumor types, but the hallmark features include immune cells, stromal cells, blood vessels and extracellular matrix (ECM).

It is believed that the TME is not just a silent bystander, but rather an active promoter of cancer progression. Cancer cells and TME components develop a dynamic, reciprocal relationship that supports cancer cell survival, local invasion, and metastatic dissemination. The TME coordinates a program that promotes angiogenesis to restore oxygen/nutrient supply and removes metabolic waste. Tumors become infiltrated with diverse adaptive and innate immune cells that can perform both pro- and anti-tumorigenic effects. The expanding literature on the TME has identified new targets within it for therapeutic intervention.

2. Chemotherapy

Chemotherapy is a distinctively different approach than surgery and radiation therapy in curing cancer. It is used as a primary treatment. Rather than physically removing a tumor or a part of it, chemotherapy uses chemical agents (anti-cancer or cytotoxic drugs) to interact with cancer cells to eradicate or control the growth of a tumor. Chemotherapy is used after surgery as an adjuvant treatment to eradicate any microscopic cancer cells and to decrease the probability of cancer recurrence. Chemotherapy is best used when guided by principles of pharmacology, tumor biology, cellular kinetics, and drug resistance. The therapeutic window is a range of plasma drug concentrations with a high probability of therapeutic success, defined as tumor shrinkage. Because chemotherapeutic agents are metabolized differently in different individuals, the therapeutic window is important. This helps ensure drug concentrations are in an appropriate range so the drug is effective for the individual.

The cell cycle is composed of 4 phases. [6] Cells that are committed to divide enter the G1 phase. Cellular processes occur, and the cell prepares to enter the DNA synthesis (S) phase. Here, the cell copies all its DNA, forming a complete extra set of genetic material. The cell then moves on to the G2 phase, where it organizes and condenses the genetic material and prepares to divide. The next stage is M, which stands for Mitosis. This is where the cell partitions the two copies of the genetic material into the two daughter cells. After M phase is complete, cell division occurs, leaving two cells, and the cell cycle can begin again. Chemotherapeutic agents might be cell cycle-specific or cell cycle-nonspecific. Cell cycle-nonspecific drugs, like alkylating agents, have a linear dose-response curve; i.e., the fraction of cells killed increases linearly with drug dose. However, cell cycle-specific drugs plateau in their cell-killing ability. For example, cytarabine is active only in the S phase.

The growth of a tumor depends upon several closely related factors. It depends on the cell cycle time, or the average time for a cell that has just completed mitosis to grow, re-divide, and pass through mitosis again. This determines the tumor's maximum growth rate. It depends on the growth fraction, the fraction of cells undergoing cell division. This fraction is vulnerable to chemotherapy. Lastly, the total number of cancer cells in the population is the total cancer burden. As the number of cells increases, so does the number of resistant cells, which reduces curability. Large tumors also have a great compromise of blood supply, and hence the drug delivery to the tumor is impaired. Variations in these factors explain the variable rates of tumor growth among different histologies, even between metastatic and primary tumors of the same histology. Tumors exhibit a sigmoid growth curve in which doubling time varies with size. They also grow more rapidly at smaller volumes. As the size of the tumor increases, the growth rate slows down because of the complex process which involves cell loss, tumor blood and oxygen supply. To maximize the chance of cure, chemotherapy must be delivered to achieve fractional cell kill in a logarithmic fashion. These concepts have led to the formation of new chemotherapy plans using alternating, intense, and follow-up treatments.

Chemotherapeutic agents can be classified by their distinct mechanisms of action. [7] Each agent targets cancer cells differently. The classes of chemotherapy include alkylating agents, antimetabolites, and natural products such as antitumor antibiotics, anthracyclines, and epipodophyllotoxins. These mechanisms ultimately interfere with cancer cell growth and division.

DNA Damage: Alkylating agents (e.g., nitrogen mustards like mechlorethamine and Nitrosoureas) impair cell function by forming covalent bonds with various biologically important molecules, such as amino, carboxyl, sulfhydryl, and phosphate groups. Their main target sites for alkylation are on DNA, RNA, and proteins. Alkylating the nitrogen at the 7th position of guanine in DNA confers chemotherapeutic and cytotoxic effects. This damages the DNA and prevents normal cell function. Platinum agents (e.g., cisplatin and

carboplatin) produce intra-strand and inter-strand DNA cross-links and form DNA adducts, which inhibit the synthesis of DNA, RNA, and proteins. Cancer cells that are subjected to these agents eventually die because they cannot replicate themselves any further.

Antimetabolites: Antimetabolites (e.g., Methotrexate, Fluorouracil, Cytarabine, Gemcitabine, etc.) are structural analogs of naturally occurring metabolites involved in DNA and RNA synthesis. They interfere with the building blocks of DNA synthesis and are therefore most active in the S phase of the cell cycle. These drugs are most effective in tumors with a high growth fraction.

Topoisomerase inhibition: Topoisomerases are enzymes that help unwind DNA during replication. Various drugs like anthracyclines (e.g. doxorubicin), etoposide (e.g. epipodophyllotoxins) and camptothecin analogs help inhibit topoisomerases. Anthracyclines get intercalated between DNA base pairs and inhibit DNA topoisomerase I and II. Etoposide inhibits topoisomerase II activity by stabilizing the DNA-topoisomerase II complex, which ultimately prevents DNA synthesis, and the cell cycle stops in the G1 phase. Camptothecin analogs inhibit topoisomerase I and interrupt the elongation phase of DNA replication. All these procedures of different drugs affect the synthesis of DNA in cancer cells, ultimately causing their death.

Mitotic inhibition: Vinca alkaloids (e.g., vincristine, vinblastine, and vinorelbine), upon entering the cell, bind rapidly to tubulin and inhibit its assembly. This binding occurs in the S phase at a site different from that associated with paclitaxel and colchicine. This blocks microtubule formation, impairing mitotic spindle assembly in M phase. Unlike vinca alkaloids, taxanes (e.g., paclitaxel and docetaxel) promote microtubule assembly and stability, therefore blocking the cell cycle in mitosis. The cell cycle arrests at this stage, causing apoptosis in the cancer cell.

Chemotherapeutic drugs, while effective in eradicating cancer cells, are also associated with several adverse effects because they act on rapidly dividing normal cells in the body if not administered at the correct dosage. [8] The dose-limiting toxicities (DLTs) of Nitrogen Mustards include myelosuppression and severe nausea and vomiting. Occasionally, alopecia, sterility, diarrhea, and thrombophlebitis may be seen. The DLT of nitrosoureas is myelosuppression. DLTs for cisplatin are renal insufficiency, peripheral sensory neuropathy, and ototoxicity. For carboplatin, the DLT is myelosuppression, especially thrombocytopenia. The major DLT of bleomycin is pulmonary toxicity. Fevers, chills, anorexia, and dermatologic toxicity are also frequently seen. Free-radical oxygen formation in anthracyclines is thought to contribute to cardiotoxicity. Myelosuppression is a DLT for epipodophyllotoxins. Peripheral neurotoxicity is a DLT for vinca alkaloids. The major side effects of paclitaxel include myelosuppression, peripheral neurotoxicity, myalgias, and acute hypersensitivity reactions. In addition, docetaxel can cause a syndrome of cumulative fluid retention, characterized by peripheral edema, and occasionally pericardial and pleural effusions. Lastly, topotecan's DLT is myelosuppression, and irinotecan can also cause acute and delayed-onset diarrhea.

Chemotherapy offers several advantages in the treatment of cancer over other methods by targeting rapidly dividing cancer cells and improving the overall treatment outcomes. Combination chemotherapy provides maximum cell kill within the toxicity range tolerated by the patient. Using drugs with different mechanisms of action helps prevent or slow the development of drug-resistant cancer cells. Combination therapy targets different resistant cell populations within a heterogeneous tumor. Drugs with different mechanisms can work together to improve tumor destruction while minimizing toxicity.

Despite its effectiveness, chemotherapy has several disadvantages and limitations. Cancer cells can become resistant due to altered gene expression. Cells in the G0 phase are generally resistant to drugs that are active in the S phase. Low drug concentrations or altered drug metabolism can also reduce effectiveness. Repeated exposure to one drug can also cause cross-resistance. Overexpression of the MDR-1 gene produces P-glycoprotein, which pumps drugs out of cancer cells. This also reduces chemotherapy effectiveness. Chemotherapy can also damage healthy, rapidly dividing cells, causing toxicity leading to various diseases like myelosuppression, nephrotoxicity, neurotoxicity, etc. Lastly, the drug concentration must remain within the therapeutic window. If it's too high, then it leads to increased toxicity, but if it's too low, it reduces the therapeutic benefit.

3. Immunotherapy

Immunotherapy is a type of therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infections, or other diseases. [9] Some types of immunotherapy target specific immune cells, while others affect the immune system more broadly. In contrast, chemotherapy and radiotherapy are direct physical impacts on the tumors using toxic drugs or high-energy radiation to kill cancer cells, often affecting the healthy cells that are present in your body too. William Bradley Coley, known today as the 'Father of Immunotherapy', was the first to attempt to harness the immune system to treat bone cancer in 1891. James Allison and Tasuku Honjo were awarded the Nobel Prize in 2018 for their meticulous work on checkpoint molecules for therapeutic resistance. Immunotherapy is considered a breakthrough in cancer research because it helps re-enable the immune system to recognize and destroy the cancer cells on its own. It also trains immune cells to remember cancer cells, conferring long-term resistance and helping prevent recurrence. It also has no side effects because it uses the body's natural defenses instead of drugs.

The immune system plays a critical role in recognizing and eliminating transformed cells through a process known as immune surveillance. Here, specialized white blood cells like T cells and Natural Killer (NK) cells continuously patrol the body. Once identified. These cells attack and destroy the cancer cells. Tumor cells have tumour associated/specific antigens on their external surfaces. Dendritic cells digest these foreign or cancerous cells and present their protein on their surface. Cytotoxic T cells and NK cells bind directly to these abnormal antigens and release toxic chemicals that destroy the cancer cells. CD4+ T cells release chemical

signals called cytokines to recruit more immune cells to the tumor site and coordinate a sustained attack. However, cancer is notoriously tricky and easily outsmarts these natural defenses. Tumors may hide from detection, release chemicals to suppress immune activity, or hijack built-in checkpoints to escape T cells. As a result, cancer develops as tumor cells evade immune surveillance.

Immune evasion represents a significant challenge in oncology. [10] It allows tumors to evade immune surveillance and destruction, thereby creating complications for therapeutic interventions. Tumor cells avoid destruction through several mechanisms. One major mechanism is tumor-induced immune suppression. Tumors create an immunosuppressive TME that inhibits immune cells, allowing cancers to survive and proliferate. Tumor cells secrete TGF-β, IL-10, and VEGF. TGF-β inhibits T-cell activation and proliferation, inhibits NK cells, and promotes Treg development. IL-10 suppresses macrophages and dendritic cells. It also blocks T-cell activation and suppresses NK cells and CD8+T cells. VEGF, on the other hand, prevents dendritic cell maturation, reduces antigen presentation, and also weakens T-cell activation. Tumors recruit various cells, such as Tregs and MDSCs, that regulate immune cells. Tregs suppress effector T-cells and NK cells, release TGF-β and IL-10, and also express CTLA-4. MDSCs suppress T cells and produce ROS, NO, and arginase. They also promote Treg expansion. Immune checkpoints normally prevent excessive immune activation. Tumors overexpress PD-L1 and CTLA-4. PD-L1 binds PD-1 on T cells. This inhibits T cell activation and proliferation. Tumors therefore escape immune surveillance. The TME, by contrast, consists of cancer cells, stromal cells, immune cells, and signaling molecules. The TME actively promotes immune suppression. Tumor-associated macrophages secrete TGF-β and IL-10, suppress CD8 T cells and NK cells, promote angiogenesis, and support tumor growth. Hypoxia increases HIF-1α and PD-L1, suppresses MHC-I, recruits MDSCs, and promotes immune escape. Loss of antigen presentation also enables immune evasion. Tumor cells downregulate MHC-I. Reduced MHC-I prevents CD8 T cells from recognizing tumor antigens. Tumors therefore escape immune destruction. Mutations in β2-microglobulin, TAP1 and TAP2 reduce MHC-I expression. This contributes to resistance to immunotherapy.

Immunotherapy comprises several therapeutic approaches that enhance or modify different components of the immune system to recognize and eliminate cancer cells. Each type of immunotherapy acts through a distinct mechanism to restore or strengthen anti-tumor immune responses. [11] There are 7 main types of cancer immunotherapy.

Immune checkpoint inhibitors: Checkpoints in our immune system stop certain responses from destroying healthy cells too. T cells have proteins on their surface called checkpoint receptors, which act like brakes. When these receptors receive a 'stop' signal from the proteins of other cells, they stop the T cell from attacking. Some cancer cells exploit this by sending too many 'stop' signals using proteins like PD-L1. This prevents the T cells from killing the cancer cells. Checkpoint inhibitors are medicines that block this process. They stop the checkpoint receptors on T cells from receiving the 'stop' signals, allowing the T cells to stay active and continue fighting cancer.

Cytokine therapy: It uses artificial cytokines that mimic those found in the human body, like interferons and interleukins, to boost the body's fighting capabilities. These are families of proteins that carry important signals between immune cells. For example, interleukin-2 (IL-2) can help promote the growth of white blood cells like T cells, which can attack cancer, while interferons like interferon-alpha can slow tumor growth and activate other immune cells. This treatment is one of the earliest approved on this list, with the first treatment for adults introduced in the 1980s. While cytokine therapy is still used today, researchers are now working on more targeted treatments. That's because cytokines affect the whole immune system and can sometimes cause unwanted side effects. Targeted treatments aim to fight cancer more precisely, with less impact on healthy cells.

Monoclonal antibodies: These are artificial antibodies designed to fight cancer. They can last longer in the body, be given in the right doses, and target cell-surface antigens specific to cancer. This means they usually cause fewer side effects because they don't harm normal healthy cells as much. Monoclonal antibodies can also be combined with chemotherapy medicines to create something called antibody-drug conjugates**.** Instead of giving chemotherapy via IV or orally, which spreads all over the body and can harm healthy cells, the drug is attached to the antibody. These carry the drug directly to cancer cells, sparing healthy ones from the toxic medicine.

Cancer Vaccines: Vaccines normally give a healthy person antigens that the immune system needs to recognize in the future (for example, by giving inactivated versions of the flu virus to enable the immune system to fight it off faster). Vaccines exist against specific viruses linked to adult cancers (like the human papillomavirus, which can cause cervical cancer). The first therapeutic cancer vaccine was approved in 2010 for prostate cancer, following decades of research into ways to get the immune system to fight cancer better. Cancer vaccines share the same general goal: deliver cancer-related antigens to immune cells, boosting the immune system's natural cancer-fighting abilities. There are currently no vaccines available for childhood cancer – but researchers are working on it.

Adoptive cell therapy: Scientists have developed treatments that remove a patient's immune cells, modify them to improve their cancer-fighting abilities, and return them to the patient. This is called adoptive cell therapy (or cellular immunotherapy), and it usually uses T cells or another type of immune cell called a natural killer cell. The most famous example is CAR T-cell therapy**,** first approved in the UK in 2019 to treat some childhood cancers. It stands for 'Chimeric Antigen Receptor T-cell' therapy, and it uses modified T cells to fight cancer. The treatment is unique to each patient: it takes the patient's own T cells and genetically modifies them by adding a special gene. The gene helps the T cells make a new receptor (called a CAR) which allows them to better recognize and bind to proteins on cancer cells. The modified T cells are grown in the lab to produce millions of trained

CAR T cells. When put back into the patient, they can hunt down cancer, finding and destroying it much more easily.

Oncolytic virus therapy: This treatment uses viruses to target and destroy cancer cells. These viruses are often engineered to infect cancer cells more effectively, with the goal of minimizing effects on healthy cells. When oncolytic viruses infect cancer cells, they fight cancer in two ways. First, they kill the cell, but when the cell bursts to release new viruses, it also releases many cancer cell antigens. This boosts the immune response, killing the cancer even faster.

Although immunotherapy has transformed cancer treatment, it is not equally effective against all cancer types or in all patients. [12–14] This happens because tumors use complex defense mechanisms to hide from, disable, or evade the patient's immune system. Some cancers, like pancreatic or brain cancer, have very few infiltrating T cells. As a result, the immune system cannot attack what it can't reach or see. Cancer cells express proteins that act like 'off switches', bind themselves to the T cells and turn off their ability to attack. These cells also recruit other cells, such as myeloid-derived suppressor cells, to create a protective environment that actively blocks and counters T cell activity. Even if a drug blocks one checkpoint, the tumor often adapts by activating backup signaling pathways to evade the attack. Immunotherapy also tends to work best on cancers with high genetic instability or multiple mutations (like melanoma or certain lung cancers) because those mutations make cancer cells look foreign. Cancers with low mutation rates provide fewer targets for the immune system to recognize. Besides, immunotherapy doesn't work in all patients. Not every patient has an immune system capable of recognizing or mounting a response strong enough to act against their specific cancer cells. Even if a tumor initially responds to immunotherapy, cancer cells can mutate over time, develop resistance to the specific drug, or spread to microenvironments where the treatment is less effective. The cancers that are highly responsive to immunotherapy include melanoma, leukemia, non-small cell lung cancer, Hodgkin's lymphoma, bladder cancer, kidney cancer, etc.

Even though immunotherapy is generally more targeted than chemotherapy, it can still produce significant adverse effects by overstimulating the immune system. [15] These problems arise when the immune system becomes overactive and attacks healthy tissues instead of exclusively targeting cancer cells. Common reactions include fatigue, skin rashes, and diarrhea. Others can be serious, including inflammation of the lungs, intestine, liver and heart. Side effects are more likely when immunotherapy is combined with another type of treatment, depending on the patient's needs. CAR-T also has different kinds of side effects. This happens because many patients experience cytokine release syndrome, an immune reaction that can cause high fever, low blood pressure, or difficulty in breathing.

Despite these side effects, immunotherapy offers several advantages over conventional cancer treatment by harnessing the body's own immune system to recognize and terminate the malignant cancer cells. [16] Unlike chemotherapy, which harms both cancerous and normal cells, immunotherapy targets cancer cells more specifically and accurately. Immunotherapy is effective long-term, which increases long-term survival rates. It is widely adaptable and can control and kill many kinds of tumors. It can restore and improve the body's immune function, identify, locate, and kill tumor cells, and effectively prevent tumor recurrence and metastasis. With thoroughness, it can also remove residual tumor cells and microscopic lesions from the body. Lastly, it has fewer side effects than traditional cancer treatments.

Despite its significant clinical success, immunotherapy has several limitations. Immunotherapy is less effective in immune-suppressive/exclusion tumors. The use of immune checkpoint inhibitors can produce negative regulation, leading to autoimmune diseases and even death. A variety of non-specific toxicities or side effects may occur in some patients. In fact, a hyper-progressive disease may also occur, accelerating the death of the patient. Lastly, the uncertain survival rates of patients and the exorbitantly high treatment costs are the biggest drawbacks of immunotherapy.

Parameter	Chemotherapy	Immunotherapy
Target	Rapidly dividing cancer cells (also affects normal rapidly dividing cells).	Components of the immune system to recognize and destroy cancer cells.
Specificity	Low specificity, damages both cancerous and healthy cells.	High specificity; primarily targets cancer cells through immune mechanisms.
Memory Response	Does not produce immunological memory.	Can generate long-term immunological memory, reducing the risk of recurrence.
Toxicity	High toxicity with common side effects such as myelosuppression, nausea, alopecia, and organ damage.	Generally lower systemic toxicity but may cause immune-related adverse events (e.g., colitis, hepatitis, pneumonitis, endocrinopathies).
Resistance	Resistance develops through altered drug metabolism, drug efflux pumps (e.g., MDR-1/P-glycoprotein), DNA repair, and gene mutations.	Resistance may occur through immune evasion, loss of antigen presentation, immunosuppressive tumour microenvironment, or checkpoint pathway alterations.
Response time	Usually produces rapid tumour shrinkage within weeks.	Response may take weeks to months as the immune system becomes activated.
Duration or Response	Often temporary; relapse is common after treatment ends.	Responses may be long-lasting due to immune memory, even after treatment is discontinued.
Biomarkers	Limited predictive biomarkers; treatment mainly depends on cancer type and stage.	Biomarkers such as PD-L1 expression, Microsatellite Instability (MSI), Tumour Mutational Burden (TMB), and specific genetic markers help predict response.
Cost	Comparatively less expensive and widely available.	Significantly more expensive, especially personalized therapies like CAR-T cell therapy.

4. Combination Therapy

Combination therapy has emerged as an effective strategy to improve cancer treatment efficacy by integrating immunotherapy with conventional therapeutic approaches. [17] Combining chemotherapy with immune checkpoint inhibitors has shown significant clinical benefits because chemotherapy not only destroys tumor cells directly but also releases tumor antigens that stimulate immune responses. Checkpoint inhibitors then block inhibitory signals that suppress T cells, allowing them to recognize and eliminate remaining cancer cells more effectively. Similarly, chemotherapy administered before CAR-T cell therapy reduces tumor burden and creates a favorable environment for the expansion and persistence of engineered CAR-T cells, thereby enhancing their anti-tumor activity.

Radiotherapy is also frequently combined with immunotherapy because radiation-induced tumor cell death releases tumor antigens that activate dendritic cells and cytotoxic T cells, strengthening systemic anti-tumor immunity. Likewise, targeted therapy combined with immunotherapy simultaneously inhibits specific molecular pathways responsible for tumor growth while enhancing immune-mediated tumor destruction, helping to overcome treatment resistance. Recent advances in nanomedicine have further improved combination therapies by using nanoparticles to deliver immunotherapeutic agents directly to the tumor site. This targeted delivery increases drug accumulation within tumors, reduces systemic toxicity, and enhances the overall effectiveness of immunotherapy.

Personalized cancer vaccines harness patient-specific tumor neoantigens to showcase a precise antitumor immune response. [18,19] These vaccines stimulate T cells to recognize and destroy the cancer cells more specifically, making the treatment of cancer more targeted than conventional methods. For these vaccines, doctors take a sample of the patient's tumor and sequence its DNA and RNA to identify unique protein changes (neoantigens). Advanced computer models map out which mutation will trigger the strongest immune response. Then, a custom mRNA or peptide vaccine is manufactured and injected so T cells can learn to destroy cells carrying those same markers while sparing healthy cells. Combined data for high-risk melanoma shows that an experimental personalized mRNA vaccine paired with an immunotherapy drug cuts the risk of cancer recurrence and death by roughly 49% for a 5-year period.

The integration of AI in cancer research and clinical practice encompasses advancing screening and diagnostic accuracy, improving precision cancer treatment, enhancing cancer surveillance, accelerating drug discovery, optimizing healthcare delivery, and elucidating cancer mechanisms. [20] AI models evaluate a tumor's entire genetic makeup or transcriptome to predict which specific chemotherapy, immunotherapy, or targeted drug a patient will respond to the best. Deep learning algorithms analyze histopathological slides to spot specific patterns, helping doctors determine tumor phenotypes and malignancy. [21]

Despite its remarkable success, immunotherapy still faces several challenges that limit its widespread use. One major barrier is its high cost, particularly for advanced treatments such as CAR-T cell therapy, which makes them inaccessible to many patients and healthcare systems. In addition, these therapies are often available only at specialized medical centers with the necessary expertise and infrastructure. Another major limitation is the development of resistance, as some tumors evolve mechanisms to evade immune detection or suppress immune responses, reducing treatment effectiveness. Furthermore, immunotherapy can lead to immune-related adverse events, in which an overactivated immune system attacks healthy tissues, causing inflammation in organs such as the lungs, liver, intestines, and endocrine glands. Overcoming these challenges through improved biomarkers, reduced treatment costs, and safer therapeutic strategies remains an important focus of ongoing research.

5. Conclusion

Cancer remains one of the most complex diseases in modern medicine because of its ability to continuously evolve, develop resistance against the body's immune system, and evade it. The complexity of these processes makes finding a definitive cure difficult, making cancer one of the most heavily researched and studied diseases globally. While conventional methods like chemotherapy have played a crucial role in improving the survival rate of patients by directly targeting and destroying the rapidly dividing cancer cells, it is also associated with significant toxicity and the development of resistance to a drug. This happens because it damages healthy rapidly dividing cells, causing toxicity leading to various diseases. In contrast, immunotherapy has revolutionized cancer treatment by harnessing the body's immune system to recognize and destroy malignant cells, offering greater specificity and long-term protection. However, immunotherapy also faces challenges, including limited effectiveness in certain cancers, immune-related adverse effects, and exorbitantly high treatment costs. Both therapies have strengths and limitations, making none of them the 'perfect' standalone treatment for a vicious disease like cancer. Advances in personalized medicine, artificial intelligence, nanotechnology, and combination therapies are transforming the future of cancer treatment by addressing many limitations of current approaches. Rather than relying on a single treatment modality, future cancer management is expected to combine multiple therapies, tailoring them to the unique characteristics of each patient and tumor. Continued research in tumor biology and cancer-immune interactions will be required to develop treatments that are safer, more accurate, effective, and more accessible for everyone. Ultimately, integrating conventional therapies with innovative immunotherapeutic approaches offers the greatest potential to improve patient outcomes and take a step closer to more precise, personalized cancer treatment.

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