REVIEW ARTICLE

Recent and Advanced Trends in Cancer Treatments

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ABSTRACT

Background: Cancer treatment remains a critical area of clinical research, with numerous approaches developed depending on tumor type and stage. Recent advances in genetic and immunotherapy, bioinformatics, and genetic science have revolutionized cancer diagnosis and treatment. Emerging technologies such as gene delivery, oncolytic virotherapy, suicide gene therapy, and CRISPR/Cas9 offer promising therapeutic avenues.

Methods: This review provides a detailed analysis of the latest techniques of Gene therapy, artificial intelligence, Nanocarrier Delivery Systems, Immunotherapy, CAR T-Cell Therapy, Epigenetics, Vaccines, and Clinical translation and assessing their therapeutic potential in cancer treatment. A review of early critical studies focused on the integration of immunotherapy, nanotechnology, and artificial intelligence (AI) in cancer therapies with emphasis on targeted delivery systems and precision medicine.

Results: The review highlights the synergistic effects of combining targeted therapies with immunotherapy, particularly immune checkpoint inhibitors and CAR-T cell therapy. Therapies such as CRISPR/Cas9 demonstrate significant potential in cancer targeting, while advancements in nanocarrier delivery systems offer enhanced precision with reduced side effects. AI's role in improving cancer diagnosis and personalized treatment is also underscored.

Conclusion: This comprehensive analysis of recent therapeutic approaches and technological advancements addresses gaps in previous reviews and offers updated insights into cutting-edge cancer treatments. The review emphasizes the evolving role of immunotherapy, nanotechnology, AI, and nanotechnology, providing clinicians and researchers with the most current and relevant information for optimizing cancer treatment strategies.

Keywords: Cancer treatment, CAR-T cell therapy, Gene therapy, CRISPR/Cas9, Nanocarrier

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INTRODUCTION

As the second most common cause of death globally, cancer has only recently been superseded by cardiovascular illnesses as a significant public health problem.[1] It is typified by too-rapid cell proliferation, which frequently results from somatic changes in signal transduction pathways, genetic disorders, or cell cycle regulators.[2] Tumor heterogeneity, metastasis, recurrence, and treatment resistance, even with conventional therapy approaches used, are the causes of the high death rate.[3] Chemotherapy, the most often used treatment, suffers from insufficient absorption and indiscriminate dispersion.[4] The efficacy of the available treatments is greatly restricted by the tumor's intrinsic geographical and temporal variability.[5] Nanomedicine has become a very exciting area that offers methods to improve the bioavailability and localization of chemotherapeutic drugs inside malignant tissues because of its biocompatible delivery systems.[6,7] Natural antioxidants and other phytochemicals are under investigation for potential use as adjunctive medicines in treating cancer.[8] Treatment approaches concentrating on particular molecular targets try to reduce damage to healthy tissues.[9] The CRISPR-Cas9 technique has improved the possibility of long-term treatment for inherited disorders by allowing precision with which genetic abnormalities can be fixed.[10] The growing number of clinical trials and state-of-the-art methods in this area confirms the growing desire to use gene therapy to overcome traditional treatment challenges.[11] Under this paradigm, gene therapy is one of the key approaches to promote the expression of genes that shrink tumors or induce apoptosis in cancer cells. Concurrently being investigated as site-specific treatment modalities are thermal ablation and magnetic hyperthermia. Customized treatment strategies are also made possible using radiology and pathology imaging data analytics. This review examines these novel therapeutic approaches and describes the progress made to overcome the limitations of traditional cancer treatments. Non-invasive treatments meant to minimize harm to both diseased and non-cancerous tissues have drawn increased attention as cancer treatment has developed recently.[12,13] Gene therapy alters genes to treat cancer by correcting mutations, introducing new genes, or editing DNA to stop tumor growth.

Conversely, immunotherapy enhances the immune system's ability to recognize and attack cancer cells using antibodies, vaccines, or modified immune cells like CAR-T therapy. Current techniques are designed to elicit a systemic immune response that only targets tumor cells, lowering adverse effects and reducing the rate of spread of metastatic cancer.[14] Previously, incurable head and neck malignancies have shown great potential for treatment using photoimmunotherapy (PIT), a revolutionary technique that offers therapeutic effects with less harm on surrounding healthy tissues.[15] In the interim, nanotechnology has made a major contribution to these developments through specific uses in precise medication delivery, cellular sorting, and high-resolution imaging.[16] This compilation of cutting-edge cancer treatment approaches attempts to demonstrate their revolutionary potential to revolutionize the therapeutic approach to cancer.[17] One major development in oncology that has shown to be an alternative to traditional treatment approaches is immunotherapy.[18] One of the main contributing reasons to treatment resistance and disease progression is the existence of cancer cells avoiding immune surveillance.[19] Using the natural processes of the immune system to recognize, target, and eliminate cancer cells, immunotherapy is a therapeutic method that has fewer side effects and higher effectiveness.[20] This paradigm change in cancer treatment towards immunotherapeutic approaches promises better clinical outcomes and patient quality of life.[21] This review primarily explores the most current developments in cancer treatment and addresses approaches to surpass the drawbacks of traditional therapies like radiation and chemotherapy.[22] In this review, novel immunotherapy, nanomedicine, and photoimmunotherapy strategies all of which efficiently target cancer cells while reducing cell loss to healthy tissue.[23-25] This review also covers the potential to completely transform our understanding of cancer treatment by utilizing gene therapy and state-of-the-art genome editing technologies like CRISPR to offer customized cancer treatment. This review looks at how these new approaches work together and could help create a future in which cancer therapy is more efficient, less invasive, and catered to the unique requirements of each patient.

Immunotherapy and Nanotechnology

In recent times, conventional cancer treatments like surgery, chemotherapy, and radiation therapy, while effective to an extent, have been known to cause significant damage to both pathological tissue and normal cells.[26] In a non-invasive cancer treatment, the main tumor should be removed, systemic immunity suited to the tumor should be boosted, metastases should be removed, and side effects should be as low as possible. A paradigm change brought about by the developments in immunotherapy and nanomedicine has replaced high-dose cytotoxic drugs with photoimmunotherapy, immunotherapy, and targeted therapy - all of which show significant benefits with lower risk.[27] While radiation therapy can cause damage to both pathological and normal cells, advancements in immunotherapy and nanomedicine offer lower-risk treatment options with significant benefits. These new treatments focus on boosting systemic immunity, targeting specific cells, and reducing side effects compared to traditional radiation therapy.

The US approval for the first human photoimmunotherapy (PIT) trial focused on incurable head and neck cancer.[28] FDA (Food and Drug Administration)

reports that phase III international clinical studies will start in 2018. The objectives of this vital initial phase in converting research into practical applications are to reduce chemical toxicity and improve therapeutic benefits. There is a need for PIT developments and their function in cancer treatment by highlighting the shift from conventional phototherapy to state-of-the-art immunotherapy methods. The $1x10^{-9}$-meter range of particles that characterize nanotechnology also show unique characteristics in biological environments and find use in cell sorting, imaging, and targeted medication administration in PIT.[29]

The precise targeting of nanoparticles to specific cancer cells has proven challenging, leading to potential off-target effects and decreased efficacy. However, ongoing research and advancements in nanoparticle technology have shown promising results in overcoming these challenges. By utilizing functionalized nanoparticles, researchers have improved the specificity of targeting cancer cells while minimizing off-target effects. This has paved the way for more effective and personalized cancer treatment approaches, offering new hope for patients with various types of cancer. As our understanding of nanotechnology continues to evolve, it is expected that the field of precision medicine will see significant growth and innovation in the coming years.

Cancer nanomedicine has become a front-runner in therapeutic innovation, particularly as patients receive first-generation therapies.[30] Furthermore, invited by this work are contributions of nanomedicine to cancer diagnosis and treatment.[31] There are over 100 subtypes of cancer, and yearly deaths from it exceed 7 million. The main public health concern of inflammation is the etiology of chronic inflammatory diseases, including diabetes, heart disease, and lung problems. It emphasizes that rapid creative therapeutic strategies are needed worldwide to efficiently manage and treat cancer and inflammation efficiently.[32] Among other novel biomaterials that must be developed are nanomaterials. Recently, immunotherapy has been included in traditional cancer treatment plans for radiation, chemotherapy, and surgical removal.[33] This innovative method differs from conventional methods that occasionally lack selectivity and have negative side effects since it uses the immune system's inherent ability to detect and destroy cancerous cells.[34] By increasing the body's immune reaction to cancer cells, immunotherapy offers a more focused and successful therapeutic approach with less chance of collateral damage to healthy organs.[35] While nanomaterials may be important for biomaterial development, they are not the only area of innovation in cancer treatment. Immunotherapy and nanomaterials offer a targeted and effective alternative to traditional methods, reducing side effects and improving patient outcomes. Since it can improve patient outcomes and the quality of life for cancer patients, this new therapeutic approach has greatly influenced oncology.

Despite advancements in cancer treatment, significant limitations remain. Conventional therapies still damage normal cells, while new approaches like immunotherapy and nanoparticle-based treatments face challenges in achieving precise targeting, leading to potential off-target effects. To rectify these issues, researchers can develop more refined delivery systems and utilize combination therapies that enhance specificity while minimizing side effects. Ongoing research and clinical trials can establish emerging therapies' efficacy and safety profiles. Furthermore, exploring personalized medicine tailored to individual tumor characteristics may improve outcomes across many cancer subtypes. Continuous innovation and interdisciplinary collaboration will be essential for addressing these challenges effectively.

The Rise of Immunotherapy in Cancer Treatment

Cancer immunotherapy uses the immune system to target and eliminate cancer cells. Using drugs that can either increase cytotoxic lymphocyte activity against malignant cells or lower immunosuppressive processes within the cancer microenvironment, Kerr and Chisholm looked at several therapies approaches to improve the immune response against tumors.[36] Better clinical results can be achieved with these immunotherapeutic strategies alone or in combination with other modalities such as radiation or chemotherapy.[37] The combined medicines simultaneously tackle several facets of immune system control and tumor biology, enhancing overall efficacy. Driven in part by Dr. Honjo's groundbreaking discovery of immune checkpoints, which resulted in the creation of immune checkpoint inhibitors, immunotherapy has lately become an essential component of cancer patients' treatment regimens.[38] Even with these developments, gastrointestinal cancers are still very difficult to cure. Hence, new therapeutic approaches need to be investigated. Four new areas of oncological research exosome-based therapeutics, microbiome regulation, enhanced immunotherapeutic approaches, and organoid-based models- that may meet this clinical need are to be developed.[39] Each of these fields provides critical information and possible approaches to improve the efficacy and specificity of cancer treatment in the next clinical trials. Long the mainstays of cancer treatment have been radiation therapy, chemotherapy, and surgery. However, immunotherapy has completely changed the area and attracted more attention worldwide.[40]

By investigating exosome-based therapeutics, microbiome regulation, enhanced immunotherapeutic approaches, and organoid-based models, researchers hope to address the challenges faced in current clinical trials. While radiation therapy, chemotherapy, and surgery have been traditional methods of treatment, the emergence of immunotherapy has revolutionized the field and garnered global interest. However, new risks and uncertainties come with these new advancements in cancer treatment. Immunotherapy, while promising, can sometimes lead to se-

vere side effects such as inflammation and autoimmune reactions. The use of exosome-based therapeutics and organoid-based models may pose unknown long-term risks that have yet to be fully understood. It is important for researchers to carefully assess and monitor these potential risks to ensure the safety and efficacy of these innovative treatment approaches.

Under normal physiological circumstances, cancer antigens would trigger a host immune response that would kill malignant cells only. Still, occasionally, the immune system either misidentifies cancer cells from healthy ones or is unable to produce a strong enough reaction, which leads to the development of cancer. Although immunotherapy has been studied for a long time, the idea of using the patient's immune system to fight cancer was not generally acknowledged until recently. The difficulties in proving the effectiveness of cancer immunotherapy sprang mostly from two problems. The immunological suppression brought on by cancer is a big barrier to start. Immunological checkpoints like PD-1 and CTLA4 deep-suppressed cytotoxic T lymphocytes (CTLs) sparked the development of immune checkpoint inhibitors.[41] These inhibitory signals are disrupted by neutralizing antibodies, which reactivate cancer-specific CTLs to target cancer cells. Immune checkpoint inhibitors are clinically effective against several solid tumors, including melanoma, lung cancer, urothelial cancer, gastric cancer, and esophageal cancer. Apart from PD-1 and CTLA4, new immune checkpoint targets, including LAG3, TIGIT, and SIRPA, are also actively investigated.[42] Response rates to these therapies are still low because they rely on the patient's immune system having cancer-specific CTLs. Better outcomes necessitate identifying the right patients using trustworthy biomarkers. The second obstacle to immunotherapy treatment is the insufficient T-cell identification of particular cancer cell antigens and the low action of immunological accelerators. To get beyond this, CAR-T cell treatment changes T cells to identify certain cancer antigens, triggering a powerful immune response. Following injection of the modified CAR into T cells derived from the patient, CAR-T cells selectively and cytotoxically target and kill cancer cells. Though cytokine release syndrome is a major and possibly fatal adverse event linked to CAR-T therapy, improving management techniques to address these risks is still a critical area of research, particularly in hematologic malignancies, including myeloma and B-cell acute lymphoblastic leukemia.[43]

Gene therapy for Cancer Treatment

Clinical trials indicate that gene therapy could be a cancer treatment option.[44] Among the various gene therapy approaches used to treat a wide spectrum of malignancies include naked plasmid or DNA delivery, microRNA targeting, oncolytic virotherapy, telomerase inhibition therapies, restoring tumor suppressor gene activity, and gene-directed enzyme pro-drug therapy.[45,46] However, despite the promising results in clinical trials, challenges remain in fully implementing gene therapy as a cancer treatment option. These challenges include ensuring the safety and efficacy of gene therapy approaches, addressing potential side effects and long-term consequences, optimizing delivery methods to target specific cancer cells while minimizing off-target effects, and overcoming immune system responses that may hinder treatment effectiveness.

Introducing functional genes that are meant to correct underlying genetic defects, this gene therapy presents a viable approach to treating cancer.[47] Mostly, modern methods try to boost immune responses, bring back genes that repress cancers, and use proapoptotic genes to target tumors.[48] specifically. Still, this area has major challenges regarding possible immunogenicity and gene delivery techniques.[49] However, despite the potential benefits of gene therapy in treating cancer, there are significant risks involved. These include the possibility of immune system responses hindering treatment effectiveness, off-target effects from delivery methods, and potential unintended consequences from introducing functional genes.

RNA interference (RNAi) has shown great potential, notably in selective gene silencing, because of its lower risk of toxicity and selectivity.[50] Catalytic polymer-based vectors and lipid-based encapsulation have improved gene delivery efficiency; problems with exact dose and managing interpatient variability persist.[51] Controlled medication release and regulated gene expression are the ultimate objectives of the current study, which will improve focused therapy and lower side effects.[52] Many human diseases, particularly cancer, have significant promise for treatment with gene therapy.[53] Sixty-six percent of the approximately 2,900 gene therapy clinical trials are now underway in cancer applications.[54] One well-used method to produce targeted cytotoxicity is administering the prodrug ganciclovir following the thymidine kinase (TK) gene delivery.[55] This approach has been used in clinical trials on gliomas and prostate cancer.[56]

Furthermore, encouraging results from clinical trials using recombinant adenoviral vectors containing the p53 tumor suppressor gene have been obtained.[57] Despite the significant promise that gene therapy holds for treating cancer, there are risks involved in this approach. For example, administering prodrugs following gene delivery can lead to potential side effects and complications. Using recombinant adenoviral vectors containing tumor suppressor genes may have unforeseen consequences on the patient's overall health and well-being. It is important for researchers and clinicians to carefully assess and manage these risks to ensure the safety and efficacy of gene therapy treatments for cancer patients.

Similar total disease regression was observed in head and neck squamous cell carcinoma treated with

radiation in combination with Gendicine, an adenoviral vector expressing wild-type p53.[58] Gene therapy still faces difficulties, nevertheless, such as determining the best expression environment, being able to target cancer cells only, and maybe neutralizing the immune system. A novel approach that targets gene suppression using RNA interference (RNAi) blocks the production of proteins by suppressing particular genes at the mRNA level.[59] Targeting particular genes involved in cell growth and metastasis might be used to treat cancer.[60] SiRNAs struggle with transport inside cells, stability, and perhaps off-target consequences.[61]

Off-target consequences in RNA interference (RNAi) therapies, such as small interfering RNAs (siRNAs), occur when unintended genes are suppressed due to partial complementarity with non-target mRNAs. While RNA interference (RNAi) shows promise in targeting specific genes involved in cancer cell growth and metastasis, some challenges need to be addressed. One of the potentials off-target consequences of using small interfering RNAs (siRNAs) is the possibility of inadvertently silencing genes that are not intended targets. This could lead to unforeseen effects on normal cell function and potentially worsen the patient's condition. As researchers continue to develop gene therapy approaches, it will be crucial to carefully consider and mitigate these off-target consequences to ensure the safety and efficacy of the treatment.

Retroviral (such as lentiviruses) mediated gene therapy leads to viral integration into the host genome. Thus, it may cause mutagenic events with possible second malignancies. One potential consequence of this integration is the activation of oncogenes or the inactivation of tumor suppressor genes, which could lead to uncontrolled cell growth and the formation of tumors. The random insertion of the viral DNA into the host genome may disrupt normal gene function, further increasing the risk of genetic mutations and tumorigenesis. As a result, careful consideration and monitoring of the long-term effects of retroviral gene therapy are crucial to minimize potential risks to patients. Achieving effective gene therapy requires precise regulation of therapeutic transgenes. This includes ensuring the expression levels are appropriate for clinical needs and that any adverse effects can be mitigated by switching gene expression off completely if necessary. The use of promoters and enhancers is critical, as they determine the duration and level of transgene expression in specific cells or tissues.

Efficiently delivering the therapeutic genes to the target tissues at effective doses remains a significant barrier. The delivery system must ensure the genes reach the diseased tissue without affecting normal cells. Novel delivery strategies are being investigated to overcome these difficulties, including conjugation with organic molecules, chemical modifications, and lipid or polymer-based carriers.[62] The requirement of carefully weighing delivery methods and regulated therapeutic uses is needed because these efforts have not completely removed the risk of toxicity from degradation.[63]

Patient selection may have contributed to clinical trial failures. Gene therapy studies enroll advanced and treatment-resistant cancer patients, similar to chemotherapy results 30 years ago. Due to patient selection biases, gene therapy studies are enrolling advanced and treatment-resistant cancer patients, possibly contributing to clinical trial failures. The similarities to chemotherapy results from 30 years ago highlight the limitations of current gene therapy approaches in effectively treating these types of patients. Several clinical studies are underway for gene treatments based on p53; a gene flawed in many malignancies. In Phase I clinical trials, the virus was well tolerated and successful in shrinking tumors; however, the response rate was lower than expected from pre-clinical investigations. This discrepancy between pre-clinical and clinical trial results underscores the complex nature of gene therapy and the challenges in translating promising lab findings into successful patient outcomes. The outcomes of these trials show the need for more rigorous testing and personalized approaches in gene therapy research. As researchers refine and optimize gene therapy techniques, there is hope that these treatments will eventually become more effective for advanced and treatment-resistant cancer patients.

Artificial Intelligence in Cancer Diagnosis

Many artificial intelligence (AI) systems have handled and investigated huge datasets, most notably machine learning applications, enabling exact forecasts of the effectiveness of treatments, clinical results, and disease recurrence. Machine learning (ML), a subset of AI, trains computer algorithms to generate predictions based on experience. It may be supervised (where the computer algorithm analyze the result data) or unsupervised. Both methods use data patterns to predict outcomes like cancer, survival, and risk groups. Natural language processing (NLP) is used in cancer and elsewhere to analyze unstructured clinical data. NLP converts unstructured free text into a computer-analyzable format, automating resource-intensive activities. ML often splits data, so models are generated and optimized on training and validation subsets but assessed on an unknown test set to minimize over-optimism.[64]

Cancer diagnostic models employ convolutional neural network (CNN) architectures, revolutionizing computer-vision research by permitting color pictures. The downstream fully linked layers mimic an (artificial neural network) ANN, except kernels slide across picture color channels to extract characteristics like edges and color gradients. The model generates a prediction based on the extracted features.[65] This prediction can indicate the likelihood of a tumor in the image or classify the type of cancer based on specific features. By utilizing CNN architectures, can-

cer diagnostic models have significantly improved accuracy and efficiency in detecting and diagnosing cancer, leading to earlier interventions and better patient outcomes.

Imaging research has also benefited from PACS's transition from radiographic film to digital images. Radiomics uses quantitative techniques to analyze radiological pictures, including CT, nuclear medicine, MRI, and ultrasound studies, which are divided into ML and DL techniques.[66] Textural characteristics from highlighted ROIs are used in standard ML techniques to measure size, shape, intensity, and heterogeneity. These characteristics train classification or prognostication models. This allows more complex patterns to be identified and analyzed, leading to more accurate diagnostic and prognostic information. Radiomics has revolutionized the field of imaging research by providing valuable insights into disease detection, progression, and treatment response.

As new pathological methods evolve, AI may help analyze their complicated data. Multiplex immunohistochemistry uses distinct chromogen labels to evaluate various cellular groups on a pathology slide.[67] This method has allowed extensive cancer immune landscape analysis in several subsites. AI can assist in identifying patterns within the complex data generated by multiplex immunohistochemistry, helping to uncover correlations between different cellular groups and their impact on cancer development. By automating the analysis process, AI can streamline the interpretation of results and potentially lead to more precise and personalized treatment strategies for cancer patients. AI and ML are two contemporary computer technologies designed to help oncologists and other medical specialists diagnose and treat cancer patients.[68] The ease of use and improvement of diagnostic procedures of these advanced technologies benefit oncology much.[69] ML algorithms have been shown to succeed significantly with medical imaging analysis, such as mammograms for breast cancer screening and radiological images for brain tumor detection.[70] Experimental evidence indicates that these machine learning-based systems could occasionally outperform even highly skilled physicians regarding accuracy and consistency.[71] One of machine learning's primary benefits is a rapid interpretation of cancer-associated anomalies in imaging examinations.[72] These methods ' reliable and consistent results lessen the effect of different degrees of physician experience.[73] Nevertheless, the need for enormous datasets for efficient algorithm learning and improvement is one of the main drawbacks of using ML technology. However, typical malignancies like breast and colorectal cancer offer a wealth of data for training AI and ML systems, providing a viable path to expanding the use of AI in oncology worldwide and eventually enhancing patient outcomes in various healthcare environments.[74]

Cancer Treatment Modalities

There are many different cancer treatment modalities. Researching different cancer treatment possibilities makes up over half of all clinical research conducted globally.[75] The cancer's kinds, locations, and degrees of advancement all affect the available therapies. Radiation, chemotherapy, and surgery resection are examples of conventional treatments. Conversely, modern approaches include immunotherapy, hormone therapy, anti-angiogenic therapy, and stem cell-based therapies, with dendritic cell-based therapies being the cornerstone. Radiation therapy can damage surrounding healthy tissues, chemotherapy can lead to various side effects like nausea and hair loss, and surgery carries the risk of infection or complications during recovery. Newer treatments like immunotherapy may cause immune-related adverse events; hormone therapy can have long-term effects on hormone levels, and stem cell therapies may have unknown long-term risks. These many approaches provide a wide range of treatment possibilities based on the particular traits of the cancer profile of every patient. New therapy techniques have drawn much interest ever since cancer was recognized as a serious threat to public health.[76] Treatment of different tumors is the main goal of gene therapy clinical trials today.[77] The type, location, and cancer stage determine its best course of therapy and outcome. Among the conventional cancer treatments include radiation-based therapies, chemotherapy, radiotherapy, and surgery. But hormone-based treatments, anti-angiogenic strategies, stem cell therapies, and immunotherapies-including those made from dendritic cells-now comprise the therapeutic toolbox.[78]

However, there are still limitations that need to be considered. These limitations can include factors such as the potential side effects of treatments, resistance to therapies, accessibility and affordability of certain treatments, and the complexity of targeting specific cancer cells without harming healthy cells. Furthermore, not all types of cancer may respond effectively to current treatment options, highlighting the need for ongoing research and development in the field of oncology. The inadequacies and side effects of conventional cancer treatments emphasize the need for new strategies. Among the emerging therapeutic approaches are those that target the angiogenic tendency of cancer, employ oncolytic viro therapy, modify genetic control of apoptotic and tumor-suppressing pathways, and employ antisense and RNA interference (RNAi) approaches.[79] The effectiveness of current treatments against a range of cancers, such as those of the brain, prostate, lungs, breasts, gastrointestinal system, pancreas, liver, head and neck, bladder, skin, ovaries, and kidneys, is also being investigated.[80]

Recent Advances in Nanocarrier Delivery Systems for Cancer Treatment

Nanocarrier delivery technologies for cancer treatment have completely changed chemotherapy

through reduced off-target effects and increased medication delivery to tumor tissues.[81] Passive targeting is one important technique where nanocarriers localized medications using the special properties of tumor vascularity.[82] It is well-recognized that tumor blood channels have far bigger endothelium gaps than normal arteries.[83] Since nanocarriers with sizes between 100 nm and 2 μ m may readily enter tumors, this enables targeted drug localization.[84,85] Furthermore, higher interstitial pressure in tumor cores than at their peripheries results from inadequate lymphatic drainage in tumors.[86] It makes it easier for nanocarriers to enter the interstitial zone, where they stay for extended periods, strengthening the anticancer effects of loaded medications. The ability of longer nanocarrier circulation times to pass through the tumor microenvironment several times increases the effectiveness of anticancer drugs in passive targeted drug delivery strategies.[87] Because cationic nanocarriers interact electrostatically with the angiogenic endothelial cells lining the blood vessels within tumors, drugs also tend to collect in tumor areas.

Conversely, active targeting strategies need to add particular ligands or targeting moieties to the surfaces of nanocarriers that identify certain receptors or antigens that cancer cells overexpress.[88] This selective binding confines off-target absorption by healthy cells and tissues to the tumor site.[89] Some targeting ligands induce endocytosis mediated by receptors to increase intracellular drug delivery and improve therapeutic results.[90] Furthermore, stimulus-responsive nanocarriers provide a dynamic approach to targeted drug delivery that improves the accuracy and efficacy of cancer therapies since they are designed to respond to particular signals in the tumor microenvironment, such as changes in pH, temperature (hyperthermia), or redox potential.[91]

Figure 1: Visuals Depicting Nanocarrier Mechanisms and Effectiveness

Targeted and Immunotherapy

More specificity and fewer side effects are associated with immunotherapy and targeted therapy than conventional chemotherapy regimens.[92] Using the distinct molecular profiles of cancer cells, which frequently vary greatly from those of healthy cells, these cutting-edge treatments allow precise targeted treatments that reduce harm to healthy organs.[93] Conventional chemotherapy acts equally on normal and malignant cells, often being quite toxic. Scientists have been developing several techniques to improve selectivity.[94] In this context, nanotechnology has gained increasing popularity, especially in the application of nanoparticles that, because of their abnormal vasculature and reduced lymphatic outflow, preferentially gather in tumors by the phenomena of enhanced permeability and retention (EPR).[95] EPR passive targeting has all the potential, but it may also exacerbate multidrug resistance (MDR) and result in uneven drug delivery.[96]

Better control is provided by functionalizing nanoparticles with particular ligands that attach to overexpressed receptors on cancer cells.[97] While nanotechnology offers promise in targeting tumors through enhanced permeability and retention, risks include exacerbating multidrug resistance and uneven drug delivery. To mitigate these risks, nanoparticles can be functionalized with specific ligands targeting overexpressed cancer cell receptors for better selectivity. Because their receptors are highly expressed in some cancers and enhance drug absorption, folic acid and biotin, for instance, are often utilized as ligands in active targeting.[98] Prostate, breast, and pancreatic cancers are among the tumors where angiopep-2, which targets the low-density lipoprotein receptor-related protein-1 (LRP1), and bombesin peptide, which targets overexpressed gastrin-releasing peptide receptors, are important ligands.[99] However, potential risks are associated with using nanoparticles with specific ligands to target cancer cells. There is also concern about the potential toxicity of the nanoparticles and the ligands used for functionalization. It is important to carefully assess and mitigate these risks to ensure the safe and effective use of targeted nanoparticles in cancer

therapy. Targeted with transferrin, a serum glycoprotein, are transferrin receptors that are often observed in solid malignancies.[100]

Aptamers are another family of promising ligands for targeted therapy; they are synthesized oligonucleotides with strong affinity and specificity for target molecules.[101] Aptamer nanoparticle coupling can help to deliver pharmaceutical medicines precisely.[102] Combining the A10 RNA aptamer with docetaxel-loaded nanoparticles improves the cytotoxicity against cancer cells.[103] The ligands in targeted therapy have probably received the greatest attention, and they are monoclonal antibodies (mAbs). Together with therapeutic drugs, these proteins can function as stand-alone immunotherapeutic agents or a drug delivery system.[104]

Because they focus on cancer cells, mAbs reduces off-target effects and increases treatment's effectiveness.[105] The critical challenge in nanoparticle coupling for drug delivery is ensuring the precise targeting of cancer cells. While monoclonal antibodies have shown promise in targeted therapy, optimizing their coupling with nanoparticles is still necessary to enhance drug delivery efficiency. Overcoming these challenges can lead to improved cytotoxicity against cancer cells and minimize off-target effects, ultimately improving the effectiveness of treatment. A further cornerstone of contemporary cancer treatment is immunotherapy, which aims to boost and activate the immune system to fight cancer.[106] Immunological checkpoint inhibitors, which block the mechanisms by which cancer cells evade the immune system's detection, and therapies that improve the immune system's innate ability to recognize and destroy cancer cells are some of the strategies used in this approach.[107] While immunotherapy and individualized treatments are far more advantageous than traditional chemotherapy, they also bring special difficulties.[108] The possibility of immune-related adverse events and off-target effects makes safety and efficacy still crucial. These methods enhance ongoing research and clinical studies since they guarantee the best results while reducing related dangers.

CAR T-Cell Therapy

Chimeric antigen receptor T-cell (CAR T cell) treatment is a ground-breaking development in oncology that reprogrammes a patient's T-cells to more successfully identify and eliminate cancer cells.[109] This approach offers a viable therapeutic route for those with few alternatives in treating hematologic malignancies, such as leukemias and lymphomas.[110] The foundation of CAR T-cell therapy is a therapeutic alteration of T-cells, a subset of lymphocytes important to the body's defense against infections and aberrant cells, including cancerous cells.[111] Cancer cells multiply uncontrolled as the immune system cannot find them.[112] T-cells from the patient are harvested during apheresis, the initial stage of the procedure.[113] Ex vivo modifications of these cells are then carried out to express specialized chimeric antigen receptors (CARs) designed to target particular antigens linked to cancer.[114] When genetic modification works, CAR T-cells multiply to a size appropriate for therapeutic injection.[115] When these changed cells are sent back into the patient biosystem, they exclusively cling to cancer cells, starting a series of events that ultimately result in the cancer cells' death.[116] However, employing CAR T-cell therapy is not without its challenges, the most important being the possibility of neurotoxicity and cytokine release syndrome (CRS).[117]

A systemic inflammatory disorder called CRS can cause high temperature, hypotension, and multiorgan malfunction. Neurotoxicity might be convulsions, confusion, or other neurological problems.[118] Therefore, medical practitioners need to closely watch patients receiving CAR T-cell therapy and use therapeutic strategies to control these hazards. The main adverse effects of the treatment need to be temporarily stopped or delayed. Cancer treatment has transformed tremendously with CAR T-cell therapy.[119] Its safety profile is being improved, and its application to additional cancer kinds is being extended to provide more long-lasting results and increase patient accessibility.[120] As this area develops, CAR T-cell immunotherapy should become a mainstay of individualized cancer treatment, providing patients worldwide with fresh hope for better results and longer remissions.[121]

Role of Epigenetics in Cancer Therapy

Cancer progresses largely due to epigenetic dysregulation or changes to chromatin structure and gene expression without changing the DNA sequence.[122] These changes affect DNA nucleosomes packed into the cell nucleus.[123] Two processes accomplish tight control of this compaction: covalent modification of histone proteins (methylation, acetylation, and other post-translational modifications) and DNA methylation at CpG sites.[124] Apart from these mechanisms, non-coding RNAs, histone variation replacement, and chromatin remodelling affect gene transcription and chromatin structure.[125] Epigenetic states can vary dynamically between open (euchromatin) and closed (heterochromatin); heterochromatin is usually associated with transcriptional inhibition, whereas euchromatin permits access to DNA by transcriptional machinery and promotes active transcription.[126] Epigenetic medicines aimed at these changes directly attacking cancer cells have been developed in response to this dynamic control.[127] Furthermore, epigenetic changes play a role in the immune evasion of cancer cells, and recent research raises the possibility of using epigenetic treatments to improve immunogenicity and immune detection.[128] Developing and enhancing new anticancer drugs that leverage these regulatory pathways to enhance immune system responses against cancer and improve treatment outcomes requires a thorough understanding of these epigenetic mechanisms.[129]

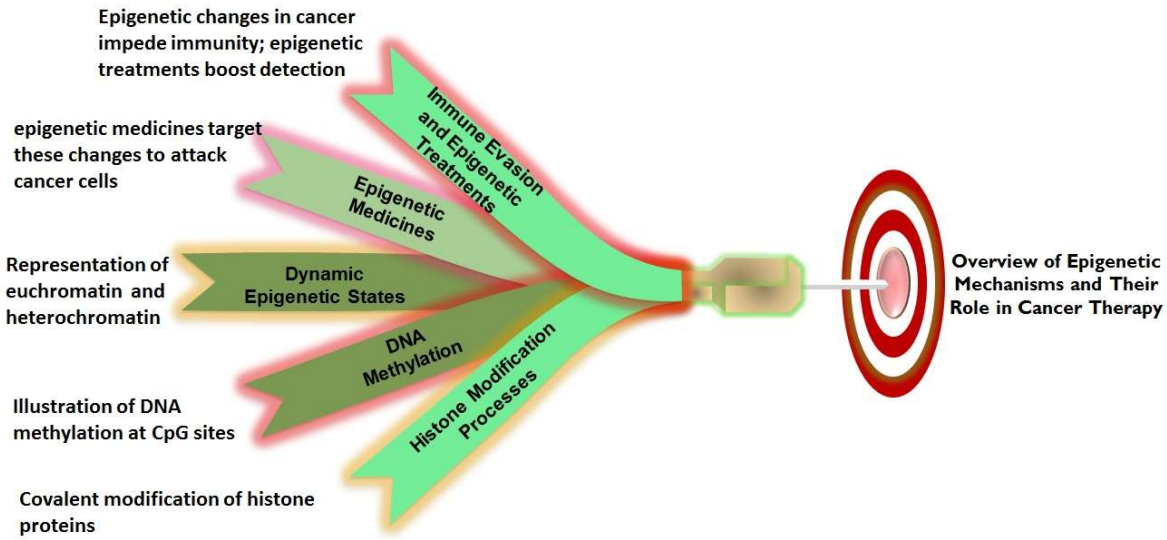

Figure 2: Overview of Epigenetic Mechanisms and Their Role in Cancer Therapy

Therapeutic Vaccines Based on Tumor Cells

Other materials used to make vaccines are synthetic, allogeneic, or autologous cells that have been radiation or chemically inactivated to stop increasing. These cells can be infected with immunostimulatory viruses such as Newcastle disease virus or genetically changed to express cytokines such as GM-CSF (as seen in GVAX, a vaccine composed of tumor cells transformed with the GM-CSF gene).[130] Typical subcutaneous delivery methods for immunizations include saline solutions, incomplete Freund's adjuvant (IFA), and various oil emulsions. Many combinations of these tumor-cell-based vaccines have been tested in clinical studies.[131] In a well-known trial, patients with pancreatic cancer received GVAX, which consists of recombinant Listeria bacteria expressing tumor-associated antigens (CRS-207) and allogeneic pancreatic tumor cells. Overall survival did rise with few side effects, even if this combination was less effective than standard chemotherapy.[132] Three groups-normal chemotherapy, only CRS-207, and cyclophosphamide (Cy)/GVAX+CRS-207 -were randomly formed from the trial participants. Out of the cohort of 213 patients, the median overall survival (OS) for the Cy/GVAX+CRS-207 group was 3.7 months, the CRS-207 group was 5.4 months, and the standard chemotherapy group was 4.6 months.[133] While Cy/GVAX combined with pembrolizumab resulted in low objective response rates for other cancer types, more research on GVAX combinations with other immunotherapies, such as ipilimumab, showed that effector CD8+ T-cells and their cytolytic activity increased in patients with metastatic prostate cancer.[134]

Advanced and Innovative Cancer Therapies

The two mainstays of cancer treatment are surgical excision and brachytherapy radiation. Brachytherapy radiation can be given either locally inserted radioactive elements or from an external beam source. Targeted irradiation, made feasible by this method, enables more focused therapy. Two new developments in radiotherapy are intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), which uses real-time imaging to enhance beam localization.[135] To reduce the amount of radiation exposure to healthy tissues and hence reduce negative side effects, IMRT modifies radiation beams. Another important development is stereotactic ablative radiation therapy (SABR), which allows high radiation dosages to be administered to a small target area with much reduced toxicity to nearby tissues. Radio resistance is a major barrier that reduces the efficacy of radiation therapy, even with recent advancements. Targeting certain mitochondrial processes may help restore radiation sensitivity since anomalies in the mitochondria have been associated with radiation resistance.[136] As proven in an esophageal cancer model where such changes correspond with treatment resistance, studies in this field have indicated that abnormalities in mitochondrial structure and energy metabolism can predict radio resistance. As such, research is now being done to assess the potential of small molecule radio sensitizers targeting mitochondrial pathways in gastrointestinal cancers. A rapidly developing area, precision medicine uses a wealth of data gathered during diagnostic and therapeutic procedures to tailor therapies for each patient. The goal of two young disciplines, patronymics, and radionics, is to extract quantitative information from pathology and radiological images to use as indicators of illness prognosis and therapy result in.[137] These disciplines can handle enormous datasets to predict treatment success, clinical outcomes, and the possibility of illness recurrence through artificial intelligence technology, especially machine learning.[138] These prediction skills make it possible to treat cancer individually and adjust treatment plans for the best possible patient results. Radiomics is the high-throughput analysis and quan-

tification of tumor features obtained from medical imaging; pathomics uses high-resolution tissue imaging to obtain a thorough knowledge of tissue structure and illness. Large, flexible databases holding data from histological research, three-dimensional tissue reconstruction, metabolic profiling (e.g., by positron emission tomography), and gene expression research are being used in these fields to create ever more complex image analysis methods.[139] Through improved description and identification of disease features, these efforts further the more general goal of precision oncology.

Monoclonal Antibodies

In targeting certain antigens on cancer cells, monoclonal antibody-based treatments are synthetic proteins given intravenously to imitate the body's immune system. There are relatively few mouse sequences in these antibodies; most are human. Among their modes of action are delivering lethal chemicals such as radioisotopes straight to the tumor, stimulating host immune responses to target malignant cells, and attaching to certain ligands or receptors to inhibit essential pathways for cancer cell signalling.[140] The monoclonal antibody gemtuzumab was used in combination with calicheamicin to treat acute myeloid leukemia (AML). The antigen CD33 is its target, and a similar anti-CD20 antibody coupled with the radioactive isotope Yttrium-90 (90Y) is called ibritumomab tiuxetan.[141] Monoclonal antibodies can also directly deliver therapeutic drugs to cancer cells as prodrug-activating enzymes or chemotherapeutic toxins, improving cancer treatments' efficacy and selectivity. Because monoclonal antibodies (mAbs) may target cancer cells with such accuracy that enhances therapeutic efficacy and lowers off-target effects usually linked to conventional chemotherapy, they are becoming essential to current cancer treatment. They can attach to specific antigens expressed only on the surfaces of cancer cells, ignoring healthy tissues, to target immune responses to malignancies or therapeutic medications.

Among the many applications for mAbs, the critical are the direct inhibition of cancer cell activity, immune system modulation, and antibody-drug conjugates (ADCs) for cytotoxic agent delivery. This focused strategy is best shown by ADCs, which combine strong chemotherapy medicines with monoclonal antibodies to concentrate cytotoxicity at the tumor location. Furthermore, precise tumor localization and therapeutic response tracking have been possible using mAbs in diagnostic imaging. Important instances demonstrating the efficacy of targeted immunotherapy are rituximab, an anti-CD20 monoclonal antibody used in non-Hodgkin lymphoma, and trastuzumab, a monoclonal antibody that targets the HER2 receptor in HER2-positive breast cancer.[142]

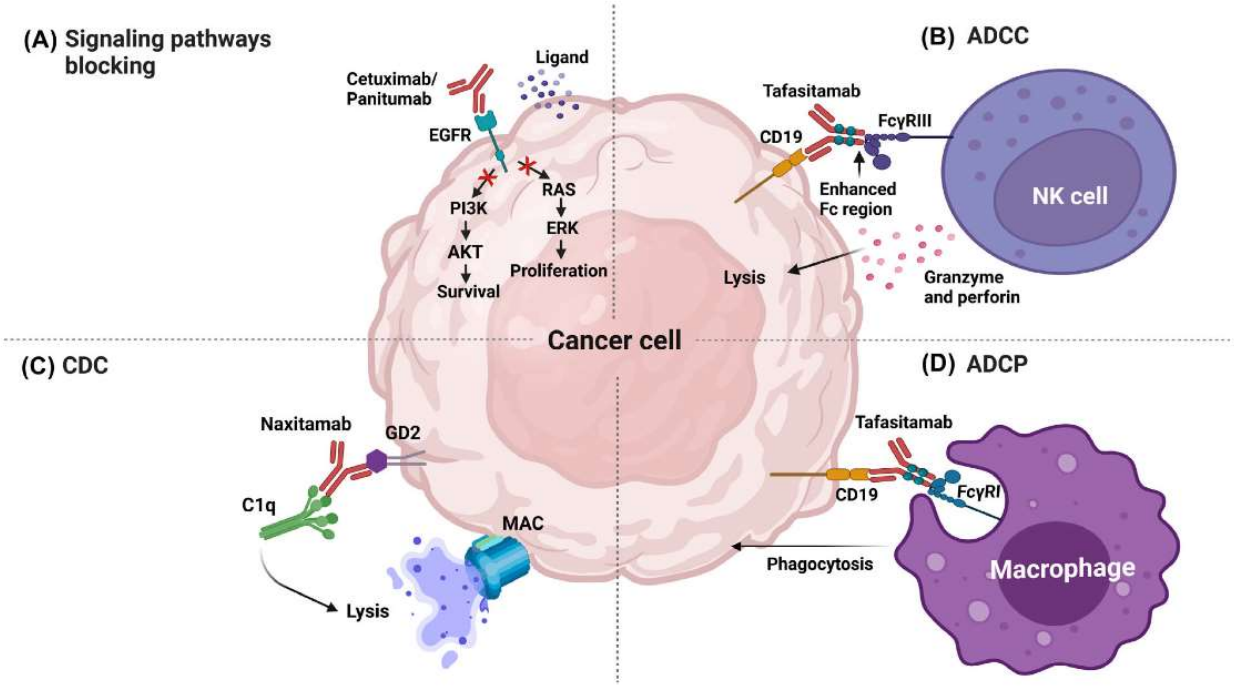

Figure 3: Effector mechanisms of therapeutic mAbs in cancer therapy

(**A**) Signaling pathway blocking. (**B**) Antibody-dependent cellular cytotoxicity. (**C**) Complement-dependent cytotoxicity. (**D**) Antibody-dependent cellular phagocytosis. AKT: Protein kinase B, ERK: extracellular signal-regulated kinase, C1q: complement component 1q, MAC: Membrane attack complex, FcγRIII: Fc-gamma receptor III, FcγRI: Fc-gamma receptor I. The image was created in BioRender (**www.biorender.com**, accessed on 20 January 2023).[143]

Because trastuzumab both inhibits HER2 signalling and encourages immune-mediated destruction, it is essential in treating aggressive breast cancer; to achieve the best outcomes, it is frequently used in conjunction with chemotherapy. Even more applications of monoclonal antibody technology are being made possible by recent developments in immunological checkpoint inhibitors and bispecific antibodies. While bispecific antibodies can simultaneously interact with several biological targets, creating novel modes of action, checkpoint inhibitors such as pembrolizumab and nivolumab retards cancer cells from avoiding immune detection. The immune system boosts the anti-tumor response, successful in lymphoma and refractory leukemia cases.

Artificial Intelligence in Cancer Treatment:

AI models would prescribe and forecast treatment response and toxicity in an AI-enabled adaptive cancer therapy framework. Quality clinical, genetic, and imaging data in sufficient volume is needed to train these AI models. The information used for training must have a good signal-to-noise ratio and be accurate and representative of varied patient groups for these AI models to function well in the clinic. Multi-omics data (e.g., imaging/radiomic, proteomic, genomic, metabolomic, etc.), histopathology data, EMR data, medical records, and clinical trial data are pertinent to precision oncology.[144] The malignancy genome atlas (TCGA) initiative makes large genomic, transcriptomic, proteomic, and epigenomic datasets from many cancer types accessible to researchers, but most patient information is stored in institutions.[145]

Data analysis using AI would be best for mining the growing data from these clinical trials to help oncologists select candidate therapies for neoadjuvant and adjuvant settings based on biomarkers like oncogene status for targeted therapy. By utilizing AI for data analysis in clinical trials, oncologists can make more informed decisions about which therapies will most likely be effective for individual patients. This personalized approach to treatment selection has the potential to greatly improve patient outcomes and overall survival rates in cancer care.

Disease status data let AI-based customizable therapy stay far ahead of the disease. The supportive therapeutic goal would indicate the reinforcement learning reward function in this situation. Managing cancer with developed treatment resistance could require an evolutionary-based method that uses clone competition.[146] Thus, a patient with advanced melanoma could benefit from AI analyzing their disease status data to predict potential treatment resistance and customize a therapy plan that stays ahead of the disease progression. By incorporating an evolutionary-based approach that considers clone competition, oncologists could adjust the treatment regimen to target specific cancer cell populations and overcome resistance mechanisms.

AI's abilities could assist in overcoming the difficulty of targeted and immunotherapies, which can offer a clear therapeutic benefit that "Response Evaluation Criteria in Solid Tumours" (RECIST) outcomes fail to capture. The assessment of response determined by tumor size implies that tumors are spherical and show homogeneous spatial change following treatment. Specific therapies and immunotherapies cause unique patterns of response that contradict RECIST-based outcomes, which may increase clinical trial failure rates and drug development costs.[147] AI's capacity to measure response-related biological processes other than size fills an essential field requirement. By analyzing complex data sets and patterns, AI can identify subtle changes in tumor composition, metabolism, and microenvironment that may not be reflected in RECIST measurements. This can provide a more comprehensive understanding of treatment response and help tailor therapies to individual patients.

Due to advances in machine learning and large data sets, AI-driven clinical decision-support systems (CDSS) are being created.[148] Machine learning algorithms can improve clinical decision-making by predicting medical outcomes beyond qualified medical experts. To turn unstructured electronic health data into discrete omics features, a radiology-driven approach combines medical token cognition (Radio-LOGIC).[149] Using machine learning algorithms to analyze this data, CDSS can provide more accurate and personalized recommendations for healthcare providers.

Although the CDSS can quickly gather and categorize stored data, hospital ratings currently dominate it, and there are few large-scale applications. CDSS, utilizing machine learning algorithms, could analyze a patient's medical history and imaging data to predict the likelihood of developing a specific disease, allowing healthcare providers to intervene early and provide personalized treatment plans.[150] However, with access to a wide range of diverse and high-quality data sources, the accuracy and effectiveness of the CDSS may be improved in real-world clinical settings.

To overcome electronic health record (EHR) constraints, including inefficient processing and information extraction, a large language model (LLM) might be used.[151] LLMs have the potential to understand and generate human language, making them valuable tools for processing and extracting information from electronic health records. In combination with machine learning algorithms, LLMs can enhance the predictive capabilities of CDSS, ultimately leading to better patient outcomes and more effective healthcare delivery.

Clinical translation and patient outcomes

Clinical trials utilizing replication-defective adenovirus vectors (Ad–p53) delivered intratumorally, intravesically, and intravascularly showed p53 gene expression in tumors but no upregulation of p53-dependent genes or substantial anti-tumor effects.[152] Further research is needed to determine the potential of Ad-p53 vectors in cancer treatment. Different delivery methods or combinations with other therapies may enhance the efficacy of p53 gene therapy. Investigating the mechanisms behind the lack of p53-dependent gene upregulation could provide valuable insights into improving the outcomes of gene therapy for cancer. In most ovarian cancer patients, the clinical trial drug Ad–p53 caused transgene expression and elevation of p53-dependent genes.[153] This was safe to give with systemic chemotherapy, but effective treatment was not found, perhaps due to dominant mutant p53, which is often expressed in ovarian malignancies and forms inhibitory heterodimers with wild-type p53. Some ovarian cancer patients may have had transgene expression and higher levels of p53-dependent genes after intraperitoneal Ad-p53. However, the treatment failed could also be due to different types of tumors or resistance mechanisms that weren't related to mutant p53 expression. Randomized phase II trials of intratumoral Ad–p53 followed by radiation for individuals with head and neck squamous carcinoma or nasopharyngeal carcinoma showed considerably higher subjective response rates than radiotherapy alone.[154] Thus, these circumstances need phase III studies to evaluate p53 gene therapy's survival effects. The promising results from the phase II trials suggest that intratumoral Ad-p53 followed by radiation may be a valuable addition to standard treatment protocols for these types of cancer. Synthetic oligonucleotides that hybridize to specific mRNAs can inhibit protein expression. Pre-clinical research on anti-sense therapy suggests that this treatment is safe and does not cause any adverse effects.[155] Clinical trials are underway to further investigate the potential of antisense therapy in treating various genetic disorders and diseases. Phase III clinical trial cancer gene-therapy study randomized primary brain tumor patients to surgery and adjuvant radiation with or without HSV-TK. Retrovirus-producing vector producer cells (VPCs) injected into the resection site delivered the enzyme-encoding gene, followed by systemic GCV injection.[156] Clinical benefits were absent, and the Phase III clinical trial results were disappointing as no significant clinical benefits were observed in the patients who received the gene therapy. This led researchers to reevaluate the efficacy of HSV-TK in combination with surgery and adjuvant radiation for treating primary brain tumors. Cytosine deaminase–5-fluorocytosine and nitro reductase–CB1954 pro-drug combinations have also been investigated. However, clinical studies have not shown substantial clinical efficacy.[157] Inefficient vectors may explain inadequate transgene expression despite the strong bystander impact found with these combinations in pre-clinical mice. While inefficient vectors may play a role in limited transgene expression, it is also possible that the lack of substantial clinical efficacy is due to other factors, such as tumor heterogeneity or resistance mechanisms that are not fully understood. Clinical trials have shown that tumor-specific virus replication can happen in various tumors after the virus is given through an intratumor, hepatic arterial, intraperitoneal, or intravenous route. Furthermore, there was no evidence of dose-limiting toxicity for up to $2X10^{12}$ virus particles.[158] The ability of the virus to replicate specifically within tumors shows great promise for targeted therapy with minimal side effects. Adenoviruses that have a deletion in the early adenovirus gene E1A Rb-binding site reproduce preferentially in tumors lacking pRb. Research shows this vector is more powerful than dl 1520, and clinical studies are underway.[159] The ability of the modified adenovirus to selectively target cancer cells while leaving healthy cells unharmed has made it a potential breakthrough in cancer therapy. If these clinical trials continue to show success, this new vector could revolutionize how we treat cancer in the future. In actively proliferating cells, HSV without ICP34.5 could proliferate.[160] Phase I research showed viral replication in malignant brain tumors after direct injection. Injection into the resection bed of surgically resected brain tumors is safe and may be an effective adjuvant treatment. Long-term follow-up is necessary to assess the overall survival and quality of life of patients who receive this novel therapy. Retrovirus inhibits many human cancers cell lines in pre-clinical research. In vivo investigations have shown lysis of human tumor xenografts and sparing of normal tissue, and clinical trials are ongoing.[161,162] The development of reovirus as a cancer therapy could lead to improved outcomes and quality of life for patients battling this devastating disease. Pre-clinical studies of a replication-competent HSV vector encoding the TK gene demonstrated that GCV reduced cytotoxicity, probably because of an anti-viral effect of the activated pro-drug.[163,164] Human tumor xenografts have been lysed, and normal tissue has been spared in in vivo investigations. Clinical trials are ongoing. The ability of the HSV vector to specifically target and destroy tumor cells while sparing healthy tissue is a significant advancement in cancer treatment.

Conclusion

The future of cancer treatment is increasingly shaped by cutting-edge technologies, with gene therapy, AI, and nanotechnology standing out as key players. While gene therapy holds significant promise, particularly in selectively targeting cancer cells through techniques like microRNA targeting, oncolytic virotherapy, and tumor suppressor gene restoration, challenges in delivery, safety, and immune responses persist. Complete integration of gene therapy into clinical practice, optimizing these delivery methods and addressing long-term side effects is critical and

essential. Similarly, RNA interference (RNAi) therapies offer high specificity and lower toxicity, but dose management and interpatient variability need refinement. AI's integration into cancer diagnostics and treatment planning is revolutionizing clinical decision-making. Machine learning algorithms, particularly convolutional neural networks (CNNs), have enhanced the accuracy of cancer detection and prognosis, making personalized treatment a reality. However, for AI to be fully effective, access to diverse, high-quality data remains a challenge. AI's potential to predict treatment response and manage resistance could dramatically improve survival rates, but real-world clinical integration is still in its infancy. Nanocarrier systems have transformed chemotherapy by improving drug delivery and reducing side effects. While passive targeting through the enhanced permeability and retention (EPR) effect is promising, challenges like multidrug resistance and uneven drug delivery remain. Overall, integrating these advanced modalities into routine cancer care will require addressing technical, logistical, and biological complexities to ensure broad, effective clinical applications.

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