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Review Article

USE OF NANOTECHNOLOGY IN CANCER TREATMENT: A REVIEW

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Abstract: *Nanotechnology has become a revolutionary instrument in cancer treatment, providing unparalleled possibilities for boosting drug administration, increasing treatment selectivity, and decreasing systemic toxicity. This review aims to analyze the use of nanoparticles in cancer treatment, explicitly emphasizing drug delivery methods, cancer immunotherapy, and the mitigation of multidrug resistance. This paper aims to thoroughly analyze the main developments in nanoparticle-based therapeutics by synthesizing existing research. Additionally, it will highlight essential deficiencies in the literature, including the restricted clinical use and long-term biocompatibility of these technologies. This study will evaluate research conducted in the last ten years, focusing on recent advancements in nanotechnology, specifically its ability to improve chemotherapy and radiation by leveraging synergistic effects. The investigation will also investigate the obstacles encountered in the field, such as regulatory gaps and safety issues, that hinder the broader implementation of nanotechnology in cancer. Finally, this review will provide valuable perspectives on the future of nanomedicine in cancer therapy, suggesting particular domains for additional studies, such as more rigorous clinical trials and more thorough examinations of nanoparticle interactions within the tumor microenvironment. The results will improve patient outcomes by contributing to the creation of more individualized and efficient cancer treatments.*

Keywords: Nanotechnology, Cancer Therapy, Drug Delivery, Immunotherapy, Multidrug Resistance, Nanoparticles, Clinical Translation

Introduction

One area of active research is the application of nanotechnology for cancer treatment, which significantly impacts patient care. Nanoparticles have been shown to improve drug delivery systems, provide site-specific treatment, and cause less systemic exposure, thus proving helpful in cancer management (1). However, while the research on this topic continues to grow, the practical application of nanomedicine is still in its infancy, and quite a few features associated with the biomedical use of nanoparticles remain poorly understood, including the safety of use over long-term and the ability to tackle the issue of acquired drug resistance (2). The purposes of this article are to review all the available literature on the use of nanotechnology for cancer treatment, compare and analyze the existing systems concerning therapeutic and prevention means of drug-disease-resistant pathogens focusing on the delivery of drugs, immunotherapy, and factors leading to multidrug-resistant cancers and explain the achievements and challenges in this emerging area of therapeutic technologies (3).

In current research, especially in nanomedicine and oncology, the relevance of therapies that employ nanoparticle types is increasing. Using nanomaterials has shown achievement in using chemotherapy by improving the targeting and using them as radiosensitizers to enhance the impact of radiation therapy(4). Unfortunately, these studies also demonstrate the need for more knowledge of how nanomedicines behave in the tumor microenvironment for extended periods and in different types of cancers (5). These gaps need to be addressed for the progression of such a field and the development of more effective cancer treatment strategies.

This review aims to fill in a considerable knowledge gap regarding the clinical translation of nanotechnology in cancer treatment or its harmful effects after long-term usage. With the help of an extensive literature review, this study points out some of the main drawbacks of the earlier studies; for instance, too few cancer clinical trials were conducted, and far fewer discussed the issue of the long-term safety of the conducted treatments(6). This review uses a new synthesis approach to describe the main problems and suggest innovative nanoparticle-based treatment solutions for broader applications.

Historical Development and Evolution of Nanotechnology in Cancer Therapy

Early Innovations in Nanotechnology for Oncology

Nanotechnology can be considered an important domain in battling cancer, and the various developments made in the past have provided a chance to make rapid progress in the

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field of oncology (7). The invention of nanoparticles, leading to more efficient and site-directed drug delivery for cancer treatment, is one major landmark in the development of nanotechnology-based cancer treatment (8). At the early stages of developing nanomedicine for cancer treatment, attention was placed on developing nanoparticles that can preferably target tumour tissues with their low distribution to normal cells. This was possible using the enhanced permeability and retention effect, which takes advantage of the leaky blood vessels and suboptimal lymphatics in solid tumours. Using these nanoparticles to encapsulate chemotherapeutic agents enhanced the pharmacokinetics and biodistribution of the drugs, which increased the exposure to the tumours while reducing the toxic effects on the whole system (9).

One of the notable works in this area was Maeda, and others used polymeric nanoparticles to carry the anticancer drug doxorubicin to solid tumours in animal studies (10). The outcome was a dramatic growth retardation of the tumours and improved survival as compared to the free drug, stressing the usefulness of nanoparticle drug carriers for tumour-targeting drug delivery systems (11). Encouraged by the positive results of this early effort, researchers investigated further the possible use of a number of drug delivery systems based on various nanoparticles, such as liposomes, polymeric micelles, and inorganic nanoparticles, against cancer (12). Each of these platforms portrayed some benefits, such as enhanced drug solubility, controlled release kinetics, and incorporation of multiple therapies (13).

Studies on using nanotechnology for head-on imaging and early diagnosis of cancer coincided with the creation of novel nanoparticle-based drug delivery systems (14). Using targeting or visualization-targeted nanoparticles further improved the detection of cancers at an early stage and the accurate staging of the disease(15). A specific example is the applicability of superparamagnetic iron oxide nanoparticles in magnetic resonance imaging to image cancers. When administered through intravenous injection, such nanoparticles would choose tumour tissues to concentrate, enhancing imaging by better depicting smaller and earlier lesions (16). Over the years, such treatments have been used in cancer monotherapy, with researchers coming up with ideas to make this treatment with nanoparticles more effective and safer. This encapsulates the construction of multipurpose nanoparticles capable of carrying out drug delivery, imaging, and therapy all at once (17).

From Concept to Application: The Growth of Nanomedicine

Over recent years, the concept of nanomedicine has evolved from a mere idea to a practical application, particularly in the field of cancer treatment. This transformation can be traced back to 1959, when physicist and visionary Richard Feynman predicted the control of matter at the molecular level, laying the foundation for what we now know as nanotechnology(18). More than thirty years later, sophisticated methods for fabricating, characterizing, and imaging nanostructures and nanoparticles emerged. During the latter half of the 1990s, scientists began harnessing nanomaterials for biotechnology, particularly in the diagnosis and treatment of cancer (19). The use of nanoparticles enabled a drug delivery strategy that selectively targets a therapeutic payload to the tumour, sparing normal tissues from chemoreduction(20). Furthermore, nanoscale imaging advancements have significantly improved the sensitivity and accuracy of cancer biomarker detection at early stages (15).

The successful transition of nanomedicine from bench to bedside took several significant steps, including the formulation of doxorubicin in liposomal nanoparticles. This formulation, approved in 1995, was found to improve the drug's distribution within the body and the tumour relative to doxorubicin solvate; this led to better outcomes with less heart damage (21). Ever since, a range of nanoparticle-delivered cancer therapy systems, such as polymer-drug conjugates, inorganic nanoparticles, and modified viruses, have been developed and moved into clinical testing (22).

Nanomedicine has also shown outstanding improvements in cancer detection and imaging. Imaging using nanoparticles bound to targeting ligands or contrast dynamic agents to detect tumours is more sensitive and specific as these nanoparticles home into tumours (23). Superparamagnetic iron oxide nanoparticles, for instance, have been developed as MRI contrast agents and, therefore, assist in detecting the presence of cancer spread (24). Nanomedicine research has advanced with more incredible content on nanomaterials and their acceptance with biological structures, and progress in more innovative therapeutic approaches for cancer has been observed (15). In addition, the creation of "theranostic" agents that possess both diagnostic and treatment properties has enhanced the scope of the application of nanomedicine in a more individualized and accurate treatment of cancer (25).

Types of Nanoparticles in Cancer Therapy

Overview of Major Nanoparticles: Liposomes, Dendrimers, and Metal-Based Nanoparticles

Nano-scale particles present a promising approach for the treatment of cancer, offering hope in this medical challenge. Their ability to enhance targeting, drug delivery, and efficacy surpasses that of traditional methods (26). The most prevalent types of nanoparticles currently in clinical use for cancer treatments are liposomes, dendrimers, and metal nanoparticles (27). *Liposomes* can be defined as round lipid-based nanoparticles that carry a wide array of therapeutic agents, including but not limited to chemotherapeutic agents, proteins and even genes. Their unique structure is that they comprise an aqueous core surrounded by a bilayer of lipids (28). Consequently, both hydrophilic and hydrophobic ingredients can be encapsulated and administered separately. Increasing the targeting of liposomes can be designed by attaching antibodies or peptides to them to help as more targeting agents towards the tumour tissues (29). The net result of such targeted delivery of the drugs is that it improves the therapeutic index of the drugs incorporated within the particles and lowers the systemic toxicity of the patients. There are several liposomal formulations, like Doxil, which have been clinically tested for a range of malignancies, including ovarian, breast and multiple myeloma cancers (21).

Dendrimers, sophisticated 3D nanostructures, have a wide range of applications, including drug delivery. Their modular architecture allows for the effective incorporation of critical components, such as targeting moieties, therapeutic cargos, and imaging payloads, making them versatile in the fight against cancer(30). Dendrimers can be designed to enhance the solubility, stability, and targeted delivery of chemotherapeutics. They can also serve as

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carriers for photodynamic action, gene therapy, and combination therapies (31). Research has demonstrated the effectiveness of dendrimer-based nanoparticles in targeting and treating solid tumours, such as prostate and breast cancers, with better response rates than existing approaches (32).

Over the years, many attempts have been made to therapeutically target tumours using metallic nanoparticles, particularly gold, silver and iron oxide nanocarriers. These nanoparticles can be tuned to either absorb or scatter radiation, which results in localized heating of the tumour in hyperthermia (32). They can also work as imaging contrast agents for detecting tumours, monitoring cancer and tracing the spread of cancer within the body (33). Further, the metallic nanoparticles were utilized to deliver therapeutics, such as anti-cancer drugs or photosensitizers for photodynamic therapy, into damaging magnetic tumour tissues (34).

Comparative Analysis of Nanoparticle Delivery Systems

In recent years, great progress has been made in the use of nanoparticle formulations for drug delivery in cancer, most probably because they improve the therapeutic benefit and minimize the adverse effects associated with conventional chemotherapy agents (35). Of the numerous nanoparticle platforms developed, high hopes are pinned on polymeric nanoparticles, solid lipid nanoparticles, and metal-based nanoparticles (17). Polymeric nanoparticles are made of, for example, poly or chitosan, which are biocompatible and can be used in drug delivery systems. These polymers can take in many drugs ranging from small molecule drugs to proteins and genetic materials. Their surface may also get functionalized, which helps target the tumours and decrease systemic toxicity (36). Polymer-based systems have been shown to aid in the pharmacokinetics and biodistribution of anticancer drugs and subsequently facilitate the superior accumulation of these therapeutics onto the tumours and better treatment response (37). For instance, one preclinical study showed that breast cancer-bearing mice treated with PLGA nanoparticles loaded with the chemotherapeutic agent docetaxel exhibited better antitumor activity and lesser side disorder of cardiotoxicity than free docetaxel on a diving basis (38).

Biocompatible lipids and surfactants used in solid lipid nanoparticles offer several advantages over polymeric nanoparticles, including high encapsulation efficiency of lipophilic drugs, protection of the drug from degradation, particularly if active substances are incorporated and the capacity to deliver drugs to a specific organ or cellular structures (39). The lipid nature of the compositions of SLNs also contributes to the permeability and retention of the surface active agent in the tumour microenvironment(39). Also, a recent clinical study prepared that SLNs loaded with the anticancer drug paclitaxel in advanced solid tumour patients proved effective with better tumour response and lesser systemic toxicity than customary paclitaxel formulations during and after treatments (40).

Metal-based nanoparticles, such as gold, silver, and iron oxide nanoparticles, have garnered attention due to their unique physical and chemical properties. These nanoparticles, when engineered, can enable simultaneous imaging and therapy, enhancing drug delivery systems and phototherapy (41). Notably, the development of gold and silver-based nanoparticles has shown promising results, providing selective delivery of the chemotherapeutic agent cisplatin into prostate cells without affecting surrounding tissues (42). In conclusion, the fusion of nanotechnology with cancer therapeutics has ushered in a new era in oncology. This convergence has opened up novel opportunities for targeted, tailored, and more effective anticancer therapy, a new wave of research and development in the field (1).

Table 1: Types of Nanoparticles and Their Applications in Cancer Treatment

Type of Nanoparticle	Composition/Structure	Main Application in Cancer Treatment	Example of Use
Liposomes	Phospholipid bilayer vesicles	Drug delivery, targeted therapy	Doxil (Doxorubicin-loaded liposome) for breast cancer
Dendrimers	Branched polymers with a high degree of surface functionality	Drug delivery, imaging, gene therapy	Dendrimers loaded with anticancer drugs for precise targeting
Metallic Nanoparticles	Gold, silver, iron oxide	Imaging, hyperthermia, drug delivery	Gold nanoparticles used for photothermal therapy in prostate cancer
Polymeric Nanoparticles	Biodegradable polymers like PLGA (polylactic-co-glycolic acid)	Drug delivery, controlled release	PLGA nanoparticles used for delivery of paclitaxel in lung cancer
Carbon Nanotubes	Cylindrical carbon molecules	Drug delivery, imaging, photothermal therapy	Carbon nanotubes used for delivering chemotherapeutics to tumor sites
Quantum Dots	Semiconductor materials	Imaging, diagnosis	Quantum dots used for fluorescent labeling of cancer cells
Nanocages	Hollow metallic nanoparticles	Imaging, drug delivery	Silver nanocages for photoacoustic imaging and drug delivery in tumor cells
Magnetic Nanoparticles	Iron oxide or magnetite	Magnetic resonance imaging (MRI), hyperthermia, drug delivery	Magnetic nanoparticles used for MRI imaging of tumors

The following table provides a concise overview of several categories of nanoparticles and their particular uses in the field of cancer therapy. These nanoparticles are employed for applications including medication administration,

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nuclear imaging, immunotherapy, and addressing drug resistance. The table presents a graphical overview of the several nanoparticles examined in the preceding section on "Types of Nanoparticles in Cancer Therapy."

Mechanisms of Nanoparticle-Mediated Drug Delivery

Enhanced Permeability and Retention (EPR) Effect and Passive Targeting

The Enhanced Permeability and Retention effect (EPR) is the principle that allows for the passive targeting of cancer using nanoparticles to be developed. It refers to the tendency of nanoparticles to aggregate in solid tumours due to the properties of the tumour blood vessels and surrounding tissues (43). In contrast to normal ones, solid tumours are often associated with abnormal neovascularization and inadequate lymphatic drainage, which increases the permeability of the tumour's blood vascular compartment. The effect is that nanoparticles, which range between 10 and 100 nm in diameter, can leave the blood circulation and penetrate the interstitial space of the tumour (9). Also, since there is little or no lymphatic drainage within the tumour context, the clearance of these nanoparticles is depressed, thereby helping to retain the nanoparticles at the tumour site (44).

This mechanism, EPR, has been reported to be beneficial in enhancing drug delivery to the cancer region and, at the same time, reducing toxicity (45). Thus, it is possible, because of this mechanism, that systems for drug delivery using nanoparticles will deliver chemotherapy at the tumour area and thus minimize delivery to the surrounding non-cancerous tissues (46). This limiting approach increases the selectivity of anti-cancer drugs acting on the tumour and, at the same time, prevents the adverse effects that are usually experienced in chemotherapy (47).

Numerous studies have shown that the EPR effect enhances nanoparticle-based therapies for cancer (48). For example, research has found that polymeric nanoparticles containing the chemotherapeutic agent doxorubicin and liposomal nanoparticles loaded with irinotecan could be preferentially taken up by the tumour via the EPR effect, which could enhance tumour swelling and lower generalized toxicity over the free drugs (45). In summary, the EPR effect is a very important mechanism that allows effective passive targeting of diseased cells through a nanoparticle drug delivery system (49).

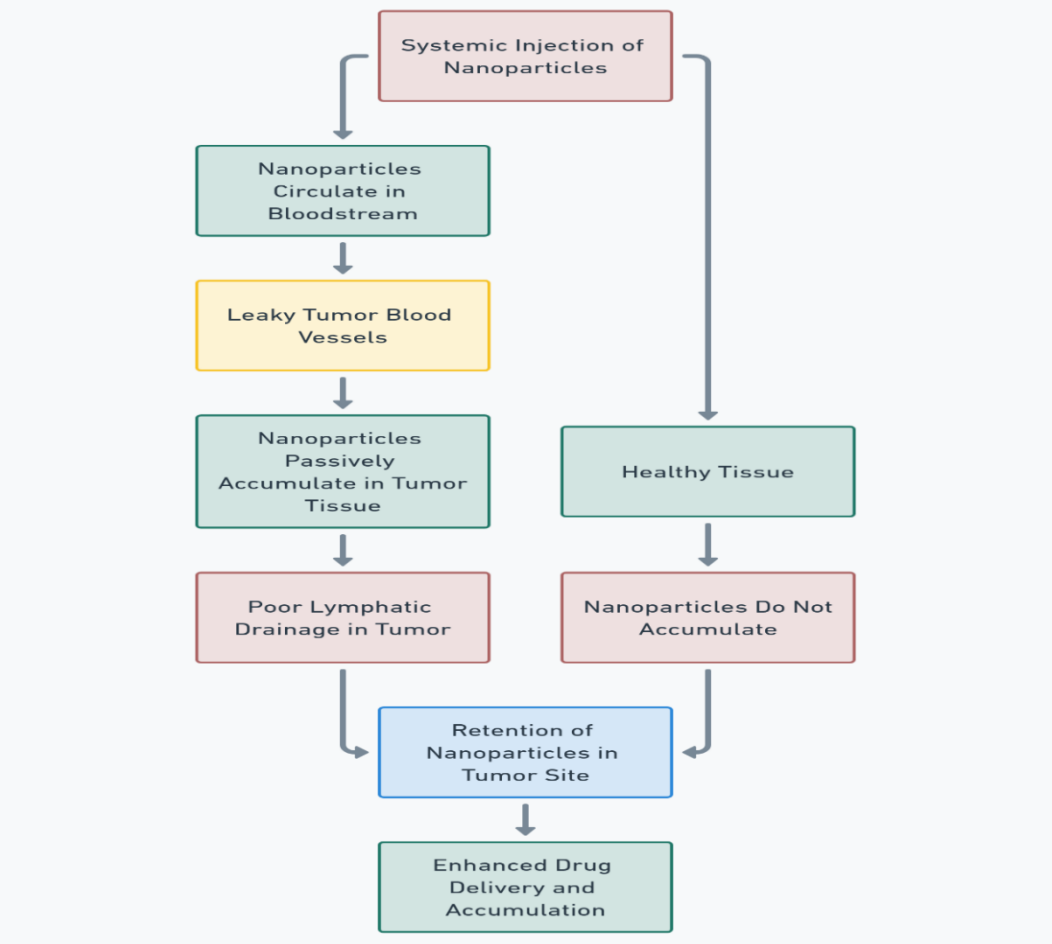

Figure 1: Mechanism of Enhanced Permeability and Retention (EPR) Effect:

The above diagram depicts the Enhanced Permeability and Retention (EPR) Effect, which is a mechanism enabling the accumulation of nanoparticles in tumor tissues owing to the distinctive properties of tumor blood arteries. The technique

commences with the administration of nanoparticles via systemic injection, following which the nanoparticles enter the circulatory system. Tumor blood arteries in general exhibit permeability, which enables the nanoparticles to accumulate passively within the tumor tissue. Furthermore, tumors exhibit inadequate lymphatic drainage, therefore impeding the effective removal of nanoparticles and leading to their retention at the site of the tumor. Consequently, this results in Heightened Drug Delivery only to the tumor, whereas healthy tissues do not undergo the same buildup of nanoparticles, so reducing any adverse effects. This mechanism of passive targeting is fundamental to cancer treatments based on nanoparticles.

Active Targeting Through Nanotechnology

Nanotechnology-based cancer therapy, a burgeoning field, holds the potential to revolutionize cancer treatment. Active targeting, a key strategy, involves the engineering of nanoparticles with target-specific surface modifications, offering a promising future for cancer therapy (50). Active targeting entails using nanoparticles to selectively bind and identify distinct molecular markers or receptors attached to the surface membranes of the cancer cells (51). This is achieved by ligating the particle surface to ligands, peptides or antibodies with intrinsic specificity to those cancer targets. Such targeting molecules include folate, transferrin and monoclonal antibodies that recognize over-expressed surface antigens in tumour cells (52).

In contrast to passive targeting, which is solely dependent on the passive accumulation of the nanoparticles in tumour regions by the enhanced permeability and retention effect, active targeting increases the delivery of the drug by actively directing the nanoparticles toward the tumorous cells (53). This strategy implies that the therapeutic increase can be achieved where most of the drug is accumulated within the tumour region while small amounts go to the other tissues (54). According to some recent investigations, nanoparticles that can be passively or actively targeted have shown promise in the treatment of cancer (54). For example, a study in Nature Nanotechnology showed folate-targeted liposomal nanoparticles for delivering doxorubicin drugs to ovarian cancer cells (13). Actively targeted nanoparticles showed higher tumour accumulation and better antitumor activity than non-targeting counterparts in both in vitro and in vivo experiments (55).

Another instance is where nanoparticles are conjugated onto antibodies to treat solid tumours. Targeting receptors in cancer cells, monoclonal antibodies directed at surface receptors such as HER2 and EGFR have been used to direct therapeutic drugs and imaging molecules to these cells(56). This has resulted in effective tumour targeting and increased therapeutic efficiency in the preclinical use of these actively targeted nanoparticles(54). The active targeting of nanoparticles is a powerful strategy in the fight against cancer, standing alongside surgery and other nanotechnology-based treatments(13). Researchers play a crucial role in enriching nanoparticle formulations' surfaces with ligands, peptides, or antibodies that bind specifically to oncogenic tissue, thereby increasing drug retention in tumours and improving patient outcomes(20).

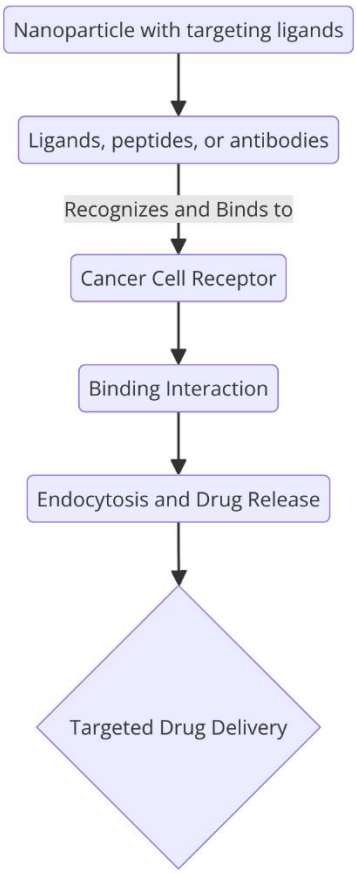

Figure 2: Active Targeting of Nanoparticles to Cancer Cells

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This diagram schematically represents the procedure of actively directing nanoparticles to cancer cells. Nanoparticles are altered with ligands, peptides, or antibodies that selectively attach to receptors located on the plasma membrane of malignant cells. The diagram illustrates the process by which these targeting molecules identify and dock with the receptors of cancer cells, therefore establishing a binding association. Upon binding to the receptor, the nanoparticle is taken up by endocytosis, enabling the precise delivery of therapeutic nutrients straight into the cancer cells. Implementing this technique increases the accuracy of drug administration, therefore minimizing adverse reactions and enhancing the effectiveness of cancer treatment.

Nanoparticles in Cancer Immunotherapy

Integration of Nanoparticles in Immune Modulation

The use of nanoparticles to carry immune cells is a prospective remedy within the cancer vaccination approach. Less than 100 nanometers in diameter, these particles might be modified to bear and transport adjuvants that activate cellular processes responsible for destroying tumour cells (57). One of the main benefits of using nanoparticles in cancer immunotherapy is the possible enhancement of the delivery and pharmacokinetics of immunotherapy agents (58). Various immune-enhancing agents, such as cytokines, immune checkpoint antibodies, or tumour-associated antigens, can be incorporated into nanoparticles to increase their stability in blood. This allows these agents to be delivered directly and persistently to the tumour region, providing higher levels of immune activation and tumour cell elimination (59).

Moreover, it is also possible to execute the design of these nanoparticles so that they seek and enter the tumour-suppressive microenvironment. These nanoparticles have the opportunity to minimize some of the issues affecting the success of these conventional immunotherapies, including the presence of suppressive cells within the tumour and more effective targeting of those cells with immune therapies (60). It has been shown through several clinical trials and preclinical studies that nanoparticle-based cancer immunotherapies may provide beneficial outcomes(58). For example, anti-PD-1 immune checkpoint inhibitors and interleukin-15 cytokine-carrying nanoparticles were made to stimulate cytotoxic T lymphocytes' activity against solid tumours (61). A preclinical investigation revealed that this nanotherapy outperformed the single agents in tumour growth inhibition, suggesting the benefits of combining different immunomodulatory agents in a nanoparticle formulation (62).

Another example is cancer vaccination strategies that apply nanoparticles loaded with tumor-associated antigens. These nanoparticles can also be designed to temporarily incorporate an antigenic structure and demonstrate specific surface characteristics to phagocytic antigen-presenting cells such as dendritic cells (63). This will contribute to the enhanced presentation of tumour-associated antigens and an effective anti-tumour immune response (64). Nanoparticles can also track and visualize the immune response while undergoing cancer immunotherapy. By embedding imaging agents like fluorescein dyes or radionuclides into these nanoparticles, researchers can control the flow, activation, and reproduction of various immune cells within the tumour microenvironment (15). Due to the multifunctionalities and specificity of targeted delivery and immune system modulation of nanoparticles, there is a high probability of enhancement of cancer immunotherapy using said nanomaterials (65).

Nanoparticles and Immune Checkpoint Inhibitors

Nanoparticles have represented a new era towards improved delivery and efficacy of immune checkpoint inhibitors in cancer therapy. These macromolecules may be tuned to enhance the specificity and the localization of these essential drugs used in immunotherapy (61). Immune checkpoint therapy, such as PD-1/PDL-1 and CTLA-4 inhibitors, deploys specific monoclonal antibodies to restore the immune system's activity against tumour cells(66). Nonetheless, the clinical applications of these inhibitors may be constrained by their pharmacokinetics, such as limited solubility, rapid clearance, and poor tumour infiltration. These limits can be overcome by using nanoparticles as carriers of the immune checkpoint inhibitors (67).

Nanoparticles can be engineered to coat or conjugate with the immune checkpoint inhibitors to prevent their destruction whilst increasing the concentration of the mAbs at the tumour region(68). It has been reported that polymeric and lipid nanoparticles are biocompatible, biodegradable, and, therefore, suitable for delivering anti-PD-1 or PD-L1 antibodies to solid tumours, thereby enhancing the inhibition of slow-growing tumours in vivo and survival in experimental animals (69). One way of enhancing the activity of immunotherapy using immune checkpoint inhibitors is improving the delivery of tumor-associated antigens owing to the use of nanoparticle-based delivery systems (70). By incorporating nanoparticles that heighten the amount of tumour-associated antigens presented to the immune system, a more robust immune response can be caused. Other drugs can be incorporated with nanoparticles targeting the tumour cells that enhance the anti-tumour immune response (58).

Clinical studies have shown that enhancing the anti-tumour immune effects of checkpoint inhibitors by combining them with nanomaterials is feasible (71). A phase I clinical trial of an anti-PD-1 antibody liposome formulation demonstrated improved pharmacokinetics and higher tumour retention of the PD-1 antibody as compared to the free antibody, with promising clinical effects in patients with advanced-stage solid tumours (72). Nevertheless, there are still obstacles to overcome in the delivery of targeted immune checkpoint inhibitors using nanoparticles, such as the effective targeting of the nanoparticles to the tumour without toxicity and the nanoparticles' pharmacokinetics (73).

Overcoming Multidrug Resistance (MDR) Using Nanoparticles

Mechanisms of Multidrug Resistance and Nanoparticle-Based Solutions

One of the hurdles in cancer treatment is the emergence of cancer cells with a high degree of heterogeneity and the development of resistance to many drugs administered. Such resistance is most commonly the result of elevated levels of efflux pump proteins, such as P-glycoprotein, which extrude toxic substances, including chemotherapeutic agents, from the cells(74). Other ways

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this multidrug resistance may develop concern the scaffolding of the apoptosis-promoting pathways, making it difficult for drug-directed apoptosis to affect the malignancy cells (75).

In this regard, researchers have taken advantage of nanoparticles as a potential solution. Nanoparticles could inhibit the ABC transporters' activity, thus reducing drug efflux and restoring drug sensitivity in cancer cells that have become resistant to conventional therapies (13). For example, specific nanoparticles have been simultaneously loaded with synthetic silencing RNA specific to the genes coding for ABC transporters, abrogating the expression of the transporters (76). Other novel loaded nanoparticles containing ABC transporter inhibitors and chemotherapeutic agents improved the accumulation of anticancer agents in cancer cells. Moreover, nanoparticles are also used to help restore apoptotic pathways in resistant cancer cells. The intriguing idea is that some kinds of nanoparticles have been designed to focus on delivering pro-apoptotic proteins or molecules that would help re-activate deregulatory pro-apoptotic pathways and lead to the death of resistant cancer cells(30). This method has been quite effective in preclinical trials, in which the delivery of agents that could induce apoptosis using nanoparticles reversed the resistance and improved treatment efficacy (77).

Nanoparticles may also be utilized more favourably in enhancing the uptake of cytotoxic agents by resistant cancer cells by applying the EPR effect characteristic to solid tumours (78). The leakage of blood vessels and poor lymphatics in the tumour microenvironment render a conducive environment for the accumulation of nanoparticles for targeted drug delivery by enabling a high drug-to-resistant cancer cell ratio (79). Recent reports have indicated the success of employing strategies of nanoparticles carrying both conventional and biological therapeutics to overcome multidrug resistance in cancer treatment. They are granting the development of such novel nanoparticle systems aimed at targeting and eliminating these resistance mechanisms (13).

Emerging Nanotechnology Strategies to Combat MDR

Nanotechnology-based strategies have become essential for dealing with globular drug resistance in cancer. One of the newest approaches is using nanoparticles in combination with RNA interference (80). Tumour cells can be managed to overexpress, or more so, the genes encoding efflux pumps or other cellular drug resistance mechanisms by embedding or mixing small interfering RNA or short hairpin RNA into nanoparticles. This combined mode of action helps to increase the amount of the chemotherapeutics absorbed by the cells and thus improves the efficacy of treatment (81).

Unlike the previous strategies, these agents employ nanoparticles for thermal or photodynamic therapy to counteract drug resistance. Nanoparticles can be designed to preferentially localize within cancer tissues and subsequently be subjected to hyperthermia or light-induced or chemical-induced killing of tumour tissues that could have retained drug-resistant cancer cells (82). For example, gold or magnetic nanoparticles can be utilized for thermal therapy, whereby heat or an alternating magnetic field is applied to the nanoparticles, causing them to overheat and disrupt the tumour cells (83). Likewise, photosensitizer-loaded nanoparticles can be applied for photodynamic therapeutic purposes. The nanoparticles target and release the photosensitizer on the tumour, followed by light irradiation, generating reactive oxygen species to kill cancer cells (84).

Novel approaches for treating cancer have emerged based on the increasing literature volume. Studies have shown the advanced properties of nanotechnology in a reversal of drug resistance and enhancement of the effects of chemotherapy (85). For instance, the creation of a multi-functional nanoparticle delivery system, which combines siRNA-mediated gene silencing with photodynamic therapy, was described (86). The nanoparticles were designed to co-deliver siRNA against the drug extrusion pump ABCG2 and a photosensitizer to ABCG2-resistant breast cancer cells. Once the light was turned on, the photodynamic therapy caused the death of the cells, while knocking down ABCG2 allowed more doxorubicin to be in the cells, leading to less tumour size in a mouse model (87). In addition, one more work focused on developing a stimulus-sensitive nanoparticle system which allows for the co-delivery of a small interfering RNA targeting the survivin gene, which inhibits apoptosis and chemotherapeutic agents (88). The nanoparticles were constructed so that the acidic targeted tumour microenvironment would trigger drug release, enabling the combined downregulation of survivin and the distribution of the anti-cancer drug. This search shows the prospects of designing nanotechnology-based strategies to overcome multi-drug resistance and increase the anti-cancer action of the therapy (85).

Nanoparticles as Radiosensitizers and Enhancing Radiotherapy

Nanoparticles as Radiosensitizers in Oncology

Radiosensitizing agents, which enhance the biological effect of radiation treatment in cancer schemes, have included novel nanoparticles. Metal-based nanoparticles, specifically those with high atomic nuclear mass, have received much focus due to their ability to improve the radiation dose delivered to the tumour, effectively killing the tumour cells (5). The mechanism underlying the radiation-enhancing effect of nanoparticles on cancer tissues is related to the structure of the nanoparticles. As the nanoparticles target and accumulate in the cancer tissues, their specific structural properties contribute to the enhanced radiation dose delivered to the tumour cells (89). High-Z metal-based nanoparticles such as the metals Au, Ag, and Pt absorb radiation energy in a way that can result in enhanced energy deposition into the tumour cells(90). Because of this, more reactive oxygen species can be created when using this combination of the two modalities compared to when radiation alone is applied, resulting in more significant DNA damage and cancer cell apoptosis (91).

The focus has recently shifted to the in vivo application of these promising nanoparticles. For example, a report published in 202 in the Journal of the American Chemical Society used a mixed-method approach to study the application of Gold Nanoshells as particle radiosensitizers in treating glioblastoma, an invasive brain tumour (92). Introducing GNPs into radiotherapy resulted in significant improvements in therapy, tumour growth suppression, and animal survival in mouse models (93). Likewise, a clinical

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study conducted at the University of Maryland School of Medicine assessed the effectiveness of hafnium oxide nanoparticles as a radiosensitizer in patients with soft tissue sarcoma (94). The findings were published in the Journal of Clinical Oncology in 2019 and illustrated that tumour control improved with HfO2 nanoparticles concurrent with radiotherapy compared to radiotherapy alone, with no increase in the adverse effects (95).

Non-metal nanoparticles such as polymer micelles have also been developed with positive results as radiosensitizers(95). In this regard, a paper appearing in the Nanomedicine journal in 2018 focused on the prospects of enhancing the radiosensitivity of prostate cancer cells using cerium oxide nanoparticles capable of scavenging free radicals. The findings suggest that radiotherapy directed at the uptake of CeO2 nanoparticles into prostate cancer cells may be a promising strategy for enhancing treatment outcomes in prostate cancer patients. Overall, that may also help lower the differential cytotoxicity (96). The emerging field of nanoparticle-mediated radiosensitization presents a fresh and promising way of augmenting the efficacy of radiotherapy in cancer treatment (5).

Synergistic Effects of Nanoparticles in Chemotherapy and Radiotherapy

Nanoparticles have become an essential tool in cancer therapy due to their ability to improve chemotherapy and radiotherapy efficiency. The New modalities facilitated by nanoparticles could bring about a synergy that transforms patients' treatment outcomes (73). There are various ways to explain the increased effect of chemotherapy and radiotherapy using nanoparticles. First and foremost, nanoparticles can selectively provide active agents at the tumour site through active targeting and controlled drug release. This would improve drug concentration at the disease site while minimizing the adverse effects of the drug's systemic administration (97). Furthermore, metallic nanoparticles can function as radiosensitizers, making tumour cells more sensitive to radiation treatment (42). Moreover, because nanoparticles can recognize and target the special culture conditions in the tumour site, they can also benefit from them. Solid tumours' enhanced permeability and retention effects mean that the nano-drug vectors tend to get entrapped in the tumour tissue selectively. This would make the localization of the cytotoxic intervention and the drug's concentration in the tumour feasible (98).

The available evidence supports the effectiveness of nanoparticle-based combination therapy in improving treatment outcomes. Surrogates have demonstrated that the use of nanoparticles together with chemotherapeutic agents and radiosensitizer agents is effective in shrinking tumours, followed by increased survival in acute models of breast cancer, glioblastoma, and other cancers(99).To sum up, using nanoparticles in the existing therapeutic protocols for treating cancers presents a unique opportunity that may soon change the practice of cancer chemotherapy and radiotherapy. Cancer research has undergone a momentous change through the development of new formulations of pharmacological agents, targeting the unique characteristics of the nanoparticles so that they augment the treatment of cancers (100). This graphic depicts the synergistic effects of chemotherapy and radiation facilitated by nanoparticles. Nanoparticles augment the transportation of chemotherapeutic medications to malignant cells, therefore enhancing the accumulation of pharmaceuticals at the site of the tumor. Concurrently, nanoparticles enhance the responsiveness of cancer cells to radiotherapy by magnifying the impact of radiation on the tumor. The synergistic effect arises from the concurrent administration of chemotherapy and radiotherapy, resulting in an augmented interaction that enhances the efficacy of cancer treatment. This methodology optimizes the therapeutic efficacy while reducing adverse effects, rendering nanoparticle-mediated techniques a highly promising stride in cancer treatment.

Clinical Translation of Nanotechnology: Progress and Challenges

Current Progress in Clinical Trials and Nanomedicine Applications

Nanomedicine has been successful in improving cancer therapies notably, and there are reports of recent clinical trials that have adopted the use of nanoparticles in the treatment of cancer, its diagnostics, chemotherapy, radiotherapy, and immunotherapy (101). In particular, considerable effort has been put into developing nanoparticle-based drug delivery for cancer treatment. These systems enhance the pharmacokinetics of the system and the distribution of the chemotherapeutic agent, thereby improving the targeting of the tumour and decreasing the toxicity to non-targeted or peripheral organs (97). For instance, a thirty-two (32) patient clinical phase II study of liposomal irinotecan formulation in patients with malignant primary tumours metastatic to the pancreatic gland demonstrates optimal overall survival instead of the best supportive care and mono-treatment alternatives(102). Also, in a phase III study, nanoparticle-bound paclitaxel plus gemcitabine for metastatic pancreatic cancer extended the overall survival time significantly (102).

Radiotherapy has also explored the use of nanoparticles for this prevention. Therapeutic radiation with radioactive gold nanoparticles was investigated in the phase I/II study for locoregional treatment of head and neck cancer, resulting in significant tumour reduction and improved quality of life for the patients (103). In addition, the employment of nanoparticles in radiotherapy as radio sensitizers has been studied to increase the effectiveness of radiotherapy by raising the dose of radiotherapy delivered to the tumour. Nanoparticle-based innovations are of great help in the diagnosis of cancers, improving the possibility of their earlier detection and constant surveillance (104). It is not the first time that one has seen the use of nanotechnology for detecting lung cancer since the phase II trial of a blood-based liquid biopsy test with gold nanoparticles was conducted, where the accuracy lessened even at very early stages of the disease (105). The development of anti-cancer drugs using nanoparticles as immuno-oncological agents is also gaining momentum. A Phase I trial of a glioblastoma-specific nanoparticle vaccine demonstrated gratifying immune responses and improved patient survival compared to chemotherapy alone (106). Developing advanced tumour vaccines that target and deliver tumour antigens through nanoparticles offers excellent potential to enhance the effectiveness of cancer therapy (63).

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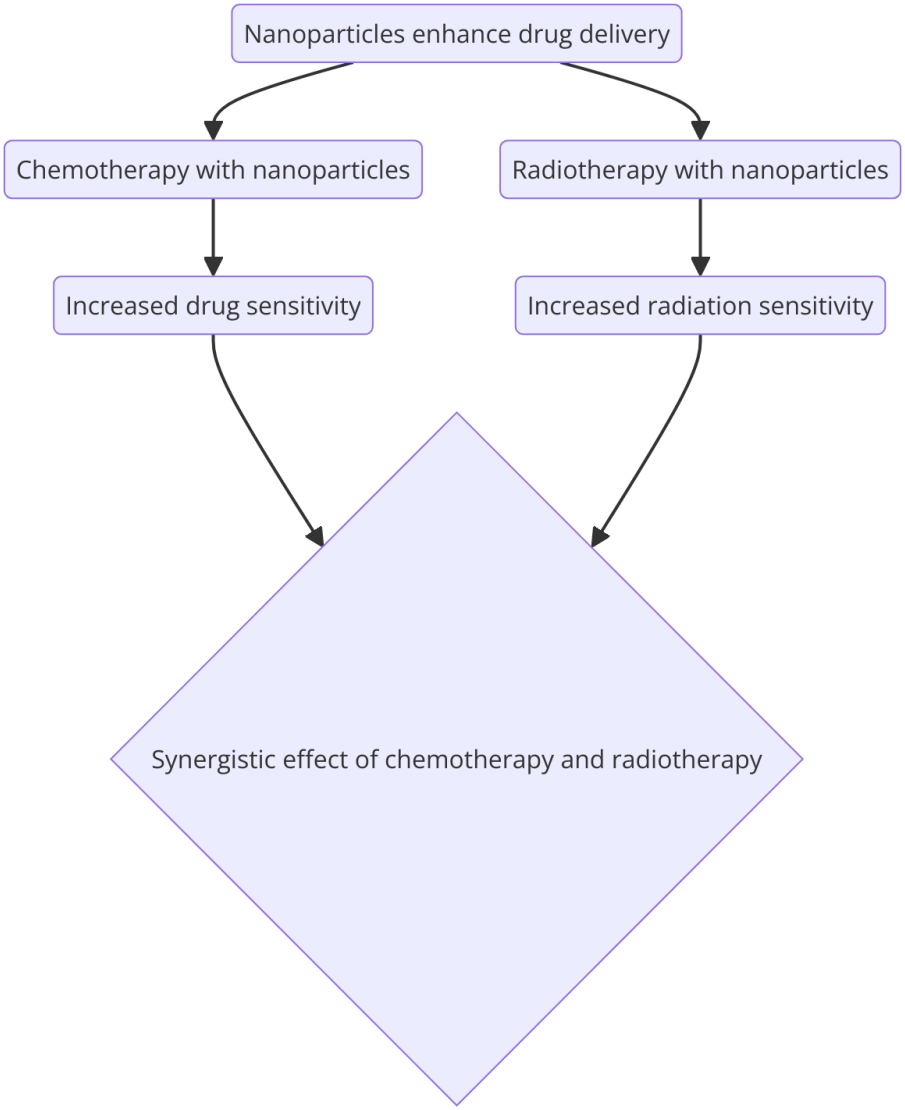

Figure 3: Nanoparticle-Mediated Synergistic Effects in Chemotherapy and Radiotherapy

Challenges in Regulatory Approvals and Long-Term Biocompatibility

Transferring technology from the laboratory to clinical practice presents a fundamental bottleneck in terms of regulatory approval and long-term outcome validation. Overall, nanoparticles have some advantages that other drugs do not, and therefore, safety evaluation against these factors will be strict (107). Obtaining regulatory approval is a critical bottleneck in the process. Nanoparticles have boundaries that have not been previously recognized since present-day regulations were developed with more giant operating pharmaceuticals and medical devices as the central focus. Due to the increase in dimension, surface area, and interactions with cellular systems, regulatory agencies have to develop new guidelines and testing strategies to check the safety and efficacy of nanoparticle onset (107). The spiralling complexity in this aspect of regulatory affairs makes the quick application of new nanomedicines into practice much harder. A further great challenge is the need to provide long-term biocompatibility (108). Since nanoparticles are small and highly reactive, they can be expected to penetrate and accumulate in many different organs and tissues, which may have unwanted consequences (109). A protracted number of animal studies are needed to ascertain the biodistribution and clearance mechanisms of the nanoparticles as well as any possible toxicity that may be associated with them over time to ensure no adverse long-term effects occur (110).

Several cases provide insight into the regulatory issues and delivered safety studies addressing these issues. There has been considerable interest in the design of nanoparticle-based delivery systems in cancer treatment, but concerns have been raised about what happens to the nanoparticles after they have delivered their load (111). The biodistribution and biodegradation of various forms of nanoparticles have also been contested, and it has been proven that some could be eliminated without toxicity to the body (112). In a similar fashion, the introduction of nanoparticles for use in medical imaging has seen umbilical cord blood stem cells exposed to them and their implications for cells and tissues (4). Safety studies composed of biocompatibility tests on inactive nanoparticle-based

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contrast agents have been conducted, which showed that normal body functions were executed with no signs of unnecessary inflammation (113). This adjustment of nanotechnology for the clinical level appears to favour the introduction of new methods and appliances with adequate care for the patient's safety. Conclusive technological advances in nanomedicine call for complementing actions from both the scientific and policy-making domains in developing commensurate methodologies and safety measures as the two are propelled in unequivocal directions (114).

Table 2: Current Clinical Trials Involving Nanotechnology in Cancer Therapy

Type of Nanoparticle	Cancer Type	Phase of Clinical Trial	Key Results/Outcomes
Liposomes (Doxil)	Breast cancer, Ovarian cancer	Phase III	Improved drug delivery, reduced side effects, enhanced survival rates
Gold Nanoparticles	Prostate cancer	Phase II	Enhanced photothermal therapy effectiveness, minimal toxicity
Polymeric Nanoparticles (PLGA)	Lung cancer	Phase II	Controlled drug release, significant tumor reduction observed
Magnetic Nanoparticles	Glioblastoma	Phase I/II	Enhanced MRI imaging, promising results in tumor targeting
Silica Nanoparticles	Pancreatic cancer	Phase I	Increased efficacy in drug delivery, early signs of reduced tumor growth
Carbon Nanotubes	Head and neck cancer	Phase I/II	Effective drug delivery, preliminary results indicate tumor shrinkage
Dendrimers	Colorectal cancer	Phase II	Improved targeting of cancer cells, reduced toxicity compared to conventional therapies
Nanocages (Silver)	Melanoma	Phase I	Enhanced imaging and drug delivery capabilities, early success in tumor targeting

The following table presents a comprehensive summary of ongoing clinical trials that are exploring the application of nanotechnology in cancer treatment. This document provides a concise overview of the several categories of nanoparticles under investigation, the particular cancer types being focused on, the stage of each clinical study, and the significant findings or outcomes found. The table summarises the pragmatic uses of nanotechnology in enhancing cancer therapy by means of increased drug delivery, decreased toxicity, and enhanced imaging capabilities. Through the presentation of these ongoing or concluded trials, it highlights the possible influence of nanoparticles in the clinical environment, offering understanding of the advancements and obstacles encountered in applying nanotechnology to practical cancer treatments.

Conclusion

In conclusion, this review is comprehensive and includes all the available information on cancer nanomedicine, aiming to overcome the challenges of malignant drug delivery, immunotherapy, and drug resistance using nanoparticle-based systems. The analysis supports the argument that nanotechnology has great promise in providing better specificity to treatments, decreasing toxicity, and, thereby, the overall efficacy of cancer treatment techniques. Also, the expansive reach of the findings indicates that nanoparticles are a solution to some of the most daunting problems in cancer therapeutics, such as targeted therapy and immune therapy, radiotherapy, among others, and would significantly contribute to developing targeted therapies. These insights are relevant in related clinical areas and thus would facilitate the progression and use of the present established nanotechnology in oncology. It is, however, essential to note that the review acknowledged the presence of such challenging assumptions as the biocompatibility of nanoparticles and the risk of preclinical studies without further clinical development. Steps should be taken to address the identified deficiencies, particularly concerning the therapeutic use of nanoparticles. Priority should be given to such clinical trials conducted with these technologies in new patient populations to test their safety, efficacy, and the combined approaches of enhancing the targeting of tumors and overcoming resistance. Although this review discussed essential issues, it was limited by a selection of articles and the biases inherent in the literature available. Among such shortcomings, this review provides clear value to the existing work in the field of nanomedicine since it puts forward valuable ideas and suggestions as to how the area can be researched further. This dynamic development of nanotechnology with applications in cancer treatment is highly encouraging. It places the area at the cutting edge of new treatment modalities that could change the face of cancer management.

Conflict of interest

The authors declared the absence of a conflict of interest.

Author contribution:

All authors contributed equally

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