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Editorial

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Recent Developments and the Effect of Antiangiogenic and Chemotherapeutic Nano formulations for Combination Cancer Therapy

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Abstract

As tumor growth and metastasis are frequently dependent on tumor vascularization, conventional chemotherapy in combination with antiangiogenesis medicines (combination cancer therapy) has demonstrated reduced tumor recurrence and better antitumor effects. But the effectiveness of combination chemotherapy-including synergistic, additive, and even antagonistic effects-depends on the optimal medication ratios in the combination. The combination therapy of chemo-antiangiogenesis for cancer is therefore excellent, and Nano formulations show a great deal of promise in this regard. Different Nano carriers for combination therapy have been designed with organic (polymer, lipid), inorganic, or hybrid materials as the basis. Particularly flexible for different forms of entrapment within the same carrier, such as physical adsorption, encapsulation, and chemical conjugation techniques, is hybrid Nano carriers made of multiple material constructs. Thus, chemo- and antiangiogenesis medicines can be delivered together with customizable drug release at target areas using these multifunctional Nano carriers. Therefore, this study aims to assess the most recent developments in Nano formulations and their influence on the combination of traditional cytotoxic and antiangiogenesis drugs in the treatment of cancer. Future prospects as well as the mechanisms and site-specific co-delivery options are covered here.

Keywords: Anticancer; Antiangiogenic agents; Nano-formulations; Combination cancer therapy

Introduction

Cancer-associated fibroblasts and myofibroblasts, neuroendocrine cells, adipose cells, immunological and inflammatory cells, blood and lymphatic vascular networks, and an extracellular matrix all contribute to the complex and dynamic process of carcinogenesis. Together, these mechanisms create a complicated cross-talk in the tumor microenvironment. Therefore, a category of disorders known as cancer are defined as having uncontrolled growth/proliferation and the spread of aberrant cells. Surgery, radiation, and systemic treatments like chemotherapy, endocrine therapy, and antiangiogenic therapy are all common cancer treatment options. This paper will outline recent advances in anticancer (chemotherapy) and antiangiogenesis agent Nano formulations [1].

Chemotherapy is a form of cancer treatment that employs a variety of anticancer medications with distinct modes of action, including blocking cell division, inducing apoptosis, and specifically targeting cancer cells. Although chemotherapy has become increasingly popular as a cancer treatment, the negative medication side effects outweigh its therapeutic effectiveness. Antiangiogenic substances, on the other hand, affect the blood vessels in tumors to stop them from growing and becoming cancerous. A physiological process called angiogenesis causes pre-existing blood vessels to produce new ones. Tumors secrete a range of growth factors, including Vascular Endothelial Growth Factor (VEGF), matrix metalloproteinase, epidermal growth factor, and platelet-derived growth factor, which are necessary for their continued growth and spread. VEGF is the most significant proangiogenic cytokine that controls angiogenesis among the growth factors discussed above. When VEGF attaches to its receptor, it activates the receptor, which then releases signals that encourage endothelial cell growth, migration, and tube creation, ultimately encouraging angiogenesis. Therefore, preventing tumor angiogenesis by blocking the VEGF pathway, either directly (with bevacizumab, for example) or indirectly preventing VEGFR2 auto phosphorylation (using sunitinib, for example), has become a therapeutic focus for treating cancer and other angiogenesis-dependent disorders [2].

The use of a single anticancer agent, such as doxorubicin (Dox), paclitaxel (PTX), camptothecin (CPT), docetaxel (DTX), cisplatin, 5-and fluorouracil, etc., is supported by a large body of research. The lack of selectivity and dose-dependent adverse effects, such as bone marrow toxicity, cardiotoxicity, nephrotoxicity, and hepatotoxicity, are these drugs' principal drawbacks. Numerous Nano formulations of these anticancer medications, such as liposomes, polymer-drug conjugates, polymeric nanoparticles, micelles, hydrogels, Mesoporous Silica Nanoparticles (MSNs), and others, have been thoroughly studied over the past few decades in an effort to get around these limitations. High efficacy, improved tumor selectivity, fewer side effects, and greater water solubility of the transported drug are a few benefits of these drug delivery methods. Their longer circulation duration and selective accumulation into tumour tissue through the Enhanced Permeability and Retention (EPR) effect are the causes of their high efficacy and increased tumor selectivity [3]. As compared to low molecular weight pharmaceuticals, these Nano sized drug delivery systems have been discovered to have enhanced Pharmacokinetic (PK) profiles, making them promising in the realm of cancer therapy. Marketed drugs, such as Doxil®, a liposomal formulation of Dox, have already demonstrated the clinical success of these Nano-formulations. This was the first Nano formulation that the Food and Drug Administration (FDA) has successfully approved for the treatment of Kaposi's sarcoma and other malignancies. Other FDA-approved Nano-formulations, such as Abraxane® and DaunoXome®, primarily lessen the parent compound's toxicity and hence raise its therapeutic index. Similar to this, a different Nano-formulation of a drug-such as the so-called Polymer-Drug Conjugate (PDC) of PTX-has been created and has demonstrated lower toxicity when compared to free PTX; it has now moved to the phase of advanced clinical trials (Phase 3rd) [4].

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Discussion

Mesoporous silica nanoparticles or MSNs, gold, and other inorganic and organic materials-based Nano-formulations have all been produced, researched, and employed for dual-drug combinations. The following is a discussion of the antiangiogenic and anticancer medications that have been developed to deliver them in order to boost their therapeutic efficacies. According to reports, the medications combined in the aforementioned Nano-formulations work synergistically, with the combined effects of the antiangiogenic and anticancer treatments being greater than the sum of their separate effects.

As discussed above, different inorganic materials have a variety of inherent features, such as superparamagnetic (iron oxides) and photo thermal (gold) activity, which make them particularly intriguing structures to use in the creation of hybrid Nano carriers for combination therapies. The inherent imaging activity of many inorganic materials makes them appropriate for tracking by various biological or medical imaging modalities. As previously indicated, this not only makes it simple to track the behavior of the Nano carrier during an assessment of its function in a biological or physiological environment, but it also suggests that they may have therapeutic potential [5]. Other instances demonstrated how the mesoporous silica matrix's resilience and modularity may be used to simultaneously load several medications while individually functionalizing the particle's surface with targeting molecules. But in order to achieve the appropriate responsiveness and, frequently, biocompatibility in the physiological milieu, as well as for the conjugation of targeted ligands, inorganic materials typically require organic functionalization. Organic coatings were used in the aforementioned circumstances, for example, to provide pH-sensitive drug release, long circulation times, minimal immunogenicity, and drug loading capabilities. While the inherent qualities of inorganic materials (robustness for drug incorporation and protection, imaging activity, photo thermal and photodynamic activity, etc.) are typically not dependent on direct contact, such properties are typically dependent on the interaction of the Nano system with the surrounding environment (sometimes referred to as the "bio-Nano interface"). As a result, creating hybrid Nano carriers using an inorganic platform with organic functionalization seems to be a particularly flexible method for creating synergistic Nano carriers for combined chemo- and antiangiogenetic therapy, even when paired with other therapeutic approaches [6].

On the one hand, traditional chemotherapy's numerous side effects and drug resistance continue to be major obstacles in the fight against cancer. Contrarily, monotherapy with antiangiogenic medications has shown only a transient response in clinical trials, along with certain serious toxicities and allergic responses that limit the dose. However, it is still exceedingly difficult to expose tumor tissue to a combination of chemotherapeutic and antiangiogenesis drugs with different chemical and pharmacological properties. To address this, various Nano formulations with tunable and predictable release of multiple drugs have been studied in preclinical studies (mice models). However, before these Nano formulations can be commercially released, they must be validated in additional species, such as rat, rabbit, and monkey, and ultimately in cancer patients. Despite the many benefits of combination chemo-antiangiogenesis cancer therapy mediated by Nano formulations, such as decreased tumor growth, control of drug resistance, and generally synergistically improved therapeutic efficacy, there are still some difficulties in their preparation and effective translation [7]. These include unidentified features of toxicity and immunogenicity, ineffective medication targeting, a lack of bench-to-bedside collaboration between experts in the relevant domains, and the price of industrial production. Although nanotechnology has made a significant contribution to medicine, particularly in the treatment of cancer, there is still no established consensus on Nano toxicology. For instance, it is necessary to assess the long-term toxicity and safety profiles of nanoparticles, but up until now, acute toxicity has primarily been studied on a case-by-case basis. Specifically, the molecular interactions between the endothelial cell lining and Nano carriers Given that the majority of these medicine formulations are taken intravenously, they must be unlocked. Certain design elements, such as overall size and physical and chemical surface qualities, as well as the choice and customization of the Nano formulations, might be taken into account in order to reduce the systemic toxicity [8].

In the best case scenario, functionalizing the Nano carrier with targeting ligands should aid to lessen side effects by specifically boosting the drug accumulation at target sites and minimizing systemic exposure, thereby improving the therapeutic outcome. In order to evaluate the bio distribution and comprehend the biochemical pathways that control cell functions, novel screening assays must also be developed. Although liposome-based Nano formulations are often utilized because they are immune-suppressive, their disadvantages include a short half-life, poor solubility, and expensive production costs. Although polymeric-based Nano formulations have the benefit of being biodegradable, from the perspective of an ideal Nano formulation, their drug release occurs in an uncontrolled manner [9].

Additionally, it is important to take into account the cost of manufacturing these Nano formulations for clinical usage, as the cost of these combination chemo-antiangiogenic Nano formulations may be greater than the combined cost of each drug individually. Bringing together interdisciplinary experts and collaborators from academics, clinicians, scientists, and regulatory bodies to ensure a goal to establish improved therapeutic outcomes of combined chemo-antiangiogenesis therapy and, ultimately, improve the quality of life of cancer patients is a potential solution to the aforementioned problems. Additionally, there is a strong case for investigating Nano formulations that combine anti-cancer medications with anti-inflammatory medications, radio ligands, and particular target genes. Studies addressing the long-term toxicity and safety of the Nano formulations would also be helpful in enhancing the therapeutic success. With the potential to make significant advancements in cancer therapy, various biodegradable linkers can be designed to deliver the parent medications in a targeted and regulated manner. The pharmaceuticals can be delivered sequentially or simultaneously via certain mechanisms in the tumor microenvironment. Additionally, the addition of imaging agents (such as radionuclides or inorganic constructions) may enable clinicians to customize combination therapy in a more individualized way and/or for complex malignancies like ovarian cancer [10].

Conclusion

In conclusion, preclinical studies have shown that Nano formulations based on various Nano carriers, including polymeric nanoparticles, micelles, hydrogels, liposomes, mesoporous silica nanoparticles, and gold nanoparticles, and containing anticancer and antiangiogenic agents, are a promising method for treating cancer. Although there is still a long way to go before practical implementation in terms of patient outcomes, these methodologies provide adaptable and reliable platforms for the realization of the combination therapy concepts that have been outlined in the future.

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