Clinical Oncology: Case Reports

Perspective

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Delivering Targeted Drugs to Treat Blood Cancers

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Abstract

A sort of liquid tumor, or cancer that exists in bodily fluids, is a blood cancer. Leukemia, lymphoma, and multiple myeloma are the three most prevalent kinds of blood malignancies. Chemotherapy, which involves systemic delivery of anticancer drugs into the blood, is the main treatment for blood malignancies. The low effectiveness of the anticancer medicines that build up in the tumor site, however, frequently results in a high incidence of relapse, which lowers patient survival rates. This suggests that a targeted drug delivery method is urgently required to increase the security and effectiveness of therapies for blood malignancies. In this review, we discuss freshly investigated and authorized blood cancer medication delivery system formulations as well as the current targeted techniques for these diseases. We also talk about the difficulties that currently exist when using drug delivery devices to treat blood malignancies.

Keywords: Blood cancers; Drug delivery; Nanomedicines

Introduction

One of the biggest causes of death worldwide is cancer. An overview of the many blood cancers, which differ from solid tumors like those in organs in that they develop in the bone marrow or lymphatic system, includes multiple myeloma, leukemia, and lymphoma. Chemotherapy, radiation, immunotherapy, and transplantation are currently used to treat blood malignancies. Although a wide variety of chemotherapeutic medications are clinically available for the treatment of blood cancers, because to the unavoidable aggravation of blood malignancies and bone metastases, there are no curative treatment techniques in clinical practice for these types of tumors. Furthermore, systematic administration of anticancer medicines at tumor locations inside the lymphatic or bone marrow is difficult to obtain in sufficient therapeutic doses to inhibit tumor growth. Chemotherapeutics require high dosage and/or frequent delivery to maintain therapeutic levels in bone marrow or the lymphatic system, which might lead to an increase in side effects. A large number of hematopoietic stem/progenitor cells that are resistant to chemotherapy and play a role in disease refractoriness/relapse are also present in the bone marrow microenvironment. For chemotherapy, developing a targeted drug delivery method for blood malignancies is a major problem.

Different kinds of nanoparticles have drawn a lot of interest in recent years for the treatment of various solid tumor types, which has produced a number of effective drug delivery systems that are now used in clinical settings. However, only a small number of efforts have been done to create drug delivery systems for the treatment of blood malignancies, with the majority of them being done in solid tumors. We outlined the tactics for medication delivery systems that are currently used to treat blood malignancies in this review.

Targeting the Microenvironment of Bone Marrow

Particularly for cancer cells, the bone marrow microenvironment is essential for maintaining cell renewal and differentiation. Numerous capillaries and blood arteries can be seen in the bone marrow. It is regarded as one of the most complicated systems and is made up of a variety of cells, including osteoblasts, osteocytes, fibroblasts, mesenchymal stem cells, macrophages, and osteoclasts. Additionally, the extracellular matrix, oxygen tension, cytokines, and mechanical stresses are all important for the proliferation of cancer cells and are connected to resistance. Drug delivery methods can be used to target the bone marrow microenvironment more effectively, either passively or aggressively. Strategy for Passive Targeting In comparison to conventional medications, Nano therapeutics have improved absorption, decreased toxicity, greater dosage response, and enhanced solubility. Through leaky vasculatures, which primarily require a delivery system for its own characteristics like the size, shape, surface zeta-potential, and other aspects, passive targeting depends on the accumulation of the drug delivery system at a certain end organ or tumor site. The reticule-endothelial cells in the blood arteries in the bone marrow are related to the drug accumulation amounts in the bone. Although the increased permeability and retention effect in solid tumors was first documented more than 30 years ago, blood malignancies have received less attention than solid tumors do. Since the transcellular pathway travels through the fenestrae between the endothelial cells in the bone marrow, particle size is important. According to some reports, the endothelium wall's fenestrae are less than 150 nm in size, making it less likely for particles larger than that to pass through. Furthermore, because reticuloendothelial sinusoidal blood capillaries have pores up to 60 nm in diameter, nanoparticles smaller than that can enter and disperse into the bone marrow interstitial space.

Additionally, nanomedicine relies on a prolonged blood vessel circulation period to obtain high efficiency for drug delivery in bone marrow. Liposomes having a diameter of less than 100 nm circulate in the blood for a longer period of time and interact less with plasma proteins. The efficacy of drug encapsulation is, however, constrained by nanoparticles smaller than 50 nm, which is another restriction of small nanoparticles. Surface charge, in addition to diameter size, is important for bone marrow uptake in nanomedicine. According to several reports, negatively charged liposomes improved the rate at which macrophages absorbed bone marrow. As a result, nanoparticles for blood malignancies should ideally range in size from 50 nm to 100 nm.

Spleen and Lymph Nodes as a Target

In blood malignancies, the spleen and lymph nodes offer a special microenvironment for tumor cells. It is thought that the spleen has a role in a variety of blood malignancies, particularly lymphomas. It has been suggested that the spleen, through attracting monocytes and macrophages to the tumor tissues, also plays a significant role in

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tumor immunity. About one-third of lymphomas involve the spleen, which can potentially advance the condition, particularly in Hodgkin lymphoma. The spleen is frequently the target of intravenously delivered nanoparticles because of the phagocytic activity of monocytes and macrophages. Tumor growth can be slowed down by siRNA-encapsulated nanoparticles, according to in-vivo tests. Additionally, spleen resident infections and hematological illnesses such malaria, hairy cell leukemia, idiopathic thrombocytopenic purpura, and autoimmune hemolytic anemia have shown therapeutic benefits from increased medication concentration in the spleen. Most immune responses that can stop malignant transformation are started by lymph nodes. In some cancers, antitumor immune responses are still present and have an effect on the course and outcome. Additionally, the cytokines in lymphoid nodes create an inflammatory milieu that can encourage the growth of cancerous cells.

Vascular System Targeting

In the majority of blood malignancies, including acute myeloid leukemia, multiple myeloma, acute lymphatic leukemia, chronic lymphatic leukemia, and Burkett's lymphoma, neovascularization is invariably linked to a poor prognosis. On the inner surface of blood vessels, endothelial surface receptors are extensively expressed. Utilizing tumor-homing immunocytokines like interleukin-2 (IL-2) is another tactic. For acute myeloid leukemia and other solid malignancies, the antibody-based delivery of IL-2 to extracellular targets expressed in the conveniently located tumor-associated vasculature demonstrated therapeutic potential. The vasculature of inflammatory and tumor sites always contains inflamed endothelial cells, which are the main source of e-selectin expression. By focusing on the vascular system, one can release chemotherapeutic medications to decrease cell growth close to the blood vessels and direct antiangiogenic agents to the blood vessels to suppress angiogenesis. For the treatment of blood malignancies, a vascular targeted co-delivery method can maximize the therapeutic efficacy of the combination.

Discussion

Only a small number of targeted Nano-based medication delivery systems are currently used in clinical settings. Many difficulties and problems still need to be overcome. Although delivery methods for Nano-based medicines are significantly improved, it is still challenging to create effective formulations that may be used in clinical settings. The challenges below are divided into two categories: biological obstacles and non-biological challenges.

Biochemical Characterization of Nano-Based Drugs The efficiency and stability of loading medications inside drug delivery devices is one of the essential factors in the development of Nano-based therapies. We can adjust the polymer/lipid characteristics and insert certain side groups, for example, to boost the compatibility between the materials, in the creation of drug delivery systems such as nanoparticles or liposomes. In order to achieve the best performance (the greatest anti-tumor effectiveness and/or the fewest side effects) for the Nano-based delivery system, it is possible to alter the properties of a Nano carrier in the lab, including molecular weight, the ratio of hydrophobic/hydrophilic blocks, and the concentration of drug carrier relative to the drug. To meet industrial demands, it is entirely different to convert a small-scale formulation into a large-scale production. This problem can be solved by precisely controlling the chemical composition, drug loading, and surface features of nanoparticles using microfluidics technology and particle replication in non-wetting template technology.

Toxicity and Adverse Reactions of Nano-Based Drugs the Nano-bio interactions, which can result in toxicity and serious side effects, is a significant barrier to the clinical application of Nano-based therapeutics. The interactions of Nano-based medications with biological substances that can cause immunoreaction, inflammation, or other related problems in people are typically what lead to their possible toxicity. The size, zeta potential, and solubility of the formulations are just a few of the factors that have a significant impact on the hazardous effect. Proteins interact and absorb nanoparticles and liposomes when they enter a biological system. The size, surface charge, stability, dispensability, pharmacokinetics, bio distribution, and toxicity profile of the nanoparticles or liposomes are altered as a result of the protein adsorption on their surfaces.

Movement and Clearance the two main organs for the uptake and elimination of Nano-based medications are the liver and spleen. The kidney, lung, and bone marrow are also involved in this process. In these organs, macrophages are essential for the removal of nanoparticles or liposomes. Surface coatings have been developed to lengthen blood circulation times in order to preserve a lengthy circulation profile and reduce detection by host cells. Highly hydrophilic molecules like polyglycerol and Polyethylene Glycol (PEG) can reduce the absorption of proteins and change the makeup of the proteins that end up on the surface of nanoparticles. One of the frequently used materials for coating in the preparation of nanoparticles that can elude immune cells is this one. Anti-PEG antibodies found in patients have reportedly been shown to hasten the clearance of PEG-modified nanomedicines. Additionally, they might make undesirable effects more common, such allergic responses. Using coronate-loaded liposomes is another method for lengthening the period that nanomedicines remain in the bloodstream. In addition, coronate liposomes' depletion of macrophages promotes the prevention of nanoparticle clearance from peripheral circulation and serves as a tool for researching the function of macrophages and other phagocytes in both health and sickness.

Studying Translation in the In Vivo Model In vitro testing, typically carried out on cancer cell lines, is the initial stage of a preclinical study to assess novel medications, including Nano-based therapies, in order to determine the biocompatibility and efficacy. Recently, new in vitro culture systems, including 3D culture systems or organoid culture systems, have been developed to imitate the microenvironment of tumors. These methods allow for the evaluation of treatments in a milieu that is somewhat more similar to the actual disease scenario. An in vivo animal model is still necessary for the creation of circulatory, bio distribution, safety, and efficacy profiles prior to the clinical trial phase, despite the fact that these innovative in vitro systems can imitate the microenvironment of a tumor or the interactions between cells. Impede the delivery of blood cancer drugs via the bone marrow Blood malignancies, as opposed to solid tumors, typically start in the bone marrow. In order to get an anticancer drug into the bone marrow or the tumor site, Nano-based medications must overcome a number of obstacles. Targeting cancers in the bone marrow is also still a challenging problem since it entails the presence of cancer stem/progenitor cells and resistances brought on by the bone marrow microenvironment. To improve sensitization and overcome resistance, it may be possible to disrupt the connections between tumor cells and the bone marrow microenvironment using two or three distinct agents or medications.

Commercialized Obstacles the difficulty in developing a predictable and repeatable synthesis process is one of the key business obstacles connected with the clinical translation of Nano-based therapies. Working on a small-scale formulation in a laboratory is simpler and largely reliant on the operator's experience, which are unsuitable for repeatable large-scale production. The formulation must also be stable to enable for long-term storage and shipment, which adds to the complexity of the situation. Due to the inconvenience they cause the pharmaceutical industry, it has been observed that Nano platforms with laborious and complex manufacturing processes rarely make it into clinical practice. Regulatory/Policy Challenges the enormous gap between scientific research and the regulatory bodies is another urgent and significant problem that has to be addressed. In the majority of nations, the government oversees the approval of new medicines in accordance with a number of regulations and laws pertaining to safety profiles, best practices for industrial manufacture, intellectual property rights, quality controls, etc. The Food and Drug Administration (FDA) is responsible for overseeing the approval process for all drugs in the United States, including biological and Nano-based medications. The creation of Nano-based medications follows the standard drug-development procedure unless there is a specific consideration for a particular Nano-based treatment. This control of standards for drugs based on nanotechnology has been contested. The lack of precise regulatory and safety criteria has a major impact on timely and successful translation to market. Currently on the market, commercially available nano-based medications have met all the regulatory requirements. However, to validate quality, safety, and efficacy for human use, these standards might not be adequate and require additional adjustment.

Conclsuion

An essential component of the efficient and secure treatment of blood malignancies is the targeted distribution of therapeutic drugs. Due to the existence of cancer stem/initiating cells and resistances brought on by the bone marrow microenvironment; targeting B cell malignancies inside the bone marrow remains a biological challenge. It is also noteworthy that the buildup of therapeutic drugs in the lymph nodes or bone marrow may hinder the immune system's response or cause cumulative toxicity to healthy hematopoiesis stem cells. Further research should concentrate on limiting the capture by healthy cells in the bone marrow or lymph node and on the precise delivery of therapeutic drugs to malignant cells. Recent advancements in the development and clinical approval of numerous innovative nanomedicines and drug delivery formulations for the treatment of numerous cancer types suggest that the development of efficient and secure tailored formulations is anticipated to improve patient care in the future. For translational research to benefit patients, scientists, business organizations, and governments should collaborate to overcome the biological and non-biological obstacles.

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