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NANOMEDICINE IN ONCOLOGY: ADVANCES IN TUMOR-TARGETED DRUG DELIVERY AND IMAGING

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ABSTRACT

Nanomedicine has made significant strides in oncology, offering novel solutions for targeted drug delivery and cancer imaging. This review discusses the advances in nanotechnology-based strategies for tumor-targeted therapies, focusing on passive and active targeting mechanisms, such as the Enhanced Permeability and Retention (EPR) effect, and ligand-receptor-mediated endocytosis. The review also explores the use of nanomaterials like liposomes, quantum dots, and polymeric nanoparticles in drug delivery, as well as their role in enhancing imaging modalities like PET, MRI, and CT. Advances in stimuli-responsive nanocarriers have allowed for improved drug delivery systems that address conventional therapy limitations, including poor solubility, rapid drug elimination, and systemic toxicity. Despite these advancements, regulatory, safety, and manufacturing challenges remain, necessitating further innovation to translate these technologies into widespread clinical use.

KEYWORDS: Nanomedicine, endocytosis, nanotechnology.

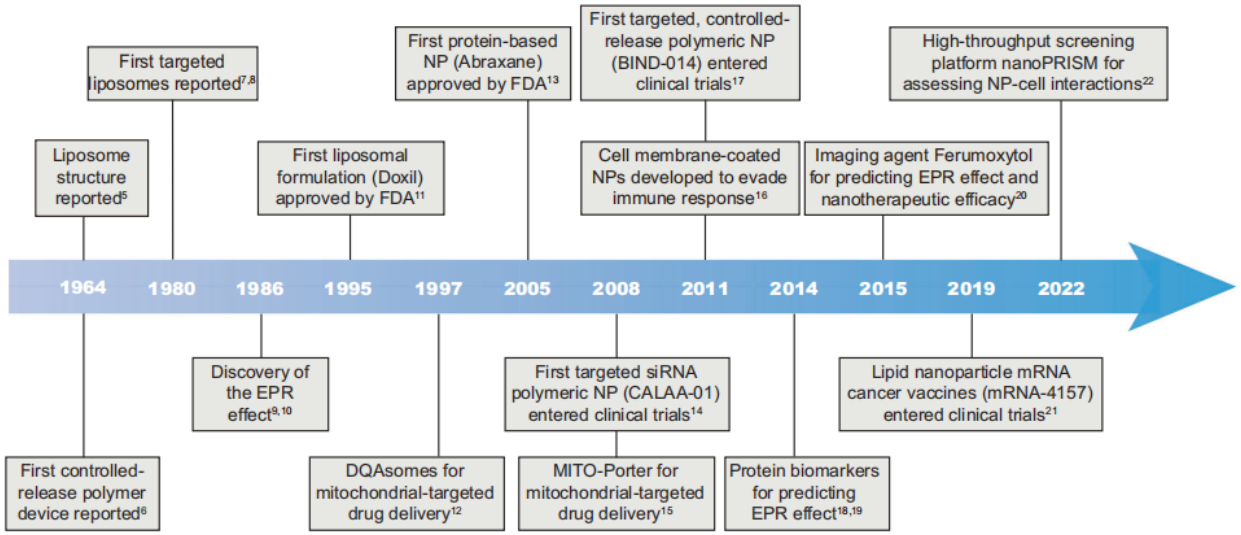
INTRODUCTION

Overview of nanomedicine in oncology

Cancer is still one of the world's most deadly diseases. The most recent Global Cancer Statistics suggest that in 2020, there would be 19.3 million new instances of cancer worldwide and close to 10 million cancer-related deaths. Over the next 20 years, it is anticipated that the incidence of cancer will rise sharply worldwide due to a variety of risk factors, including changing demographics, environmental pollution, and an increased prevalence of lifestyle choices. Therefore, there is an urgent need for effective medical interventions to lower the total cancer death rate. For many patients, traditional cancer treatments like surgery, chemotherapy, and radiotherapy have improved survival. They are not very effective in treating advanced metastatic tumors, though. Immunotherapies are a significant advancement in the

treatment of advanced malignancies, but their low patient response rates overshadow their clinical successes. At least fifteen cancer nanomedicines are currently licensed worldwide, and more than two hundred clinical trials are being conducted to assess over eighty new cancer nanomedicine.[1]

HISTORY



SIGNIFICANCE AND NEED FOR TUMOR-TARGETED THERAPIES

Tumor tissue targeting is mainly achieved by exploiting the leaky tumor vasculature and deficient tumor lymphatic system, which allow nanoscale particles to passively accumulate in solid tumors through the Enhanced permeability and retention (EPR) effect. In chemotherapy, anticancer drugs reach the tumor tissue with poor specificity and dose-limiting toxicity. Passive and active targeting are components of the fundamental strategy for targeted drug delivery.[2]

CHALLENGES WITH CONVENTIONAL THERAPIES

One of the primary treatment modalities for cancer patients, conventional chemotherapy's effectiveness is largely hampered by the antigenoplastic agents' inability to reach tumor tissue, their intolerable concentration-dependent systemic toxicity, high dosage requirements, rapid abolition, poor solubility, and inconsistent bioavailability. By using both passive and active targeting strategies, it can enhance the intracellular concentration of drugs in cancer cells while avoiding toxicity in normal cells. Most importantly, the NP based delivery of anticancer drug somehow bypass the recognition of P-glycoprotein (P-gp). Drug delivery and targeting such as pharmacokinetics, pharmacodynamics, immunogenicity, and efficiency of drugs has opened up new avenues for improving the drug delivery systems.[3]

THE LIMITATIONS OF NANOTECHNOLOGY IN ADRESSING THE ISSUES

Physico-chemical characterization of nanomaterials

Safety concerns

Regulatory issues

Manufacturing issues

DRUG DELIVERY AND IMAGING ADVANCEMENT

Positron emission tomography

Positron is one of the most commonly used medications. The cancer cells are easier to find with PET when deoxyglucose is tagged with the positron emitting radionuclide 18-flourine (18F). Following its transportation into these cells, 18F-FDG is phosphorylated to FDG-6-phosphate (FDG-6-P) by hexokinase or glucokinase. Rather than entering the usual metabolic pathways of glucose, this compound exhibits “metabolic trapping,” or accumulation within neoplastic cells because it contains fluorine at the C-2 position of the ring structure, which replaces the typical hydroxyl group found in glucose. With the completion of the EXPLORER, the first entire body PET scanner, in 2019, a significant advancement in this field is the shift from whole body to total body PET scans.30 The main cause of the imaging modality's low sensitivity is its limited field of view (FOV), which is one of the disadvantages of whole body PET scans, which are commonly used to detect metastases in melanomas.[4]

Magnetic resonance spectroscopy

One popular method of imaging used to diagnose cancer is magnetic resonance spectroscopy. It has lately been used to diagnose pancreatic, prostate, breast, cervical, and gastrointestinal malignancies in addition to brain tumor, which is where it is most commonly employed. Unlike traditional MRI, MRS measures signals from substances other than water, including carbon, hydrogen, creatinine, lactate, and N-acetylaspartate. Chemical exchange saturation transfer, or CEST, is a novel contrast enhancement method that can be used in conjunction with hyperpolarized MRI to provide high-resolution pictures of molecules and macromolecules that can exchange protons with nearby water molecules.[5] This method's increased sensitivity makes it possible to identify even the smallest amounts of cellular constituents.

X-ray computed tomography

Another imaging technique for the diagnosis of cancer is computed tomography. CT has proven to be a good screening tool for a variety of malignancies, including breast, lung, colon, and head and neck providing precise spatial and temporal tumor imaging, supporting surgery, radiotherapy, and follow-up biopsies. Numerous advances in instrumentation, including dual energy, iterative reconstruction, low kilovolt, scan speed, radiation dose, and perfusion imaging, decrease have highlighted CT-based tumor imaging's clinical value.[6]

LIPOSOMES

Liposomes are amphipathic nanoparticles based on phospholipids, which have a hydrophilic head based on phosphate and a hydrophobic tail based on fatty acids. Liposomes' ability to merge with cell membranes and subtly enhance drug absorption by cells is a result of their cell-like nature. Water-soluble drugs can be confined in the bilayer core, whereas lipid-soluble drugs can be embedded in lipophilic membranes. Traditional methods have a lot of shortcomings. To get around those limitations, some cutting-edge technologies have been created, including supercritical fluid technologies, supercritical anti-solvent techniques, and supercritical reverse phase evaporation techniques. Liposomes are potential as smart nanoparticles in the co-delivery of chemotherapeutic medicines, imaging agents, gene agents, or anticancer metals in addition to delivering imaging agents alongside chemotherapeutics[7] Lipid nanoparticle (LNP) have been found to co-delivery of Cas9 mRNA, focal adhesion kinase (FAK) siRNA, and sgRNA to improve both tumor delivery and gene editing efficacy.

QUANTUM DOTS

Quantum dots (QDs) are often made from hundreds to thousands of atoms of group II and group VI molecules because of their unique photophysical features. When this nanoparticle is used to distribute the medication at the desired place, the tumor may be seen. Most commercially available QDs consist of three parts: a capping material, a shell, and a core. PEGylated QDs can accumulate in tumor sites by the EPR effect in the absence of a targeting ligand. To actively target a tumor area, different ligands can be grafted on the QD surface, including as peptides, large proteins, and folate. Since QDs naturally glow, they are especially well-known for use in cancer imaging.[8]

PASSIVE TARGETING

The primary mechanism of action of first-generation nanomedicine medications is changing the physicochemical properties of a substance to influence its pharmacokinetics and biodistribution. First-generation nanomedicine medications based on passive targeting include nab-paclitaxel (Abraxane®) and pegylated liposomal doxorubicin (Doxil®/Caelyx®). For passive targeting, pathophysiological traits of tumors and their surroundings have been used. Specifically, the EPR effect encourages the build-up of nanomedicine medications within the tumor. The basis for this impact is the existence of leaky intratumoral blood arteries, which have endothelium fenestrated with gaps ranging in size from 100 nm to 780 nm.[9] It is generally acknowledged, therefore, that passive targeting based on the EPR effect is insufficient to completely realize the advantages of targeted administration and regulate the negative effects of cytotoxic medications.

Active-targeting

Active targeting, a high-affinity ligand is attached to the surface of a nanocarrier. The ligand binds selectively to a receptor on the target cell. Targeted delivery is ensured by the high specificity of the ligand for its cognate receptor. A wide range of ligands have been used for such purposes including small molecules such as folic acid and carbohydrates, or macromolecules such as peptides, proteins, aptamers, oligonucleotides, and antibodies. Doxorubicin-loaded immunoliposomes directed against the epidermal growth factor receptor (EGFR) are one instance of a clinical trial. The ligand selection process should minimize binding to healthy cells while permitting binding to the target cells. Naso carriers must be sufficiently stable to prevent the drug's early release and breakdown in the bloodstream in order to effectively target.

ENHACEMENT OF IMAGING TECHNIQUES USING NANOPARTICLES

Magnetic Resonance Imaging by Nanoparticles

There are three types of MNPs: superparamagnetic, ferromagnetic, and paramagnetic. Particles that are superpara- and ferromagnetic consist of a surface coating and a magnetic core. The primary building block of paramagnetic particles is chelates of paramagnetic ions without a distinct core or surface coating. They therefore have a different effect on magnetic resonance imaging (MRI) contrast than do superpara- and ferromagnetic particles.[10] Even on its alone, MRI provides exceptional soft tissue contrast. The contrast of images is further improved by the continuous growth of MNPs as contrast agents (CAs).

Imaging by Microscopic Techniques

This method was used to the imaging of SPIONs in mouse inner ear cell culture and human cochleae. Peroxidase, which is frequently added to or incorporated into NPs in the development of hydrogen peroxide biosensors, may be a helpful tool in the imaging of nanoparticles. In a similar manner, modified NPs may catalyse the peroxidase substrates'

oxidation, resulting in a colour reaction at the NPs' location. visualized and measured the location of MNPs within the primary organs using this NPs-peroxidase method to ascertain the biodistribution and organ clearance of magnetic NPs in mice.

TRANSMISSION ELECTRON MICROSCOPY

The most common method for characterizing NPs is transmission electron microscopy. A variety of nanostructures, including carbon nanomaterials, quantum dots, noble metal and metal oxide-based nanoparticles, and polymeric nanoparticles of the dendrimer type, were characterized and seen by TEM. The study of nanoparticle uptake, cellular compartmentation, transport, and accumulation in various tissues and organs is favored by the use of TEM. Recently, the presence of metal nanoparticles inside carbon nanotubes was investigated using TEM.[11] When determining and characterizing the size, shape, area, existence of pores, or eccentricity of nanoparticles (NPs), scanning electron microscopy (SEM) is an essential instrument.

NANO CARRIER LIPOSOMES

Liposomes are useful for delivering a variety of medicinal and diagnostic chemicals. Antibodies that are low in water affinity are linked with the lipid membrane of liposomes, while those that are strong in water affinity are enclosed within the watery core of the liposomes. This is how chemotherapy medications are often encapsulated. Moreover, liposomes are adaptable for multifunctional theragnostic applications since they can include a variety of medicinal substances, such as drugs, DNA, or contrast imaging components.

Surface-modified liposomes that are embellished with ligands, antibodies, and peptides locate and bind to cancer cell surfaces' overexpressed receptors. This alteration improves the effectiveness of the treatment by making it easier to transport liposomes to tumor locations. Targeting molecules affixed to cancer cells are adorning the surface of liposomes in order to facilitate targeting. As MRI contrast agents, liposomes containing superparamagnetic or paramagnetic nanoparticles may be employed. In addition to preventing tissue injury, this makes high-resolution imaging of liposomes for research of their potential medical uses possible. Gene therapy has been used to treat cancer using liposome nanoparticles.

EXAMPLES OF LIPOSOMES

Doxil (liposomal doxorubicin): It treats the ovarian cancer, breast cancer.

Annamycin: It treats the breast cancer.

Atragen: Treats the breast cancer.

Daunoxome (liposomal daunorubicin): Treats the HIV related kaposi’s sarcoma.

Abelcet (amphotericin B): It is an Antifungal medication.

Ambisome (amphotericin B): Treats the fungal infection.

POLYMERIC NANOPARTICLES

Particles made of polymers. Because of their special qualities, polymeric nanoparticles are useful in biological applications, fostering novel forms of collaboration between biologists, chemists, engineers, and physicians. Major biotechnological advancements in drug delivery, tissue engineering, biomaterials, and medical device development have been facilitated by the discovery of polymeric nanoparticles, which signify a medical revolution. The revolution showed that proteins, nucleic acids, and other physiologically active compounds may be used as more potent

medicines. Additional developments include the capacity to combine materials with various chemical compositions to produce materials with synergistic qualities, such as organic-inorganic and organic-organic compounds. A variety of inorganic materials, including graphene, polymers, carbon nanotubes, silica, and metal oxide nanoparticles, can be combined to create polymeric nanoparticles.[12]

Applications of polymeric nanoparticles

1. Polymeric nanoparticles in targeted drug delivery.
2. Polymeric nanoparticles in cancer therapy.
3. Polymeric nanoparticles in cancer diagnosis and imaging.
4. Polymeric nanoparticles in ocular cancer.
5. Polymeric dendrimer nano carries for neuro degenerative diseases.
6. Polymeric micelle for nano carries.

INORGANIC NANOPARTICLES

GOLD NANOPARTICLES

Gold nanoparticles' adaptability and wide range of possible biological applications have made them a viable tool in therapeutics. They are useful for non-invasive imaging due to their high surface-to-volume ratio and distinctive optical characteristics. Targeting, diagnosis, therapy, and monitoring are all integrated into gold nanoparticles, removing the drawbacks of conventional diagnostic and therapeutic methods. Enhancing treatment accuracy and reducing systemic exposure, the development of stimuli-responsive drug release systems also results in the controlled release of therapeutic payloads from gold nanoparticles and the triggered release of therapeutic cargos at the site of targeting.

SILICA NANOPARTICLES

Tetraethyl orthosilicate is hydrolysed and then condensed to create silica nanoparticles. This process is often accomplished by adding amine or thiol groups to the surfaces of the particles within the tetraethyl orthosilicate matrix. The development of mesoporous silica nanoparticles, which provide fine control over pore size during production, is one notable accomplishment. In the acidic environment of tumors, silica nanoparticles can be generated in reaction to pH shifts, allowing for disintegration or greater transparency. Silica nanoparticles can be functionalized via attaching to their surface such imaging agents like quantum dots, magnetic nanoparticles, or fluorophores to change their characteristics. Since they can be photographed, scientists have been able to detect and monitor them in living organisms. Silica nanoparticles have shown considerable potential in drug administration, attaining the best drug loading concentration and release kinetics is still complex. To achieve high accuracy with the surface functionalization and imaging capacities of silica nanoparticle, the practical attachment of targeted ligands and imaging agents is essential.

MAGNETIC NANOPARTICLES

Originally, magnetic nanoparticles were made as magnetic resonance imaging contrast agents. These nanoparticles appear to be particularly promising for targeted medication delivery applications due to their responsiveness to magnetic fields. The primary drawback of traditional chemotherapy medications is typically their vague nature. The cytotoxic medication will target not only the tumor cells but also the normal and healthy cells. The application of a magnetic field can direct drug-loaded magnetic nanoparticles toward the tumor cells, thereby minimizing the drug's systemic distribution and related side effects. Amazing new features of iron oxide nanoparticles include

superparamagnetism, high field irreversibility, high saturation field, additional anisotropy contributions, and shifted loops upon field cooling.[13]

PASSIVE AND ACTIVE TARGETING STRATEGIES

FACTORS AFFECTING EPR EFFECT

There are several endogenous factors that can alter EPR effect in the tumor tissue.

Bradykinin (BK), prostaglandins (PGs), vascular endothelial growth factor (VEGF), nitric oxide (NO), peroxynitrites, and matrix metalloproteinases (MMPs) are a few of them. Since each of these elements is crucial to the process of tumor angiogenesis, knowing them may help with the development of appropriate techniques or medication delivery systems that specifically target tumor tissue.

LIGAND RECEPTOR TAGETING

Small Molecules-Based Targeting Ligands

Receptor-Mediated Endocytosis of Folate-Linked Nanocarrier System

Aptamer (Nucleic Acids DNA or RNA)-Based Targeting

Carbohydrates-Based Targeting Ligand

Galactose

Mannose

Antibody-Based Targeting

Peptide-Based Targeting

Glycoprotein-Based Targeting

STIMULI – RESPONSIVE NANOCARRIERS

The heterogenetic distribution and low specificity they typically exhibit in tumors, however, may compromise the effectiveness of internal stimuli-sensitive nanocarriers. This section will concentrate on current developments in tumor theranostics nanocarriers that respond to internal cues, primarily pH, hypoxia, redox, and enzymes. Stimuli-responsive nanocarriers still face a number of obstacles: (1) the complexity and heterogeneity of patient tumors compared to animal tumor models; (2) concerns about the toxicity, biosafety, and biodegradability of nanocarriers; (3) stable stimuli-responsive function in vivo; (4) the need for clinical trials to demonstrate the tumor accumulation and therapeutic efficacy of stimuli-responsive nanocarriers; (5) the need to clarify factors influencing the stimuli-responsive properties in vivo; (6) research should be done to determine the appropriate dose and mode of administration, such as intravenous injection (i.v) and intraperitoneal injection (i.p). Future research would therefore concentrate on improving the formulations based on clinical trial lessons and translating the stimuli-sensitive nurses into the clinic.[14]

CASE STUDIES AND CLINICAL TRIALS

FDA APRROVED AND EMERGING NANOMEDICINE

One of the most effective nanomedicines was the PEGylated doxorubicin liposomes (DoxilVR/CaelyxVR), which was approved by the FDA in 1995. Since then, numerous liposomal nanomedicines have been created, clinically tested, and released onto the market. The Celgene Corporation's AbraxaneVR, a paclitaxel albumin-based formulation, and DoxilVR/CaelyxVR were reported to be the top-selling nanomedicines, with expected revenues of $252 million and 950 million, respectively. Currently, 51 products from the medical nanotechnology platform are undergoing clinical testing. These clinically studied nanomaterials are aimed at various therapeutics; 18 are chemotherapeutic candidates;

15 are antimicrobial agents; 28 are for various medical applications, such as autoimmune disorders and psychological diseases, among others; and 30 are for treatments based on nucleic acids (FDA 2020.For example, dexamethasones, a COVID-19 therapeutic drug that comes in various nano-formulations, has significantly improved COVID-19 treatment. Furthermore, a significant advancement in nanomedicine has been made with the expedited development and approval of Phase 3 clinical trials of the liposomal mRNA vaccine (BNT162b) created by Pfzer/BioNTech.[15]

Quantum Dots and Iron Oxide Nanoparticles:
Applications in Fluorescence and MRI Imaging:
Tumor diagnosis and therapy
Cell labelling
Ezyme activity measurements
Atatomical localization
Real time assesment during surgery

GOLD NANOPARTICLES AND THEIR USE IN CT AND PHOTOACOUSTIC

Uses of Gold nanoparticles in computed tomography (CT), photoacoustic imaging (PAI), and other applications. CT contrast and sensitivity are significantly improved by nanoparticles. To improve the visualization of anatomical features, contrast agents with high atomic numbers, such iodine or gold, are frequently used. These nanoparticles efficiently absorb X-rays, increasing CT image contrast and facilitating the accurate detection of anomalies such tumors and vascular irregularities. CT scans have enhanced the precision and efficacy of targeted medication delivery, including thermoablation, radiofrequency ablation (RFA), and other localized treatments radiofrequency ablation (RFA), ablation, and further targeted therapies. The great ability to absorb light, gold nanoparticles are very beneficial. This method is useful for diagnosing diseases like cancer and for viewing vascular architecture because it offers high-resolution imaging with improved depth penetration. Because of their versatility, nanoparticles in PAI can target specific molecules, which helps with early diagnosis and biomarker discovery. Using PAI in combination with nanoparticles is a powerful approach for cancer theranostics. The high-quality, real-time images that PAI provides have improved cancer diagnosis, monitoring, and therapy. PAI has been used to track the movement and activation of therapeutic genes carried by nanoparticles. PAI has been used to trackic genes carried by nanoparticles. Researchers have utilized polymerase chain reaction (PAI) in conjunction with gene delivery vectors and gold nanoparticles to treat breast cancer.

MOLECULAR IMAGING AND THERANOSTICS

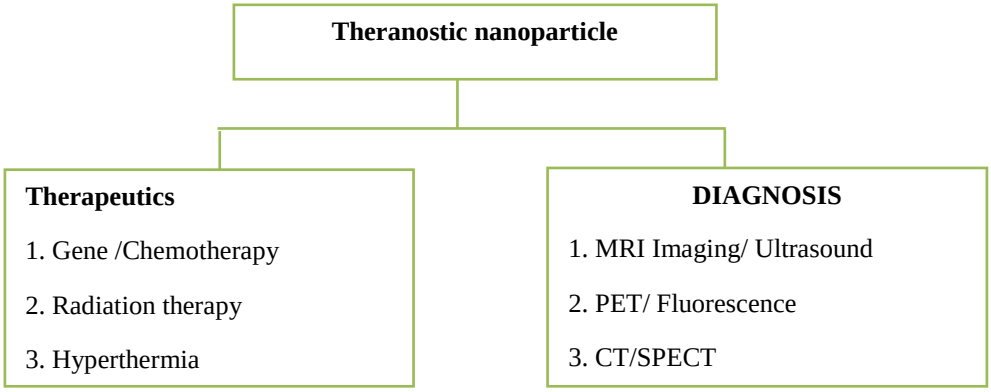
Molecular imaging is a non-invasive medical imaging technique that allows biological processes occurring at the molecular and cellular levels in tumor to be seen, described, and measured. Molecular imaging uses medical imaging modalities with or without tracers to reveal the physiological activities or expression status of particular molecules within a tissue or organ, in contrast to conventional imaging modalities that primarily image differences in the structure of tissues or organs.

Multiple-modal imaging

Researchers have tried to combine two or more distinct imaging modalities to develop a new imaging mode, commonly referred to as multimodal molecular imaging, in order to get around these restrictions and produce more reliable and consistent data. Nowadays, the majority of multimodal imaging methods have two modes: optical imaging in

conjunction with CT, MRI, PET, or SPECT, or PET and SPECT in conjunction with MRI or PET. Preclinical and clinical research has made use of multimodal molecular imaging for early diagnosis, illness staging, treatment response assessment, surgical navigation, and prognosis evaluation.[16]

DUAL ROLE IN THERAPY AND DIAGNOSIS



CLINICAL TRANSLATION CHALLENGES

Numerous formulations have been clinically translated as a result of the developments in stimuli-responsive nanocarriers. For the treatment of cancer, two magnetic-sensitive iron-based nanocarriers are undergoing clinical trials: iron oxide magnetite and doxorubicin-loaded iron and carbon (MTC-DOX). For the purpose of treating male prostate cancer with thermal ablation, iron oxide magnetite underwent a Phase I clinical trial to assess safety, retention, and distribution following injection. For MTC-DOX, three clinical trials have been submitted: Phase II and III, which examines the safety, tolerance, and efficacy (survival time) of treating unresectable hepatocellular carcinoma (NCT00034333); Phase I and II, which assesses the feasibility of preventing the progression of hepatocellular carcinoma following injection with an external magnet (NCT00054951); and Phase I and II, which examines liver metastasis (NCT0 0041808). Additionally, the following three clinical investigations have made use of the temperature-sensitive doxorubicin-incorporated liposomes (ThermoDox): PhaseI and II research examining the effects of hyperthermia, safety, pharmacokinetics, and the maximum tolerated dose in patients with recurrent regional breast cancer (NCT00826085); ThermoDox's clinical trial is also intended to assess the safety and effectiveness of HIFU in combination with the treatment of multiple tumors (Phase II, NCT01640847), such as adenocarcinoma, breast carcinoma, non-small cell lung cancer, and painful bone metastases. Additionally, the trial will investigate the treatment of hepatocellular carcinoma in conjunction with standardized radiofrequency ablation (phase III, NCT02112656) using standardized radiofrequency ablation in conjunction with treatment for hepatocellular cancer (Phase III, NCT02112656). Radiofrequency ablation (NCT02112656, Phase III).[17]

RECENT ADVANCES AND INNOVATIONS

Smart Nanocarriers and Personalized Nanomedicine

Colloidal nanoparticles known as "smart nanocarriers" are able to carry small molecules, such genes or enzymes, that have a low molecular weight and can be used to deliver anticancer medications. Because of their increased permeability and retention effect (EPR), which allows them to carry significant doses of medication over extended periods of time, and the ability to preferentially target tumor location, nanocarriers (10–400 nm) were selected as drug carriers. Smart nanocarriers are employed to counteract multidrug resistance (MDR), which is produced by the P-glycoprotein, a drug efflux transporter that is frequently expressed on the surfaces of tumor cells. The present state of smart nanocarrier

technology, including dendrimers, liposomes, quantum dots, micelles, superparamagnetic iron-oxide nanoparticles, gold nanoparticles, and carbon nanotubes. When employed for tumour targeting, smart nanocarriers lead to enhanced drug release, more intracellular and internalization delivery, pharmacologic and pharmacokinetic profiles, higher and more regulated specificity, and-above all-a reduction in adverse effects.[18] Leaky blood arteries and insufficient lymphatic drainage are two characteristics that tumors frequently share. Active targeting and passive targeting are two key forms of medication targeting.

PASSIVE TARGETING

Nanocarrier characteristics such as charge, size, and surface chemistry, along with the constraints imposed by unlikely cell targeting within malignant tumors, all have an impact on EPR-based passive targeting to tumors. If long-circulating smart-nanocarriers can evade immune surveillance, the EPR effect will be greatly enhanced. It is possible to obtain very large concentrations of drug-loaded smart nanocarriers at the tumor area in 1-2 days, which are 10-50 times greater than in normal cells. One barrier to the effective deposition of drug-incorporated nanocarriers in cancer cells is interstitial fluid pressure (IFP)

ACTIVE TARGETING

Tumour cells and surface-modified targeted nanoparticles are used in active targeting. Certain on-surface cells, such as cell surface antigens and folic acid, have been shown to be increased and overexpressed by tumour cells. Active ligands are coupled with drug-induced nanocarriers, where these ligands will recognise their overexpressed target on the surface of tumour cells. Aptamers, transferrin, peptides, folate and antibodies are the most commonly studied ligands. Further method for the active targeted delivery of anti-tumor drugs is the use of immunoliposomes, also known as antibody conjugated liposomes. Similar to liposomes, immunoliposomes contain anti-tumour drugs; but, because they are paired with a tumour-specific antibody, they offer highly concentrated cancer cell targeting.

NANOMEDICINE IN IMMUNOTHERAPY

ENHANCING IMMUNE RESPONSES

1. pH -Responsive Nanomedicine for Immunotherapy
   pH-Responsive Nanoparticle for Immunotherapy Based on Acid-Labile Bond
   pH-Responsive Nanoparticles for Immunotherapy Based on protonation

Based on other types

2. GSH-Responsive Nanomedicine for Immunotherapy
3. ROS-Responsive Nanomedicine for Immunotherapy
4. Hypoxia-Responsive Nanomedicine for Immunotherapy
5. Enzyme -Responsive Nanomedicine for Immunotherapy
6. ATP-Responsive Nanomedicine for Immunotherapy
7. Multiple- Responsive Nanomedicine for Immunotherapy
   pH-GSH-Responsive Nanomedicine for Immunotherapy
   pH-and Enzymes responsive Nanomedicine for Immunotherapy
   GSH-and ROS-Responsive Nanomedicine for Immunotherapy
   GSH-and Enzyme-responsive Nanomedicine for Immunotherapy
   Triple-Responsive Nanomedicine for Immunotherapy

COMBINATION THERAPIES

Nanocarrier-based combinations of small molecule drugs only

When a patient has a hormone-dependent cancer, such as breast cancer, small molecule anticancer therapy often consists of chemotherapy and, on occasion, hormonal therapy. In therapeutic settings, combining numerous small compounds is common practice because it may boost their anticancer potency. A similar pattern can be seen in the development of cancer combination therapies based on nanocarrier technology. Anticancer medications with distinct cytotoxic mechanisms combined with extra benefits of nanocarrier technology are typically included in the combo. The Wu group created DMPLN, or DOX and MMC co-encapsulated polymer-lipid hybrid nanoparticles (PLN) nanoparticle formulation, based on a comprehensive comprehension of intracellular molecular pathways that resulted in an increase in DNA double strand breaks and cell death. In vitro tests using DMPLN against several human and murine breast cancer cells showed a synergistic anticancer effect with CI <1. In orthotopic breast tumor murine models, DMPLN selectively delivered drugs at fixed effective ratios to the breast tumor and extended the survival of breast tumor-bearing mice by prolonging the circulation of both DOX and MMC, as compared to free DOX-MMC combination.[19]

Nanocarrier-based combinations including large molecule drugs

Proteins and peptides, antibodies, and nucleic acids (RNA and DNA) are examples of large molecule medications. These big molecule medications' low stability, poor permeability, and propensity to be removed from the systemic circulation by the reticuloendothelial system (RES) limit their delivery. If appropriate nanocarriers are used for delivery, these restrictions can be removed.

Co-delivery of anti-cancer genes and chemotherapeutic agents

Conventional gene therapy delivers nucleic acids, such as DNA and RNA interference (RNAi), into cancer cells via a viral vector, enabling the cancer cells to self-destruct or halt their own growth. Notwithstanding, patients may be exposed to dangers associated with this delivery technique, including but not limited to severe immune system reaction, viral vector antigenicity, and possible virus infection. Moreover, rapid liver clearance and a lack of flexibility in gene packaging impede the potential of cancer gene therapy to become a successful clinical intervention. The high transfection effectiveness for loaded genes via both passive and active targeting cancer cells is made possible by non-viral nanoparticles, which allow for greater nucleic acid packaging and a high degree of surface modification. However, gene therapy administered alone to treat cancer only has a limited and temporary anticancer effect. By producing a synergistic antitumor impact, co-delivery of a gene and additional anticancer medications within a single nanoparticle holds potential for overcoming MDR, encouraging apoptosis, and inhibiting angiogenesis.

Combining antibody and chemotherapeutic drugs

Because monoclonal antibodies (mAbs) selectively target antigens expressed on the surface of cancer cells and cause cytotoxicity through distinct signaling pathways, they are a key biological medication used to treat cancer. In clinical settings, however, mAb monotherapy has only a minimally beneficial impact. An extended patient survival rate and a synergistic effect against cancer may be achieved by combining mAb with chemotherapy medicines. As an illustration, a phase III clinical trial found that the anti-HER2 antibody (marketed under the brand name Herceptin®) in combination with anthracycline and cyclophosphamide extended the progression-free survival rate and raised the tumor response rate. Medications can be directly attached to mAb to minimize side effects and direct chemotherapeutic medications to the tumor site; this process is referred to as antibody-drug conjugates (ADC). Using the benefits of

monoclonal antibodies' selectivity, ADC delivers powerful anticancer medications to tumor cells that overexpress certain surface antigens.[20]

CHALLENGES AND FUTURE PERSPECTIVE

Safety concerns

Since nanoparticles are used so widely, toxicity concerns for the environment and human health must be addressed. Products in the field of nanomedicine have a nanoscale dimension with intracellular organelles and biomolecules that are involved in cell signaling. Numerous investigations have indicated that there could be a connection between nanoparticles and detrimental biological interactions. As a result, nanotoxicology is now a recognized area of study on its own. Data on the toxicity of nanoparticles are becoming more and more accessible. Comparing the toxicity of macromaterials and nanoparticles is still challenging. The toxicity tests now in use for nanomaterials are identical to those for conventional medications. By integrating increasingly sophisticated or even predictive diagnostic technologies with innovative targeted strategies, risks in clinical development may be reduced. This makes it possible to identify "safe-responders" and implement tailored cancer treatment. Significant potential exists in this direction with theranostic techniques.

REGULATORY AND MANUFACTURING CHALLENGES

REGULATORY ISSUE

The FDA and European Medicines Agency (EMA) have approved many nanomedicine products for use in cancer therapy. They meet the most recent safety standards that these organizations have established. FDA, EMA, and other regulatory agencies, however, have not yet put explicit guidelines for pharmaceutical goods containing nanomaterials into effect. A recent article describes the FDA's strategy to regulating nanotechnology items. Nanomaterials are described as engineered materials having a minimum of one dimension ranging from 1 to 100 nm. Materials that display nanoproperties, meaning that quantum effects can be observed, are also included, even if their dimensions are smaller than 1 μm. It is anticipated that the EMA definition will be updated in 2015.

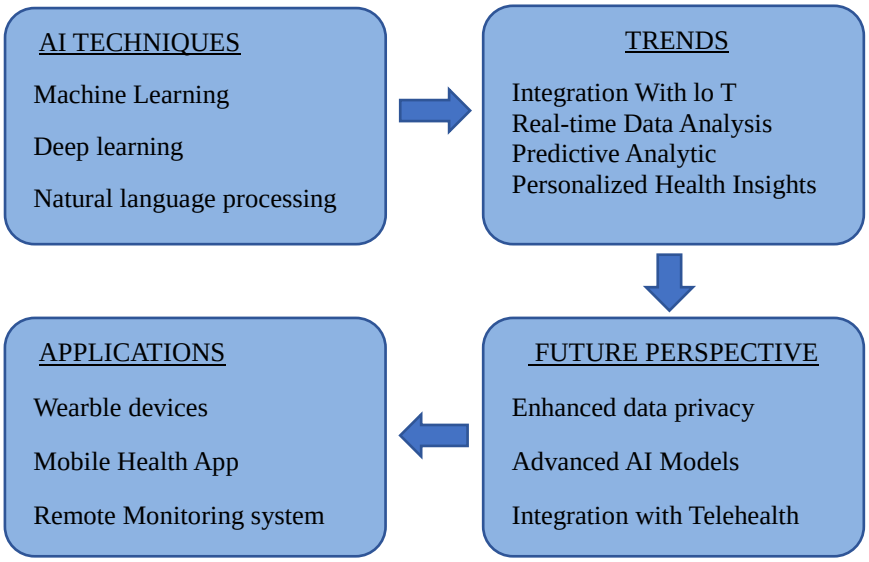
Regulatory choices about nanomedicine therapies are made based on an individual's evaluation of the advantages and dangers in the absence of data and guidelines. Nevertheless, this procedure takes a long time and could cause delays in the approval of nanomedicine products.

MANUFACTURING ISSUES

Commercializing nanomedicine products requires sophisticated manufacturing techniques and production that complies with Good Manufacturing Practices (GMPs), which presents significant challenges. Preclinical and early clinical research has often used a tiny amount of nanomaterial. The polydispersity of the nanomaterial may lead to batch-to-batch changes in the physical and chemical properties during large-scale manufacture. Accordingly, stringent batch-to-batch control over physico-chemical characteristics is necessary for the industrial production of cancer therapies based on nanoparticles. The chemistry, manufacturing, and control (CMC) process becomes increasingly difficult as a result. The shortage of Doxil® serves as an illustration of the difficulties involved in producing nanomedicine therapies. November 2011 saw the suspension of Doxil® manufacture because of sterility and manufacturing problems. A different manufacturing strategy for Doxil® was adopted, and patient therapies were postponed and medicine costs rose as a result of the subsequent Doxil® shortage, which persisted until 2014. For example, in order to prevent hydrolysis, typical bioconjugation techniques like maleimide or succinimide processes take place at a relatively narrow pH

interval. Advanced pH-responsive nanomedicine compounds require maintaining the pH interval throughout the entire manufacturing process. As a result, precise production procedures are needed.[21]

Future Trends: Highlight Emerging Areas like Ai-Driven Design Real Time Monitoring.



CONCLUSION

Nanotechnology has revolutionized cancer therapy, offering more precise drug delivery and enhanced imaging capabilities. By leveraging passive and active targeting, nanocarriers improve drug bioavailability and reduce off-target toxicity. Innovations such as stimuli-responsive nanoparticles and multimodal imaging techniques provide a comprehensive approach to both diagnosis and treatment. However, challenges related to manufacturing, regulatory approval, and toxicity must be addressed to ensure the safe and effective clinical application of these technologies. The future of nanomedicine lies in further enhancing personalized treatment, improving safety profiles, and addressing the complex biological interactions within the tumor microenvironment.

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