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A REVIEW ON RECENT ADVANCES IN NANOPARTICLE BASED DRUG DELIVERY SYSTEMS FOR CANCER THERAPY

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ABSTRACT

Drug delivery systems that are based on nanoparticles have become a potential instrument in studying cancer treatment with advantages in terms of drug dissolution, stability, and targeting of the site, and decreased systemic toxicity. Liposomes, polymeric nanoparticles, dendrimers, metallic and inorganic particles, and biologically adjusted systems such as exosomes and cell-membrane-covered nanoparticles are some of the nanocarriers implemented in order to increase the effectiveness of the therapeutic use. Liposomes are biodegradable nanoparticles between hydrophilic and hydrophobic agents which are encapsulated within phospholipid bilayers, but polymeric nanoparticles like poly(lactic-co-glycolic acid) provide biodegradability and sustained release of drug. Dendrimers offer ultimate control of the molecular architectural and drug carrying capacity, and the inorganic nanocarriers such as silica, gold, and iron oxide nanoparticles allow the use of the nanocarrier in a combination of diagnostic and therapeutic delivery. These platforms make use of passive targeting effect by the increased permeability and retention effect, and active targeting by ligand conjugation.

Moreover, the tumor microenvironment that is hypoxic, acidic, and enzyme-active sends signals to intelligent nanocarriers to achieve site-directed release. Nanomedicines that are clinically approved such as liposomal doxorubicin and albumin-bound paclitaxel have been found to be safer and more effective than the conventional chemotherapeutics. Although these have been made, there are still restrictions on large big scale reproducibility, long-term biosafety, and regulation translation. This review is dedicated to recent advances in nanoparticle design, target, and therapeutic activity, of 202025, covering both difficulties and the new opportunities of next-generation nanocarrier-based cancer therapy development.

KEYWORDS: Cancer Nanotherapy; Clinical Translation; Dendrimers; Inorganic Nanoparticles; Liposomes; Nanomedicine; Nanoparticle Drug Delivery; Polymeric Nanoparticles; Targeted Drug Delivery; Tumor Microenvironment.

1. INTRODUCTION

One of the largest issues of the global health sector is cancer, with an annual death and new cases of up to 19.3 million and 10.0 million respectively. Traditional therapeutic procedures like surgery, chemotherapy and radiotherapy are not normally tumor specific leading to dose limiting toxicity. As an example, anthracyclines and taxanes are good anticancer agents but their oncological effects sometimes can be extremely harmful to normal tissues and sometimes result in multidrug resistance.

Nanotechnology has come up as one of the available solutions to these shortcomings. Nanomedicine refers to a deliberate and selectively designed application of nanoscale carriers (1-200 nm) to entrap or conjugate therapeutic agents to further their delivery and activity to tumors. Nanoparticles have the potential to enhance cellular uptake, surface charge, biodistribution and drug half-life through optimization of parameters of size, shape, functional groups and surface properties.

It is important to note that the majority of tumors possess permeable vasculature, and inadequate lymphatic drainage resulting in passive accumulation of nanoparticles (50-200 nm) by the enhanced permeability and retention (EPR) effect. Except the passive targeting method the active targeting methodology uses ligands like antibodies, peptides and aptamers that are specific to tumor associated receptors thereby enhancing site-specific drug delivery.

Together these emerging technologies have resulted in the number of clinically approved nanomedicines with liposomal doxorubicin (Doxil) being the first in 1995. However, the fact that heterogeneous EPR effects, immunogenicity, and scalability have become obstacles to large-scale clinical translation poses. The type of nanoparticles, their targeting methods, the process of tumor reorganization through nanoparticles, clinical and preclinical studies, and the present-day problems in cancer nanotherapy are discussed in this review.

2. CANCER DRUG DELIVERY TYPES OF NANOPARTICLES

The use of nanoparticle in drug delivery has revolutionized the treatment of cancer by supplying the ability of the carrier to improve drug solubility, stability, pharmacokinetic and tumor targeting. Generally, nanoparticles (NPs) are all classified as organic, inorganic and biomimetic systems. Table 1 is a summary of examples, limitations, major types of nanoparticles, and their advantages.

2.1 Liposomes

Liposomes can be described as the spherical vesicles, which are composed of one or more layers of phospholipids which encloses an aqueous core. They can trap hydrophilic drugs in the centre and hydrophobic at the bilayer. PEGylation (stealth liposomes) has the advantage of extending the circulation of time by reducing opsonization and clearance by the mononuclear phagocyte system (MPS). In oncology drug-doxorubicin drugs (Doxil), cytarabine and vincristine have been widely applied in liposomes.

The various processes involved in releasing the content of the liposomes include endocytosis and fusion with tumor cells membranes and rate of release depends on the bilayer composition and environmental physiological signals, like pH and temperature.

Advantages: Biocompatible, capable to deliver multiple types of drugs, reduce systemic toxicity.

The system is also thwarted by the three principal limitations that incorporate leakages and different tumor storage capability and inconsistent tumor accretion designs.

2.2 Polymeric Nanoparticles

The biodegradable and biocompatible polymers of PLGA, PLA, PEG, chitosan are transformed into polymeric nanoparticles in the form of micelles either as solid nanoparticles or as mixtures. The drugs can be literally encapsulated, chemically conjugated or stuck on the

polymer. Controlled release is that of polymer degradation, diffusion or stimuli responsive bonds. The killing of tumors by polymer NPs like nab-paclitaxel (Abraxane) relies on natural transport (albumin-binding) pathway.

Mechanism Drug delivery occurs in hydrolysation of polymer matrix, endocytosis and intracellular release. The surface can be actively targeted through the assistance of ligand modification.

Advantages: Surface functionalization, adjustable size and degradation.
Limitations: Polymer can develop toxicity with a large dosage, liver/spleen accumulation.

2.3 Dendrimers

The dendrimers are highly branched and structured wood-like polymers. Their internal cavities are able to factor in small molecules or genes and the surface to have functional groups so as to be stealthy by conjugating them with targeting factors, imaging agents or PEG. The polyamidoamine (PAMAM) are the most researched dendrimers.

Mechanism: Dendrimers release cargo by degrading or breaking of bond by using pH or by the process of the dendrimers endocytosing into the cell. Multivalency allows multiple ligands used to target to be conjugated to a single particle.

Advantages: EX says to be precise in terms of size and shape, multi-functionally usable, and drug-loading capacity is great.
Limitations: Scale-up may only be accomplished in complicated synthesis, cationic toxicity and scaling up expense.

2.4 Protein Nanoparticles

Protein NPs make use of natural proteins such as albumin, ferritin, gelatin or collagen. They are naturally biocompatible, biodegradable and can exhibit natural tumor tropism. Albumin NPs are also utilized in Abraxane that targets gp60 receptor and SPARC protein within the tumors adopting a better delivery of paclitaxel.

Mechanism: Endocytosis due to receptor-mediated uptake (int) sort of release drug into intracells (e.g., albumin-gp60).

Merits: The immunogenicity is also low, the target itself is naturally bound, the examples are approved by the FDA.

Weaknesses: Limited loading capacity of drugs, aggregation can occur.

2.5 Inorganic Nanoparticles

Not all inorganic NPs include gold, iron oxide, silica and quantum dots which provide unique physicochemical functions such as significance of magnetism, photothermal conversion and creation of contrast. They are used in therapanostics in the field of combined therapy and diagnostics.

Mechanism: Photothermal therapy (PTT) or magnetic hyperthermia can be used in the physical property but drug delivery in the surface conjugation. The consideration of such factors as clearance and long-term toxicity are essential.

Advantages: imaging-based therapy, high stability, multifunctional.
Limitations: Non-biodegradable, may be toxic in the long-term, not scalable easily.

2.6 Carbon-Based Nanomaterials

Graphene oxide and fullerenes can be utilized to obtain high surface area of drug loading and as photothermal agents, carbon nanotubes (CNTs). Functionalization allows solvability and targeting.

Advantage: high drug loading degree, photothermal and imaging services.
Limitations: Safety, clearance, lesser clinical translation.

2.7 Biomimetic Nanoparticles

In biomimetic nanoparticles, the view to the synthetic NPs is that platelet cell membranes (or any other cell membranes of cells e.g. RBCs, platelets, cancer cells etc.) or exosomes cover the NPs. The approach utilizes natural target immune evasion and homotypic targeting.

Weaknesses: It has been the case of more circulation lifespan, immune system protection, and tumor targeting.
Weaknesses Multifaceted construction, scale issues, legal impediments.

Table No. 1: Comparison of Major Nanoparticle Types for Drug Delivery.

Type	Composition	Size (nm)	Advantages	Limitations	Examples
Liposomes	Phospholipid bilayer (±PEG)	~50–150	Biocompatible; encapsulates hydrophilic drugs; PEGylation prolongs circulation	Stability/storage issues; potential leakiness	Doxil (doxorubicin)
Polymeric NPs	Biodegradable polymers (PLA/PLGA, PEG)	10–200	Tunable release; protect payload; surface modifiable	Possible toxicity; RES clearance	Abraxane (albumin–paclitaxel)
Dendrimers	Branched polymers (e.g., PAMAM)	~5–20	Precise size; multi-functional ends	Complex synthesis; toxicity (cationic charge)	Polyamidoamine dendrimers (investigational)
Protein NPs	Endogenous proteins (albumin, ferritin)	~50–100	Biodegradable; low immunogenicity; inherent targeting	Limited drug loading; potential immune recognition	Abraxane (albumin–paclitaxel)
Inorganic NPs	Metals (Au, Fe_3O_4), silica	~5–100	Unique optical/magnetic properties; imaging/therapy	Non-biodegradable; potential long-term toxicity	Nanotherm (iron oxide for thermal ablation)
Carbon NPs	CNT, graphene, fullerenes	~50–100 nm (tube diameter)	High surface area; photothermal	Poor solubility; safety concerns	Graphene oxide (investigational)
Biomimetic NPs	Cell membranes (RBCs, cancer cells) on cores	~100	Immune evasion; homotypic targeting	Complex fabrication; scalability	Exosome-mimetic vesicles (investigational)

3. NANOPARTICLES AS TARGETED THERAPY ON CANCER RESEARCH

The penetration of nanoparticles into tumors relies on a successful targeting methodology that is anticipated to obtain the desired treatment plan and lead to the fraction into the tumor and that which is appropriated to the tumor cells without triggering body toxicity. The targeting

strategies can be classified into general categories into passive or active strategies or stimuli-subsistence or both.

3.1 The third form of targeting is the passive targeting (EPR Effect)

Passive targeting exploits known permeability and retention (EPR) effect where nanoparticles (50-200 nm) preferentially accumulate in tumors due to the ruptured vasculature and lymphatic drainages. EPR was the mode of delivery to tumors being used with the first generation liposomes and the polymeric nanoparticles.

Key Points: EPR varies greatly based on the kind of tumor and pancreatic cancers are low permeability tumours where renal cancer are highly vascular tumours.

EPR is typically overdone in preclinical models and therefore becomes challenging to translate clinical.

Predicting which tumors can be utilized in EPR based therapies can be done using the stratification of patients and imaging biomarkers.

3.2 Active Targeting

Active targeting enhances the uptake of nanoparticles by chemically coating the surface with analogous ligands of which tumor-specific receptors are attached. Common ligands include.
Antibodies: anti-HER2, anti-EGFR.
Peptides: RGD, FAK ligands
Small molecules: transferrin, folic acid.
Aptamers: nucleic acid agents of targeting.

Mechanism: As cells become activated through the interactions between ligands and receptors, this induces a more efficient action of receptor-mediated endocytosis and causes increased delivery of drugs into cells. Active targeting is normally used to complement the use of passive targeting because nanoparticles must first of all extravasate into the tumor tissue.

Examples: Antibody-drug conjugate (ADCs), even in the development of folate-ligand liposomes.

3.3 of Stimulus-Reactive(Smart) Targeting.

There is the ability to design smart nanoparticles to behave in accordance with the required tumor-relevant stimuli and deliver its cargo to particular locales. Stimuli include.

pH: when the tumor environment can be classified as acidic, it leads to the release of the drug out of liposomes or polymeric micelles.

Redox: when glutathione levels are high in cancerous cells, linkers are redox cleaved.

Enzymes: the availability of excess phosphatases or phosphatases is in favour of drug release.

Extrinsic factors NPs in response to temperature, light, or magnetic fields may include an external stimulus such as thermosensitive liposomes or iron oxide particles.

Side effects Greater location-specific delivery, less off-target toxicity and more therapeutic effect.

3.4 Combination Targeting

Nanoparticles can deliver two or more therapeutic agents in the same manner, resulting in synergies.

Possible combinations of chemotherapy two drugs in NP at fixed ratios.
Chemo + siRNA/gene therapy: This implies dual concomitant cancer signaling and cytotoxicity changes.

Chemo + immunotherapy: immunomodulators and combination of cytotoxic drugs are used as anti-cancer therapy.

Vyxeos (CPX-351): Cytarabine and daunorubicin liposomal co-formulation with a 5:1 ratio and an overall survival rate are superior to the free-drug combos in the AML.

Table No. 2: Key Approved Therapies.

Product	Carrier Type	Payload	Indication(s)	Year (Regulator)
Doxil	PEGylated liposome	Doxorubicin	Kaposi sarcoma, ovarian, breast, MM	1995 (FDA)

Caelyx	PEGylated liposome	Doxorubicin	Breast, Kaposi sarcoma, MM	1996 (FDA)
Abraxane	Albumin NP	Paclitaxel	Breast, NSCLC, pancreatic	2005 (FDA)
Onivyde	Liposomal	Irinotecan	Metastatic pancreatic cancer	2015 (FDA)
Vyxeos	Liposomal	Cytarabine + Daunorubicin	AML (therapy-related, MR-AML)	2017 (FDA)
Apealea	Polymeric NP	Paclitaxel	Ovarian, peritoneal, fallopian tube	2018 (EU)
Lipodox	Liposomal	Doxorubicin	Similar to Doxil (China)	2013 (China)

4. NANOPARTICLE INTERACTION AND TUMOR MICROENVIRONMENT (TME)

The Tumor microenvironment (TME) is a rather critical aspect that influences the efficacy and the delivery of nanoparticles therapy. It has cellular and non cellular products that influence nanoparticle penetration, retention and release of drugs.

4.1 Components of the TME.

The TME is comprised of Extracellular Matrix (ECM): webs of tough collagen and fibronectin that can have an actual restrictive effect on nanoparticle diffusion.

Abnormal Vasculature: Tortuous and leaky vessels are found to create a heterogeneous perfusion, which is also one of the contributory factors to unevenly distributed nanoparticles.

Hypoxic and Acidic Zones: Conditions of low oxygen and acidic pH (Warburg effect) affect the stability of the nanoparticles and the release of the drugs.

Stromal Cells: Tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), myofibroblasts and immune cells control the intake of nanoparticles.

Immune Modulators The migration or uptake of nanoparticles Cytokines and immunosuppressive cells have the ability to alter bioavailability.

4.2 Barrier Effects

Pressure in Interstitial Fluid: Tumour high pressure can work against penetration of nanoparticles.

Metalloprotein thick stroma: Typical stroma which has been characterized by collagen which limits movement of larger or hard nanoparticles.

Harsh variant EPR: It refers to a variation in vascular permeability, i.e. portions of a tumor may be inaccessible to NPs.

4.3 Nanoparticles Design Opportunities

Nanoparticles can be made to exploit the TME cues

pH Responsive NPs: Activate drug in acid tumors.

Enzyme-Responsive NPs: Cargo released after cleavage by an enzyme (e.g. MMP), or other tumor enzymes.

Oxygen-Carrying NPs: Hypoxia: Prevent the effect of hypoxia to improve chemotherapy and radiotherapy.

Immune Modulatory NPs: Stimulate TAMs, or inject immunostimulatory substances to escape immunosuppression.

4.4 TME Modulation Strategies

It has nanoparticles that are designed to remodel the TME

Stroma-Modifying NPs: Carry antifibrotic enzymes or collagenase to increase the permeation of nanoparticles.

VesselNormalization: Vessel normalization NPs is shown to enhance perfusion and drug delivery.

Combination Therapy: it can occur through NP mediation of Chemo + immune modulators; this will not only target cancer cells but also manage the TME.

4.5 Clinical Implications

Due to knowledge of the TME, the treatment of nanoparticle can be conducted at a personal level

Imaging and biomarkers can be used to Stratify patients and inform NP selection.

Stabilized Formulations: NP size optimisation, charge and surface chemistry optimisation increase penetration in specific tumour types.

Predictive Modeling: These are the computational models that can make predictions on the NP behaviors when the conditions are heterogeneous across TME.

5. NANOPARTICLE-BASED THERAPIES PRECLINICAL AND CLINICAL DATA

5.1 Preclinical Studies

Nanoparticle formulations have presented increased efficacy and safety profile than free drugs in the preclinical research works, both in vitro and in animal models, continuously.

Key Findings

Enhancement Tumor Accumulation: Tumor accumulation of the drug is enhanced with improved Programs in the cellulation of liposomal and polymeric nanoparticles by EPR and targeted uptake.

Improved Pharmacokinetics: Nanoparticles raise the circulation time, reduce the clearance and maintain the levels of the therapeutic agent.

Combination Delivery: Co-encapsulation of drugs with each other implies that a number of drugs are administered simultaneously, and this enhances synergy. It is true that in the murine models the polymer-doxorubicin conjugates and liposomal paclitaxel worked better in controlling tumor.

Nanoparticles have applications in the administration of siRNA, CRISPR products as well as immunomodulatory agents to tumors.

Theranostics: Nanoparticles of combo drugs and molecular imagings can be made to detect the location of drugs and therapeutic outcomes.

Representative Study: In a meta-analysis, Benderski et al. (2025) have found that a two-drug system consisting of no-toxic nanoparticle was found to improve the tumor-inhibition and survival of one-drug system.

5.2 Clinical Nanomedicines

Nanoparticle formulations which have been successfully translated into clinical use of the nanomedicine principles are a number of FDA and EMA approved formulations.

Clinical Insights

Nanomedicines have a low propensity to toxicity (liposomal doxorubicin is not as cardiotoxic with nanotechnology, Cremophor hypersensitivity is avoided with Abraxane).

Survival advantages are not typically enormous, and it is an expression of the complexity of tumor biology.

Recent research is now being conducted in the areas of targeted and combination NPs nanoparticle therapies as in antibody-targeted liposomes and NP based immunotherapy.

5.3 Preclinical Success cannot be translated to give a translation account.

The clinical translation is problematic due to multiple hindrances: despite good preclinical evidence.

1.Tumor Heterogeneity: This is changeable and it is tough to reach certain regions in tumors.

2.Immunogenicity and Clearance: It may result in complement activation and enhanced blood clearance through repeated immunization potentials.

3.Complexities Multifunctional NP Manufacturing should be individually synthesized and characterized.

4.Regulatory Hurdles: Nanomedicine is not regulated by much specific guidelines and, hence, it is difficult to have it approved.

5.Individual Patient Conditions: Genetics of tumor, past stroma contents and treatments determine NP efficacy.

Conclusion Preclinical research ought to demonstrate the potential of nanoparticle treatments, however to introduce them to the benefits that can be reliably helpful in the clinic, there must be patient selection, combination optimization and rigorous clinical trial design.

6. FUTURE PERSPECTIVES AND PROBLEMS OF CANCER THERAPY USING NANOPARTICLES

6.1 Nanoparticle- Based Cancer Therapy is problematic

Despite all these accomplishments, nanoparticle (NP) drug delivery is prone to several critical challenges:

Tumor Heterogeneity and Variability of EPR

The presence of enhanced permeability and retention (EPR) effect is not found in every tumor.

Dense stroma defines or low vascularization of certain cancers (e.g. pancreatic) as a limiting factor to NP accumulation.

The fact that predictive biomarkers are lacking contributes to making the process of selecting patient in the case of NP therapy a problem.

Safety and Immunogenicity

There are those NPs that cause immunological reactions, including infusion related reactions.

Protein corona formation in blood makes the NP biodistribution modified with uncertainty.

Non-biodegradable inorganic NPs have a long-term toxicity especially.

Multidimensional Scalability and Production

Multifunctional NPs demand complex synthesis and so do stimuli responding and targeting ligands.

At least not easily, it is achievable to have batch-to-batch reproducibility.

Serial production is both expensive and highly technical.

Regulation barriers and Cost barriers.

Nanomedicine has no many regulatory guidelines.

To make IP and natural polymers development costly, the high cost of development might be encouraged.

Biological Barriers

Mononuclear phagocyte system (MPS) removes a great number of NPs in a very short period of time.

PEGylation or biomimetic coats are employed to evade clearance at a large expense, but may lead to increased blood clearance on repeat perforation.

High-density entry of the tumor tissue remains a challenge.

Patient-Specific Factors

The tumor genomics, past treatment and stroma composition can influence NP efficacy.

Nanotherapy is not yet standardized, and it has to be administered to individuals with the help of companion diagnostics.

6.2 Future Directions

Nanomedical studies are formulated to be able to solve the existing issues and come up with more precise cancer treatment.

Multi-Functional and Stimulus Reportive NPs

Combine gene therapy, immunomodulators, and chemotherapy.

Free drugs TME based (pH, enzyme, redox).

Biomimetic Nanoparticles

Immunoevasion and tumor targeting involving cell membranes or exosomes.

Early exosomes were also shown to deliver siRNA or CRISPR products to tumors via the exosome-based NP.

Nano- Vaccines and Immunotherapy The treatment of cancer involves the use of NPs consisting of tumor antigens and adjuvants with the help of cancer vaccination.

Immune checkpoint inhibitor Co-delivery to memory is being studied.

AI and Computational Design

Machine learning approximates the interrelationships between NP and biology and develops formulations.

Al Museum-driven design accelerates the discovery of good structures of nanoparticles.

Personalized Nanomedicine

Tumor biology (receptor expression, TME characteristics) NP therapy individualization.

Image-guided dosing or liquid biopsy dosing enhances the outcome of the treatment.

Regulatory Pathways

Establishing the standard testing (e.g., Nanotechnology Characterization Laboratory) so that it can be translated with ease.

Organizing international regulatory framework so as to support clinical licensing.

CONCLUSION

Nanoparticle delivery of drugs in a cancerous cure is a ground breaking technique of curing medication and could potentially improve the solubility and stability of the drug administered, the targeted delivery of medication to the tumor and the reduction of systemic toxicity in drugs. Depending on the therapeutic needs, different nanocarriers exist that include liposomes, polymeric nanoparticles, dendrimers, protein-based, inorganic, carbon-based, and biomimetic nanoparticles.

Key findings of this review

Targeting Strategies Passive (EPR effect) and active targeting (ligand-mediated) increase tumors accumulation whereas Stimuli-responsive systems provide tumor-specific drug delivery. One can also have an opportunity to co-deliver synergistic agents with combination strategies that increases therapeutic outcomes.

Tumor Microenvironment (TME): TME should not be ignored because it significantly affects the penetration of NP, its distribution and efficacy. Clinical translation is enhanced by the TME modulation and use of strategies specific to the patient. Preclinical Data Preclinical trials show a higher level of efficacy and safety of NPs. They are applied to the clinics with the accepted nanomedicines (Doxil, Abraxane, Vyxeos) that have been proven to be valuable, but it is not always the case that the survival is improved which makes it obvious that further innovation is needed.

Issues and Future Projections: Wariability of EPR, immunogenicity, complicated production and regulatory impediments are major challenges. Multifunctional NPs, multi-functional biomimetic NPs, stimuli-responsive NPs, artificial intelligence-based design, nano-vaccines and personalized nanomedicine are the future.

Overall, nanoparticles have a tremendous potential to serve oncologists as the toolbox to perform precision-guided therapies, and further interdisciplinary research on nanoparticles will be able to lead to the development of safer, more efficient, and personalized treatments against cancer.

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