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Nanomedicine and nanoparticles in a new oncologic era

Nanomedicina y nanopartículas en una nueva era oncológica

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ABSTRACT

Cancer is a global health challenge. Nanotechnology and nanomedicine, the synthesis and use of materials with dimensions on the atomic or molecular scale (diameter ≤100 nm), has become increasingly utilized for medical applications and is of great interest as an approach to killing microorganisms and neoplastic cellular transformation. These particles exhibit characteristic effects owing to their high surface-area–to-volume ratio with unique chemical and physical properties. Ongoing research is applying this novel and innovative technology for cancer diagnosis and treatment. Studies include tumor-specific drug delivery nano-vehicles, modulation of drug interactions with the immune system, active targeting and better retention and uptake of drugs, stimuli-responsive drug delivery, nanocarriers containing therapeutic and imaging agents, allowing selective detection of cancer cells through real-time imaging techniques, to exosome nanoparticles used for cancer detection through liquid biopsy. It seems certainly worth-looking into this new frontier, as part of the modern cancer diagnosis and treatment.

Keywords: Nanoparticles, nanotechnology, oncology.

Level of evidence: III

RESUMEN

El cáncer es un reto de la salud global. La nanotecnología y la nanomedicina, la síntesis y uso de materiales con dimensiones en escalas atómicas o moleculares (diámetros de ≤ 100 nm), se han utilizado cada vez más en la medicina y se consideran de gran importancia en cuanto a su capacidad de matar microorganismos o su papel en la transformación de células neoplásicas. Estas partículas exhiben características únicas debidas a su alta tasa de volumen a área de superficie con propiedades químicas y físicas únicas. En la investigación contemporánea se puede apreciar esta nueva tecnología para el diagnóstico de cáncer y su tratamiento. Estudios que involucran a las nanopartículas incluyen vehículos para administración directa de medicamentos, modulación de interacciones entre medicamentos y el sistema inmune, activación de blancos terapéuticos con mejor retención y recepción de drogas, nanopartículas que contienen agentes terapéuticos y de imagen que permiten la detección selectiva de células neoplásicas a través de técnicas de imagen en tiempo real hasta la detección de células neoplásicas mediante biopsia líquida dirigida por nanopartículas de exosomas. Sin duda, esta frontera en la oncología moderna requiere de una revisión que permita conocer nuevas herramientas en el diagnóstico y tratamiento de neoplasias.

Palabras clave: *Nanopartículas, nanotecnología, oncología.*

Nivel de evidencia: *III*

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Abbreviators:
HIC = High income countries.
LMIC = Low and middle income countries.
CO = Carbon hydroxide.
O_2 = Two atoms of oxygen.
CRISPR/CAS9 = Clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9.

INTRODUCTION

Despite COVID-19, cancer still stands as the fiercest pandemic of the 21st Century, representing one of the leading causes of morbidity and mortality worldwide. Its incidence continues to rise in both high (HIC), and especially in low and middle-income countries (LMIC). Prevention is crucial, but implementation has been slow and incomplete, even in HIC. Also, prevention is a long-term strategy, and not all cancers can be prevented (CONCORD-3).[1] To reduce cancer mortality, both, reduction of cancer incidence and improvement of cancer survival need to be addressed, for the malady will continue to cause not only personal sorrow, but substantial manpower and economic loss for the foreseeable future.

Many patients will continue to be diagnosed with cancer for decades to come. It is estimated that every year, around 15 million people are diagnosed with the disease worldwide. In children, over the next 30 years (2020-2050) 13.7 million kids will be diagnosed with cancer globally.[2] Since most children with cancer live and die in low and middle-income countries, where survival ranges from 25-50%, it is thus expected that without any further interventions, more than 11 million children will die to cancer in the next three decades.

Nanotechnology has demonstrated potential for addressing serious healthcare challenges, and nanomaterials have been used as delivery platforms, anti-virals, and even anti-neoplastic compounds.[3,4] Citrus-derived compounds are effective busters of the immune system, with clear clinical benefit against viral infections and overall healing. Flavonoids and terpens have anti-inflammatory, cytotoxic, anti-neoplastic, and anti-viral activity. Their inhibitory or stimulatory effect on key metabolic enzymes, influence signaling pathways, cellular function, and gene expression.[5-9]

HISTORICAL PERSPECTIVE

The term nanotechnology was coined in 1974 by Nomo Taniguchi. Nanoparticles measure a millionth of a meter. Several chemical structures and compounds have been utilized, each with distinct textural, optical, electric and magnetic properties. Word-mentioning examples include magnesium, titanium, silver, zirconium, and silicium or silicone. In 1990, the term catalytic nanomedicine was created by the European Journal of Medical Chemistry as a way of obtaining inorganic bio-catalyzers capable or breaking carbon – carbon and carbon – nitrogen bonds in cancer cells, in particular, with platinum, silicone and titanium compounds. In this pivotal study, Wistar rats were utilized as a model of glioblastoma multiforme in which compounds such as Pt/SiO_2, Pt/TiO_2 and H_2PtCl_6/SiO_2 intertwined with platinum salts were evaluated for tumor regression. The platinum compound containing H_2PtCl_6/SiO_2 proved to be the most active of the evaluated nanoparticles, translating in a tumoral reduction of approximately 60%, which was later observed via DNA and protein electrophoresis. In 1991, The Journal of Physical Chemistry reported that metals such as platinum, palladium, and ruthenium mixed with materials such as silicon dioxide and prepared in a sol-gel method utilizing initially tetra-ethoxy titanium, may occupy octahedral sites within a nanoparticle web compound.

In 2003, in Mexico, research regarding cancer and neurodegenerative diseases begins in the Nanotechnology and Nanomedicine Laboratory of the Metropolitan Autonomous University, as well as the National Institute of Neurology and Neurosurgery. Their goal was the prevention, diagnosis, and treatment of the aforementioned diseases, control of their progression, pain management, and tissue reconstruction. In 2006, in a journey from nanotechnology to nanomedicine and its clinical applications, titanium nanostructures began to be utilized as a controlled liberation mechanism for central nervous system tumors. It is important to note that the medication used would not loose efficacy as it would not be metabolized via the liver. As of 2009, biocompatible nanostructures started to be investigated in several of tumors, looking to break bonds between malignant cells in order to inhibit their growth. Specifically, it was noted that nanoparticles displaced the cellular nucleus to create a catalytic reaction and break the above-mentioned carbon – carbon and carbon – nitrogen bonds, as well as hydrolysis of nucleotides in the tumor cells DNA. Specific chemotherapeutic agents such as temozolomide, methotrexate, doxorubicine and paclitaxel were evaluated in 2010, combined with titanium or silicone nanoparticles, creating

nanostructured biocatalists. The first nanoparticle to be approved as a first line therapy was nab-paclitaxel in 2015, to treat advanced pancreatic cancer in combination with gemcitabine.[10]

COMPREHENDING NANOPARTICLES

One of the main benefits of nanomedicine pertains to its ability to make different drugs or molecules readily available to specific tissues, bypassing others and consequently, its related adverse effects.[11] Due to their size, medications and molecules used in nanotechnology do not go through the blood stream nor are metabolized through the liver. Thus, offering a longer half-life and protection against enzymatic attacks and acid degradation. Nano-compounds are liberated by first order kinetics, and released to the body through structured micropores, while changing to zero-order kinetics, which in turn undergo constant elimination regardless of plasma concentration, following a linear elimination phase.

Characteristics such as stability and biological activity must not be affected during the encapsulation process of the nanoparticle, which in addition, must retain a high rendering to synthesis reaction, the purity of the nanoparticle must correspond to 99.99%, and it must be reproducible. The aggregation of particles will determine its porosity and the capacity the structure has to accumulate drugs within the compound. With this so-called miniaturization of medicine, surface contact is maximized and reactivity of the elements which constitute it are amplified. An electron microscope is needed to be able to observe nanoparticles.

While some nanoparticles are used for treatment, others are useful for timely detection, or used for tissue regeneration and photodynamic therapy, among many others. Possibilities for this new form of drug administration may be endless. Hydrogel nanoparticles measuring 5-100 nm in diameter, aid in tissue growth, encapsulation, cellular liberation and axonal regeneration. Depending on the adjuvant used, a certain speed of diffusion may be sought out, or facilitate drug clearance from the system. Amongst these are collagen, albumin, or polysaccharides such as quinine. Biodegradation of the compound depends on the drug used, the way and place of implantation, its form, density, and molecular weight of the employed polymer. An example of this would be how the addition of zirconium to titanium may increment the molecule's specific area. The intramolecular forces which are used within nanoparticles to be able to maintain stability include ionic and covalent bonds, as well as weak intermolecular forces.

Other interesting concepts to note are the transport and dissolution of a medication by gradient concentration, fulfilling the first law of Fick. The activation of an atom occurs when a photon rids its excess energy by irradiation, a concept which is reflected in the actions and characteristics of nanoparticles. Charge transitions may change depending of the metal incorporated, the anatomical interactions which are generated by the metal and it's web of support, which in turn chance the behavior of the nanostructured catalyzer.

Nanoparticles exhibit characteristic effects owing to their high surface-area–to-volume ratio with unique chemical and physical properties that, interestingly enough, do not follow the classic chemistry and physics laws of the macro world.

Ionic compounds are crystalline solids soluble in H_2O. They are arranged in an organized structure and possess good electric conductivity, and have high boiling and fusion points because of their strong bonds. Phosphate ions stabilize solids, modify acid-base properties and may transform the catalytic properties of nanoparticles. The smaller the particle, the greater its catalytic activity and resistance to degradation. The effects of nanoparticles begin when molecules of CO and O_2 are absorbed in its surface. O_2 is dissociated into two atoms of oxygen and one of them interacts with a molecule of CO on the metal surface of the nanoparticle, such that CO_2 is created and the materials may be released into the tissue in question. Nano –delivery permits nanoparticles to cross the cytoplasmatic and nuclear membrane to introduce chemical biological and genetic material into determined tissues, organs, and cells. The way the medication is released also depends on the intermolecular attractions between the drug and the nanoparticle which transports it. The velocity of liberation is a direct result of the interaction between the medication, the reservoir, or the nanoparticle itself, and its diffusion. A better control of function is achieved by modifying the velocity of hydrolysis, condensation, and mechanical resistance during the regulation of the compound itself. Parameters which may affect a nanoparticles physio-chemistry are the relationship between H_2O and CO, the temperature and pH in which such reactions occur, the type of solvent used, the time of gelation, and the diverse alkylating groups of the chosen precursor material.

The sol-gel approach is essential to the comprehension of modern nanotechnology, as it

An Med ABC. 2022; 67 (2): 131-136

involves changing a material from a liquid (sol) to a solid (gel) phase. This process is a method to produce solid materials from small molecules, a technology which may be used to prepare fibers, microspheres, and nanoparticle compounds. Once drugs are stabilized in nanostructured silicone, a porous material which contains a high quantity of OH groups, oxide materials are obtained by the preparation of a solute and the elimination of a solvent. Reactions for this include hydrolysis, condensation, and polymerization. The conditions in which this occurs determine the structure and texture of the final product. Solvents have an established polarity and may favor the formation of electrophilic ions, increase the velocity of hydrolysis, and form hydrogen bonds in condensed states. With the sol-gel method, the product obtained is more homogeneous. And the particle size is controlled, as well as its surface area and the size of its pores. The process also proves a better thermic stability and therefore, a lesser degradation of nanomaterials and greater ease in the addition of certain elements to the nanoparticle structure.

NANOTECHNOLOGY AND NANOMEDICINE IN ONCOLOGY

Difficulties with drug penetration and poor site specificity into tumors are some of the most challenging problems of chemotherapy.[12] The ability to efficiently deliver drugs to specific tumor sites is possible through nano-delivery vehicles which not only allow the drug to reach its target, but reduce unwanted side effects, increase target efficacy and efficiency.[13] Drug distribution within tumors is preferential due to the presence of fenestrations within the imperfect tumor blood vessels[14] and the poor lymphatic drainage of the tissue, which in combination create the enhanced permeation and retention effect (EPR). Biological processes also encompassed by this phenomenon include lymphangiogenesis, heterogeneities in tumor genetic profiles or tumor microenvironment, hemodynamic regulation, vascular permeability and angiogenesis.[15] Other factors which may also alter the efficacy of drug delivery in this scenario are interactions between the mononuclear - phagocyte system and timely release from the delivery vehicle.

Cell surface markers have often been utilized to guide therapeutics, notwithstanding, expression levels may be relative to normal cells and may be expressed at low levels in many normal tissues, leading to unwanted toxicity in cancer therapies. Taking this into consideration, ligand - mediated targeting or active targeting aims to improve retention and uptake of nanoparticles. These actively targeted particles must be in the vicinity of their molecular target to be able to interact with it, thus the amount of particles available at the tumors´ blood supply is crucial. Ergo, these nanoparticles must be designed to have extended circulation times and extravasation from circulation at the tumor site.[13]

Nanomedicine may be utilized via antibody - drug conjugates, liposome-based delivery platforms and albumin - bound nanoparticles. Examples of antibody conjugates include brentuximab vedotin which targets CD 30, overexpressed in lymphomas, or trastuzumab emtansine, which is utilized for HER2 metastatic breast cancer. Liposomes are artificial vesicles made up of several layers of phospholipids and an aqueous core into which drugs are loaded, intended for hard - to - treat cancers with poor prognosis and dose limiting side effects. Examples of these are doxorubucine (Doxil), daunorubicine (DaunoXome) and vincristine, (Marqibo). Albumin–bound nanoparticles are geared towards the delivery of drugs with poor aqueous solubility, achieving a large distribution volume, such as paclitaxel (Abraxane).

The transport of a nanoparticle delivery platform into a cell involves the binding of such platform to the cellular surface, triggering external release or utilizing the conditions of the target tissue to trigger release. This depends on cell surface, the ability of the nanoparticle to be translocated across the cell membrane, and its stability and lack of destabilization or degradation in blood circulation. Other entities to take into consideration include stimuli responsive drug delivery systems, which may control drug release, imperative to the decrease of side effects of the attached drugs. Stimuli responses may be divided into endogenous stimuli which includes pH, and redox and enzyme responsive materials, exogenous stimuli such as light, temperature, magnetic field response materials or ultrasound and lastly, multi-stimuli response materials.[16] Stimuli response drug delivery permits high drug loading capacity, favorable biocompatibility and a higher security and effectiveness in relation to traditional drugs.

An example of targeted nanoparticles tailored towards optimal delivery include the newly published ferritin decorated with tumor-homing penetration peptide tLyP-I which is engineered to deliver paclitaxel inside the cell via receptor -

mediated endocytosis. Studies on this molecule published in The International Journal of Nanomedicine in early 2021 show enhanced tissue penetration, anti-tumor efficacy and improved site specificity.[12] Another interesting study published in Nanomaterials in February 2021 show polyethylene glycol coated magnetic nanoparticles geared towards hyperthermic and magnetic treatment, looking to forward thermal conducting properties, which have a favored radiation effect on cancer cells, of laser induced self-heating drug carriers. This may be utilized both for cancer treatment as well as contrast agents in magnetic resonance imaging.[17]

Nanoparticle in cancer therapy has been evaluated in the majority of solid tumors. Interesting examples to note, published the last year, are doxorubicin conjugated iron oxide particles in osteosarcoma,[18] and the role ionizing radiation plays in the internalization and cytotoxic effects of the nano-carrier mediated drug delivery, mannose modified cyclodextrin with regorafenib in colorectal cancer to attenuate inflammation and inhibit tumor associated macrophage activation by targeting macrophages whilst improving regorafenib's anti-tumor effect by potentiating kinase suppression,[19] combination chemo-photodynamic therapy using lipid encapsulated polymeric nanoparticles against platinum resistant ovarian carcinoma cells, Yang et al., the use of lipid polymer hybrid nanoparticles constructed for CRISPR/CAS9 plasmids targeting drug resistant glioblastoma,[20] sorafenib nanoparticles as targeted ferroptosis-induced treatment of hepatocellular carcinoma,[21] and photothermal therapy and radio-sensitization using silver nanoparticles in triple negative breast cancer without affecting non-malignant mammary epithelial cells are some compelling examples.[22]

The use of cancer theranostics combine anticancer targeted therapy and diagnosis by nanocarriers which contain therapeutic and imaging agents allow the selective detection of cancerous cells and their visualization through real time imagine techniques.[23] Tumor localization may be achieved through chemical, thermal or optical signals, and drug release *in vivo* may also be evaluated with recent advances in nanoparticles systems. Nanoparticles which fall into this category are magnetic, contain nanocarriers such as gold, carbon nanotubes, quantum dots, nanobubbles, liposomes and polymeric nanoparticles.[24] Further research is aimed at developing triggered release systems to light, pH, heat or other such factors so that not only proper drug localization is achieved but also the determination of released drug concentration. Gel permeation chromatography has been utilized to calculate drug encapsulation efficiency, and the loading content of nanoparticles.[25]

Exosome nanoparticles have been more recently used for cancer detection, specifically exosome based liquid biopsy, now aiming to be utilized as well for the detection of mutation against anti – cancer therapies. The size and concentration of isolated exosomes were characterized by nanoparticle tracking analysis systems and dynamic light scattering technologies. Platinum nanoparticles are now being utilized to induce de biosynthesis and release of exosomes in lung epithelial adenocarcinoma.[26] Although this process was initially studied in blood samples of patients with lung cancer, the current trend is to apply it in other bodily fluids, such as cerebrospinal fluid or saliva breast cancer and melanoma.

As a caveat to nanomedicine in oncology, the morphology of tumor vasculature, the components of the extracellular matrix, or the presence of tumor infiltrating lymphocytes and other immune cells, may all alter the distribution of nanoparticles. With this, binding, internalization, toxicity, and drug efficacy might also be altered. Different drugs may also be combined in a single nano-particle to timely co-deliver agents which inhibit distinct, essential pathways

CONCLUSIONS

If the above-mentioned experiments achieve translational significance, the potential positive impact on health and economy could be extensive.

Further studies are needed in order to establish the clinical effectiveness and safety of nanotechnology in cancer patients.

Nano-medicine has the potential to improve outcomes for this international healthcare problem.

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