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APPLICATIONS OF NANOTECHNOLOGY IN ONCOLOGICAL TREATMENT: A NARRATIVE REVIEW

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Abstract: In this study, we seek to elucidate the most recent research on nanotechnologies for oncology therapy, exposing its advantages, challenges and expectations regarding the efficiency of these methods. This is a theoretical bibliographical review article on the applications of nanomaterials in the treatment of cancer. In addition, the limitations and adverse effects of the main oncological treatments currently used were also discussed, as well as the benefit of combining these therapies with nanotechnology, through nanocarriers or nanoparticles, and the importance of searching for more satisfactory methods for cancer treatment.
Keywords: Nanotechnology; nanomedicine; oncology.

INTRODUCTION

According to the Pan American Health Organization (PAHO, 2020), in 2018 cancer was the second leading cause of death in the world. Its pathogenesis is based on the hyperproliferation of cells resistant to apoptosis and capable of invading host tissues, as well as metastasizing to distant sites, which explains its lethality (ABBAS; LICHTMAN; PILLAI, 2019). Cancer treatment can be performed through radiotherapy, surgery, chemotherapy or bone marrow transplantation, and it is commonly necessary to combine more than one modality (INCA, 2021). Chemotherapy is the treatment of choice, alone or not, for most types of cancer (INCA, 2021) and consists of the use of drugs that spread through the blood, destroying the neoplastic cells that make up the tumor (INCA, 2021). However, this way, nanotechnology can minimize side effects, in addition to enhancing the beneficial effect of chemotherapy (SYKES, et al., 2016), since nanoparticles, due to their high biocompatibility with drugs, can carry them in large quantities and release them at specific times and places, given their ability to diffuse across cell membranes (ZHAO, et al., 2018). For this, this technology makes use of nanomaterials that can be designed with different shapes, sizes and surface chemistry, as well as being assembled into hierarchical nanosystems (SYKES, et al., 2016). In this sense, this review seeks to elucidate the benefits and obstacles of using nanotechnology in cancer treatment.

LITERATURE REVIEW

HISTORY OF NANOMEDICINE

Nanomedicine emerged from nanotechnology, a new technology that uses nanometric materials, in the 21st century (SARTORI, 2013) and consists of the introduction of microscopic materials manufactured with nanotubes into the bloodstream, through the manipulation of atoms and molecules with the aim of to perform various tasks, promoting the cure for numerous diseases. The first nanodrug approved for clinical use was Paclitaxel bound to albumin (Abraxane ®) created by Scheffel and colleagues in 1972 (KOPECKOVA, et. al., 2019). In medicine, nanomaterials are being widely used, from the manufacture of drugs, cosmetic products, to application in prostheses, however, the application of nanomedicine is a controversial issue, especially when seen in the light of environmental ethics. In Brazil, the government is increasingly investing in projects in the sector, including the inauguration of the Nanoscience and Nanotechnology Multiuser Laboratory (Labnano) in Rio de Janeiro, which aims to boost research in the area of nanostructured materials, with applications also in medical diagnostics (SARTORI, 2013).

CONVENTIONAL ONCOLOGIC THERAPY

The main types of cancer treatment involve surgery, radiotherapy, chemotherapy and bone marrow transplantation and, in most cases, it is necessary to combine two or more modalities of therapy (INCA, 2021).

CHEMOTHERAPY

Chemotherapy is the therapy of choice in the treatment of metastatic cancer (PÉREZ-HERRERO; FERNÁNDEZ-MEDARDE, 2015) and consists of the use of a series of drugs administered orally, intravenously, intramuscularly, subcutaneously, intrathecally or topically, with the aim of destroying cancer cells and preventing them from spreading. This treatment can be applied in an outpatient environment, when there is no need for hospitalization, or in a hospital environment, when there is a need for hospitalization (INCA, 2021).

Chemotherapy treatment has been widely used in the clinic due to its simplicity and convenience (ZHAO, et al., 2018). However, this therapy is nonspecific and ends up reaching, in addition to cancer cells, normal cells with rapid proliferation rates, such as bone marrow cells, hair follicles and gastrointestinal tract. Therefore, the occurrence of several side effects is common. (PÉREZ-HERRERO; FERNÁNDEZ-MEDARDE, 2015), such as: hair loss, constipation, diarrhea, mouth sores, nausea and vomiting, hyperpigmentation, anemia, leukopenia and thrombocytopenia (INCA, 2021).

RADIOTHERAPY

Radiotherapy treatment consists of the use of radiationionizing ions that aim to prevent the proliferation of cancer cells. (INCA, 2021). This type of treatment can cure many types of cancer, especially those located, and can even be used as a palliative treatment. In addition, when radiotherapy is combined with surgery or chemotherapy, an increase in cure rates is observed. (GALE, 2020).

However, radiotherapy, like chemotherapy, has its limitations. Malignant and normal cells are destroyed with irradiation and therefore it is always necessary to weigh the benefit of treating cancer cells and the risk of damage to normal tissue (INCA, 2021).

CANCER SURGERY

Oncological surgery consists of an operation whose intention is the total or partial removal of the tumor. In its initial stage, malignant neoplasm can be controlled or cured by this treatment, however, in more advanced stages of the disease, it can be performed as palliative treatment, aiming at reducing the number of tumor cells or relieving symptoms. There are several examples of palliative surgical treatments in oncology, which can be mentioned: control of hemorrhages and perforations, decompression of vital organs, pain control, diversion of air, digestive and urinary transits, among others. Surgical treatment is also performed as a way to assess the extent of the disease. (INCA, 2021).

However, surgery is an invasive treatment and can lead to complications that limit the patient's prognosis. Among the possible postoperative complications, the main ones are: infection, skin lesions, injuries to the surgical incision, musculoskeletal and vascular alterations, and cardiac and pulmonary complications. In addition, there are some complications that can be caused due to the use of anesthesia to perform the procedure, among them are hypoventilation, immobility and impairment of the central nervous system (SANTOS, et al., 2020).

BONE MARROW TRANSPLANT

The bone marrow consists of a liquid-gelatinous tissue, found inside the bones, responsible for the production of blood components. Therefore, treatment with bone marrow transplantation, which consists of replacing the affected bone marrow with healthy bone marrow cells, is indicated when the bone marrow is deficient, such as in patients with leukemia and lymphomas. Bone marrow transplantation can be autogenic, allogeneic and from bone marrow precursor cells. In autogenic transplantation, the transplanted bone marrow comes from the individual who will receive it, in allogeneic transplantation the bone marrow comes from a donor and in transplantation made from precursor cells it is done by obtaining these cells in the blood of a donor or the from umbilical cord blood.

However, this treatment is complementary to the previously mentioned conventional therapies (radiotherapy and chemotherapy) and presents risks, such as infections and rejection of the transplanted bone marrow (INCA, 2021).

NANOTECHNOLOGY

As explained in this review, current therapies for the treatment of cancer show results, but limitations and the existence of adverse effects support the need to find new, more targeted and effective therapies to fight cancer. In this sense, nanotechnology represents an additional therapy to combat this disease.

Currently, it is believed that cytotoxic drugs are targeted to different types of tumor by administering specific nanomedicines, which would increase efficacy and minimize the risk of side effects, however this approach provided insignificant improvements in patient survival and quality of life with cancer (MARTIN, et al., 2020).

Nanoparticles are designed for tumor-targeted therapies and usually consist of nanocarriers and an active agent, although nanoparticle formulations of the drug alone are also possible. The main advantages that nanocarriers have are: protection of the drug against degradation in the body, better absorption of the drug in the tumor tissue and alteration of the pharmacokinetics of drugs (ZHAO; ZHU, 2016).

Nanocarriers are promising carriers of cancer drugs. Nanocarriers are colloidal systems on a nanoscale, responsible for transporting low molecular weight drugs or anticancer macromolecules, such as the genes and proteins. In indirect approach situations, targeted therapies prevent healthy tissues from being reached by the medication and optimize its action on the tumor, thus achieving a cytotoxic concentration for it and reduced toxicity to normal tissues(PÉREZ-HERRERO; FERNÁNDEZ-MEDARDE, 2015). The composition of nanocarriers differs according to the material used, which can be phospholipids, lipids, dextran, chitosan or various synthetic polymers, carbon, silica or metals (KOPECKOVA, et. al., 2019), with liposome nanocarriers, chitosan, being most used, silicon nanoparticles, and polymeric nanoparticles (ZHAO; ZHU, 2016).

One type of nanocarrier constructed was thin film zinc oxide (ZnO) chips deposited on glass substrates. In research with raji cells, it was suggested that the ZnO chip could selectively induce apoptosis in cancer cells. ZnO nanoparticles increase the production of hydrogen peroxide, a reactive oxygen species (ROS) that causes oxidative stress, inducing apoptosis. In addition, zinc ions downregulate anti-apoptotic proteins (MOON, et. al., 2016).

One of the most frequent applications of nanomaterials in oncology is related to improving the performance of anticancer drugs in terms of bioavailability, safety, and specificity by taking advantage of the properties of nanoscale particles. Chemotherapeutic drugs can be carried on nanomaterials by physical entrapment, adsorption through non-covalent interactions or by covalent binding to the nanomaterial surface. The surface characteristics, adjustable size and shape of nanomaterials allow the production of nanomedicines with high stability, solubility and compatibility with biological fluids and allow their incorporation to hydrophilic and hydrophobic substances (BREGOLI, et al., 2015).

Nanoparticles could be used to enhance immunotherapy and to improve the induction of the abscopal effect by capturing tumor-derived protein antigens (TDPAs), promoting cancer immunity (MIN, et. al, 2017); however, the nanoparticle faces challenges: (1) tumor tissues have intact depth and three-dimensional structure, moreover, the vascularization is anomalous, making it difficult for the particles to penetrate deep into the tissues and restricting the ability to eradicate such cells; (2) another point is that there is a complexity in the large-scale production of nanoparticles, which makes the process impractical; (3) moreover, the materials used may cause long-term toxicity in vivo, requiring the introduction of non-toxic materials for the development of nanoparticles (ZHAO, et al., 2018). Arsenic trioxide (ATO), for example, is effective in treating hematological malignancies and solid tumors through mitochondrial targeting. However, its toxicity and side effects are severe, hindering its clinical application (WU, et. al., 2020).

The combination of cancer immunotherapies and nanomedicines is of intense interest, since many patients undergoing ongoing cancer treatment develop adverse events, such as, for example, the release of potentially fatal toxins, which can be reduced with the use of nanomedicines. However, one of the main causes of failure of nanodrugs and immunotherapies is the tumor microenvironment (TME), which limits the delivery of drugs and can compromise efficacy, even when agents accumulate in this space. Thus, it is important that nanomedicines incorporate not only anticancer drugs, but also agents capable of stabilizing the TME components and functioning, which will lead to better tumor perfusion and reduced levels of hypoxia. This normalization effect has the potential to facilitate drug and oxygen delivery to slow tumor progression and convert an immunosuppressed EMT into an immunostimulatory EMT (MARTIN, et al., 2020).

FINAL CONSIDERATIONS

In view of the analysis carried out on conventional oncological treatments, it is concluded that nanotechnology emerges as a promising alternative to optimize these therapies. By exploiting the advantages offered by nanotechnology, it is possible to improve the effectiveness of treatment, improve the prognosis and quality of life for patients. However, to enable and implement this therapy in health services, further studies and research are needed to ensure the safety, efficacy and greater cost-effectiveness of the treatment. Thus, nanotechnology can be considered an important ally in the fight against cancer, but it is essential that more efforts be made to improve the technique, in order to consolidate its clinical application.

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