Rev. Saúde Mult. 2023 mar, 14(1): 199-206

NANOPARTICLES USAGE IN THE TREATMENT OF CANCER

Uso de nanopartículas no tratamento do câncer

Rafaella Alves Ribeiro de Oliveira[1], Alex de Oliveira Martins[1], Danielle Pereira Silva[1*]

ABSTRACT
Nanotechnology is an emerging scientific field that allows manipulation of the environment at the atomic and molecular level. The term cancer is given to a group of diseases whose main characteristic is the rapid multiplication of abnormal cells. Conventional treatments used for cancer are based mainly on the use of chemotherapy, radiotherapy, and surgeries, nonspecific treatments concerning target cells, because antineoplastic drugs can reach normal cells, especially those that have constant renewal, causing adverse reactions. Nanomedicine, when focused on cancer treatment, offers patients an alternative and less invasive form of treatment. Its mechanism is done utilizing drug nanocarriers, which offer flexibility in dosage and release kinetics. Even with several articles demonstrating the potential advantages of nanoparticles over diseases, this technique encounters several clinical challenges concerning their development. Thus, the combination of advances in nanotechnology and biomaterial development becomes the most promising hope for the survival of cancer patients. This study aimed to explain briefly the factors related to cancer by focusing on the applications of nanoparticles in the treatment and diagnosis of the same. It is also important to highlight that this study will describe its benefits compared to conventional pharmacotherapy.

Keywords: Basic sanitation. Health. Pandemic. Low-income population;

1. Department of Biofunctional Sciences, Morgana Potrich College, Mineiros, Brazil
*Autor para Correspondência. E-mail: danidielle@live.com

INTRODUÇÃO

Nanotechnology is a developing scientific field that carries with itself the promise of allowing the manipulation of the environment at the atomic and molecular level. When focused on the medical area, especially in the treatment of cancer, nanomedicine, it is important to reduce social expenses because it allows cancer to be detected early, with high probabilities of cure through therapeutic methods that use nanocarriers at specific points, which minimizes side effects and adverse reactions when compared to conventional treatments that have high chances of tumor growth return with severe adverse reactions and devastating for the lives of patients [1].

Cancer is defined as a general term for a group that reaches more than one hundred diseases. Its main characteristic is the rapid multiplication of abnormal cells. These cells tend to be aggressive and uncontrolled, which can lead to the invasion of parts close to the affected organ and disperse to other organs. This process is known as metastasis [2].

The difficulty in diagnosing cancer early is the most significant circumstance about its complications since the cells with some alteration are only observed in the blood from the moment they are in high concentration. Early diagnosis and efficient treatment are essential for lives to be saved [3].

Every year 7.6 million people worldwide die from cancer. The National Institute of CANCER (INCA) estimates that by 2025 the forecast is 6 million deaths from the disease, in which 1.5 million deaths per year can be prevented with the necessary measures and appropriate treatments [4].

Among the forms of conventional antineoplastic treatments, we have chemotherapy and radiotherapy that are the most used. They are known to cause side effects in patients such as fatigue, hair loss, nausea, infections, bruising, bleeding, diarrhea, food aversion.

The intensity of side effects can vary according to the individual, which may imply the quality of life and causing patients not only physical but also psychological and social disorders [5].

In addition to the negative factors that patients present in conventional therapy, such as lack of specificity and toxicity in the body, affect healthy cells of the body, increasing their problem's use. But the use of nanoparticles enables targeted therapy, accurately reaching only tumor cells, enabling a faster form of diagnosis, resulting in a less aggressive treatment at the physical and emotional levels [6,7].

Nanomedicine is one of the most promising branches of current science when focused on cancer. It offers patients an alternative and less invasive form of treatment. Its mechanism is done through drug nanocarriers, which offer flexibility in dosage and release kinetics. Therefore, it considerably decreases aggression to normal cells and tissues that are not sick, which increases treatment efficacy [8].

This study aims to briefly explain the factors related to cancer by focusing on the applications of nanoparticles in the treatment and diagnosis of it, as well as to describe its benefits compared to conventional pharmacotherapy.

General aspects of the Genetic and Molecular Bases of Cancer

Studies on molecular cytogenetics enable the training of an in-depth approach on the karyotypes of cancer variants, amplifying convincing data on the malignant disease's progression, involving multiple genetic factors. The analysis technique developed to describe tumor characteristics is based on the gene's detection rearrangements and changes in sequential DNA copies [9].

Amplification of oncogenes or removal of tumor suppressor genes occurs involving cellular mutations, in which six biological characteristics for tumor progression in humans describe this process. They include the support of proliferative cells through proto-oncogenes, evasion of growth suppressors undergoing mutations becoming oncogenesis. Thus genetic sequences can develop carcinogenesis, producing defective proteins called oncoproteins, which causes resistance to cell death, allowing replicative immortality, inducing angiogenesis, and activating invasion and metastasis [10,11].

Pro-oncogenes can be converted into oncogenes not only by substitution of amino acids but by macroscopic chromosomal changes. One of the tumor-specific genes is MYCN (N-myc) susceptible to amplification in cancer cells, in which it encodes the transcription factor that plays a physiological role in stimulating cell proliferation, usually increased in cases of neuroblastoma in children [12].

Cancer-causing genes, or oncogenes, encode proteins directly involved in cell replication, including growth factor receptors (platelet-derived growth factor receptor, PDGR)) or the epidermal growth factor receptor (EGFR, from the epidermal growth factor receptor). It is believed that chemotherapy treatment for patients with these mutations does not allow the desired therapeutic effect, requiring an inhibitory treatment with a specific target [12].

Tumor biomarkers are used to identify the target. These biomarkers are substances found in the tumor and biological fluids. When found these substances, they are associated with the growth of neoplastic cells, which can be an indication of the existence of tumors. They can be formed by the organism or by the tumor cells themselves. The

usefulness of it occurs in the clinical diagnosis of the patients. It contributes to the development's evaluation of the therapeutic response. It also contributes to the recurrences' identification, prognosis, and creating new forms of treatment. The quantification can be done through immunohistochemical means in the tissues or biochemicals in the blood and genetic tests [13].

These biomarkers can be of several types of molecules, divided into oncofetal antigens, enzymes, and isoenzymes, hormones, genetic markers, glycoproteins, and mucins. The oncofetal antigens are differentiation antigens (Alfafetoproteína - AFP and Carcinoembrionário Antigen - CEA) that are expressed by tumor cells, and are found during the development of the fetus.

However, they are not demonstrated during adult life. Enzymatic tumor biomarkers are an extremely important tool for the differential diagnosis of tumors since their increased increase is directly related to a tumor. The tumor produces enzymes that accumulate inside organelles also inside the cell.

After possible tumor necrosis or alteration in the cell's permeability, these enzymes are released into the bloodstream. Isoenzymes are becoming excellent candidates for enzyme markers, as it is believed that they may represent products in which synthesis occurs due to a recent activation of the malignancy and cell transformation genes. Some hormones, depending on the dosage, can be used to detect and monitor certain tumors. Its involvement as a tumor marker can happen in two different ways: due to high production by endocrine tissue or by ectopic production and by some tissue where it normally does not have the function of producing hormones.

The adrenocorticotropic hormone (ACTH) is an example of these two forms because it is found in pituitary tumors and small cell lung tumors. Among the genetic markers, the main ones are the suppressor genes, the oncogenes, and the protein products of the oncogenes. These biomarkers have great diagnostic potential since it is already known that, for a normal cell to become neoplastic, it may be necessary that several genetic modifications happen.

Thus, the possible chance of identifying these modifications can become a mechanism for establishing the risk of cancer early. Glycoproteins and mucins are proteins with high molecular weight and rich in carbohydrates, being located on the surface of neoplastic cells, being CA 125, CA 15-3, and CA 19-9. These biomarkers demonstrate greater specificity and sensitivity when compared to oncofetal antigens [14].

Even with the advances that have occurred in recent decades, there is no distinction in the patients' treatment who have the disease in situ for patients who have advanced disease, where the probable heterogeneities that exist between patients and the biology of neoplasms are disregarded. Bearing this in mind, the identification of tumors capable of behaving even more aggressively, leading to early metastases, frequent resurgence, and those that may need different therapeutic interventions becomes of paramount importance [15].

Conventional treatments available

The conventional treatment used for cancer is based on using three different treatments: chemotherapy, radiation therapy, and surgery. Although these methods are the most used, the diagnosis and prognosis are insufficient due to their nonspecific biodistribution. Pathology also causes physical waste. The process of adherence to conventional treatment causes psychological and social disorders. The most common are nausea, vomiting, hair loss, oral ulcers, amputation, sterility, and brain damage, in addition to some procedures being invasive and painful. Current treatments are limited, there is a deficit in the speed of diagnosis and low survival rates [16-19].

When using chemotherapy as a treatment, it is administered a combination of cytotoxic drugs to act in different phases of cell division, eliminating the cells that demonstrate some functional change in their growth process. Because it is a type of treatment that is not specific to the target cells, antineoplastic drugs are capable of reaching normal cells, especially those that have constant renewal, causing adverse reactions [20]

Chemotherapy aims to promote the eradication or control of micrometastases, which increases the patient's survival against the disease. For this reason, chemotherapy is performed at intervals defined by cycles, reducing the damage of healthy cells during treatment [21].

Radiotherapy consists of emitting local ionizing radiation in neoplastic cells and healthy cells of soft and hard tissues, generating changes in its DNA, causing the cell’s apoptosis, and consequently causing collateral damage. This treatment is more effective in cases of head and neck cancer, but it can have many side effects such as dry mouth sensation, inflammation of oral tissues, ischemic bone necrosis, radiation decay, among others [22,23]. Radiotherapy is also widely used in cases of cancer in the pelvic region and, although it has a potent effect, this form of treatment creates strong side effects, generating sequelae to the pelvic floor, which leads to a series of disorders related to the genital and urinary systems [24].

Oncological surgery is a procedure that consists of extracting the tumor through operations on the patient's body,

being a common process that aims to remove the largest portion of the tumor with a safety margin. With this in mind, the nutritional status of the patient before and after the surgery and the organic response to operative trauma is of paramount importance, as these factors can determine the loss of skeletal muscle function and postoperative functional capacity (INCA, This loss in the nutritional part of the patient, due to the operation, directly affects the muscle fibers, which can cause a gradual loss of mass, reduced strength, and as a result, the loss of muscle function.

All of this impairs the patient's ability to practice daily activities, directly impacting the quality of life and early mobility in the postoperative period, increasing the risk of complications [25,26].

Use of Nanoparticles (PN) in the treatment of cancer

The need to use new technology with specific targeting in target cells was first presented in December 1959 during a lecture to the American Physics Society (APS) by physicist Richard Feynman with the concept nanotechnology, the term was only used approved in 1974 by the Tokyo Scientific University, and its development in laboratory tests only started in the year 2000 [27,28].

The study of nanotechnology-enabled the development of nanoparticles (NPs) that are structured with dimensions from 1 to 100mm, in which their size is much smaller compared to normal cells in the body. Its application in health demonstrates a technique of interaction with the immune system, stimulating communication with various biological components (cells, receptors, proteins, etc.), allowing a quick and accurate diagnosis, in addition to an effective treatment for a wide range of diseases [29].

Benign tumor tissues have little permeability due to an outer layer composed of collagen fibers wrapped around the tumor, showing compartments that are quite vascularized around their morphology, in which two distinct forms are presented: “rare” cancer stem cells and another population larger number of normal cells. However, the vascularization of malignant tumors contains flow rates greater than normal cells, causing a high concentration of macromolecules and possible toxicity since the tumors have little lymphatic clearance to excrete the drug [16].

With the arrival of NPs in the pharmaceutical market, it was possible to count on drugs capable of specifically targeting organs affected by the disease, showing excellent results in therapeutic efficacy. When using both together with conventional treatments to decrease toxicity in normal tissues and increase their spectrum of action involving targeted delivery.

This process occurs due to the stimulation of the immune cells from the body, in which NPs are directed to innate immunity, intentionally modulating this system, controlling its specific function, its molecular structure (size, charge, shape, hydrophobicity, and rigidity), in addition to helping in the interaction with pathogens, reducing side effects and enhancing therapeutic results, in addition to promoting the recognition only of cancer cells and facilitating their elimination [30-33].

Some scientific data point out advantages in the therapeutic and diagnostic functions in the treatment of neoplastic cells using NPs, in which the diagnosis includes the early identification of tumor markers and the stages of cancer, previously not efficiently detected by conventional imaging techniques, in addition to treatment intended for the use of nanoparticles as carriers of cytotoxic drugs, to infiltrate defense cells in a tumor microenvironment, causing pro-inflammation making it more sensitive for combat [34].

However, even with several articles demonstrating the potential advantages of PN over diseases, this technique encounters several clinical challenges about its development. Only a few types of NPs have been approved for clinical use. The complexity and physical-chemical characteristics require careful and rigorous research regarding the nanopharmaceuticals.

The challenges in laboratory tests involving a nanostructure are specific when compared to conventional drugs. The nanopharmaceuticals must cross multiple biological barriers and not degrade, maintaining high systemic bioavailability in their nanoformulation [35].

Chemotherapy treatment destroys most cancer cells in a short time. However, cells called metastatic continue to generate new cells and reconstitute the tumor. NPs use methods capable of reaching micrometastasis, preventing tumor recurrence, in which the passive method has the Permeability and Retention Effect (RPE), to increase the concentration of nanopharmaceuticals in the neoplasia and the action has a selective recognition helping the destruction of cancer cells [36].

In 2018, the Massachusetts Institute of Technology proved through research that treatment with NPs could choose tumors and prevent them from recurring. With their low molecular weight, NPs encompass their functionality, absorbing or transporting DNA, RNA, proteins, and probes molecules,in addition to having a high carrier capacity to incorporate hydrophilic and hydrophobic substances, they help in the compatibility of different administration routes. With this, the NPs were adapted to treat brain tumors, and they have obtained significant results, crossed the blood-

brain barrier, and went to the tumor to start the degradation process [37].

With the high complexity involving laboratory studies of nano-oncology, computational applications called nanoinformatics have been developed. This research area has enabled the development of algorithms that anticipate the results on cell uptake, toxicity, properties of enzymatic activities, absorption, metabolism, and excretion of NPs, overcoming barriers in vitro [28].

Regarding research areas, technological advances are increasingly adhered to by modern society, in which the combined techniques of in vitro tests and nanoinformatics enable the anticipation of results, demonstrating whether they are reliable and of quality. The algorithms evaluate the adverse effects of possible treatments and prevent scenarios of errors, and this method's use can be applied in several areas of science, not only in oncology [38].

Types of nanoparticles

Based on some physical-chemical characteristics and targeted study platforms, we can divide the nanoparticles into basically two groups: naturally-derived nanoparticles and synthetic nanoparticles. These groups have subgroups with the following specific characteristics: natural accidents such as volcanic eruptions and forest fires are included in natural NPs, while synthetic nanoparticles are derived from gas dispersion (aerosols), diesel combustion, among others [31].

However, some authors specify NPs as inorganic and polymeric, they consist of several forms with multiple functions, and some stand out due to their greater clinical use, they are lipid NPs (solid or liposomes), nanoemulsions, dentin NPs, polymeric micelles, NPs magnetic, gold NPs, and carbon nanotubes and fullerenes [39,40].

Lipid nanoparticles have liposomes. Liposomes are composed of a phospholipid bilayer, they have a spherical shape, and stand out for their ability to act as a transporter for hydrophilic and hydrophobic drugs covering a wide variety of chemo drugs and having low toxic susceptibility. Besides, lipidic NPs are included, the solid form, which are new specific structures for solid tumors, differing from liposomes only by the structural characteristic, they are more fluid and lipids having greater rigidity [41].

The nanoemulsion is a capsule that does not have a polymeric coating, but rather a stable, amorphous, transparent, and translucent surface, which can be dispersed in water, oil, or both at the same time, has a size of 20 to 500 mm, one of its advantages is to present improved physical stability [42].

The trimer's nanoparticles are complex, very organized macromolecules, known as cascade molecules, are branched like branches of trees, and the drug is fixed between the spaces of the branches. It is binding to molecules that occur easier, due to its high specificity for a large number of functional groups on its surface [43].

Polymeric micelles contain a simple structure called amphipathic because they have a nonpolar and a polar layer; it allows controlling the drug's distribution and increases its permeability, resulting in more direct contact with the site of action of neoplastic cells [7].

Other types of NPs are the magnetic ones, administered intravenously, acting as drug carriers, and being used through the magneto-hyperthermia technique. Hyperthermia is a process of magnetic healing in the fight against cancer, in which a specific region of the body is exposed to high temperatures to eliminate tumor cells. Magnetic NPs are used to enhance the therapeutic reach of hyperthermia in the body's deepest tissues, surpassing biological barriers, for example, plasma and blood-brain membranes. Besides, they can also be directed to any part of the body through an external magnetic field, usable as contrast agents in magnetic resonance [44,45].

Gold nanoparticles are coated with a biocompatible material, which prevents their aggregation. They are most used in diagnosis because they can reflect a large amount of radiation identifying cancer cells; size less than 100 nm; carry drugs across the cell membrane, and can be used in conjunction with radiotherapy in the heating process. In this context, the application of gold NPs commonly to the radiotherapy's heating induces cell suicide in the tumor region since the tumor cells have less heat resistance than the normal ones [46].

Other important nanoparticles are carbon nanotubes and fullerenes. They are cylindrical carbon compounds such as diamond or graphite they have a great temperature and electricity transport capacity, they also have extraordinary mechanical properties, being very resistant and can be used in several fields of science [7]

CONCLUSION

Nanotechnology is a field of science in continuous development that encompasses several areas of knowledge.

Several types of nanoparticles are being created aimed at the treatment and diagnosis of cancer. The characteristics that comprise the organization and chemical composition of these nanoparticles made them become an instrument of paramount importance in inducing the cancer cells' death, minimizing these effects, and the adverse reactions caused by molecular specificity, which can be

found in most chemotherapeutic agents and antineoplastic agents used in anticancer therapies. Another important characteristic is the material used in its manufacture, which, depending on the chosen one, can cause the nanoparticles to behave in different ways in the human body, changing cytotoxicity and specificity.

With this in mind, the development and use of functional nanoparticles containing molecules that allow cell recognition and biomarkers, in addition to allowing the diagnosis and location of cancer cells to occur early, also contributes to improving the orientation of the active principle in cancer, which enhances the effectiveness of the suggested treatment, due to the characteristic pharmacokinetic properties such as a long time of the agent within the blood circulation, the volume of distribution, absorption, and half-life.

Even after a lot has been discovered about pharmacokinetics and nanoparticles' pharmacodynamics, it is still necessary to carry out many studies aimed at limitations such as nonspecific phagocytosis and protein absorption on the cell surface. Thus, the hope for cancer patients' survival became more promising after the combination of the advances in nanotechnology and the development of biomaterials.

REFERÊNCIAS

1. Keskinbora KH, Jameel MA (2018) Nanotechnology Applications and Approaches in Medicine: A Review. J. of Nanoscience & Nanotechnol. Res., v. 2, n. 2, p. 1-5. Disponível em: <http://www.imedpub.com/articles/nanotechnology-applications-and-approaches-in-medicine-short-review.php?aid=23517> Acesso em 17 de novembro de 2020.

2. INSTITUTO NACIONAL DO CANCER (INCA) (2020). Câncer. O que é câncer? Disponível em: <http://www1.inca.gov.br/conteudo_view.asp?id=322>. Acesso em 17 de novembro de 2020

3. Santos ASE, Martins AAF, Lima JS, Meye A (2016) Mortalidade por câncer entre pintores brasileiros das regiões Sul e Sudeste do Brasil. Cad. de Saúde Colet. 24(4): 413-419. Disponível em: <https://www.scielo.br/scielo.php?pid=S1414-462X2016000400413&script=sci_arttext> Acesso em 17 de novembro de 2020.

4. INSTITUTO NACIONAL DE CÂNCER (INCA) (2020). Estimativa 2020: incidência de câncer no Brasil. – Rio de Janeiro, p.120. Disponível em: <https://www.inca.gov.br/sites/ufu.sti.inca.local/files/media/document/estimativa-2020-incidencia-de-cancer-no-brasil.pdf > Acesso em 17 de novembro de 2020.

5. Wakiuchi J, Marcon SS, Oliveira DC, Sales CA (2019) A quimioterapia sob a ótica da pessoa com câncer: uma análise estrutural. Texto & Contexto-Enfermagem, v. 28. Disponível em: <https://www.scielo.br/scielo.php?pid=S0104-07072019000100329&script=sci_arttext&tlng=pt> Acesso em 17 de novembro de 2020.

6. Parreira DB, Eugénio J (2011) Nanopartículas para aplicação oncológica. Inst. Nacional da Prop. Ind. Disponível em: <https://inpi.justica.gov.pt/Portals/6/PDF%20INPI/Nano%20inova%C3%A7%C3%B5es/Nanoparti%CC%81culas%20para%20aplicac%CC%A7a%CC%83o%20oncolo%CC%81gica.pdf?ver=2017-08-28-152143-250> Acesso em 17 de novembro de 2020.

7. Safari J, Zarnegar Z (2014) Advanced drug delivery systems: Nanotechnology of health design A review. J. of Saudi Chemical Society, v. 18, n. 2, p. 85-99, abr. Disponível em: <https://www.sciencedirect.com/science/article/pii/S1319610312001986> Acesso em 17 de novembro de 2020.

8. Vieira DB, Gamarra LF (2016) Avanços na utilização de nanocarreadores no tratamento e no diagnóstico de câncer. J. Einstein (São Paulo), v. 14, n. 1, p. 99-103, mar. Disponível em: <https://www.scielo.br/scielo.php?pid=S1679-45082016000100099&script=sci_arttext&tlng=pt> Acesso em 17 de novembro de 2020.

9. Palumbo E, Russo A (2016) Chromosome imbalances in cancer: molecular cytogenetics meets genomics. Cytogenetic and Genome Res., v. 150, n. 3-4, p. 176-184. Disponível em: <https://www.karger.com/Article/Abstract/455804> Acesso em 17 de novembro de 2020.

10. Rashid S (2017) Hallmarks of Cancer Cell. In: Cancer and Chemoprevention: An Overview. Springer, Singapore. p. 3-13. Disponível em: <https://link.springer.com/content/pdf/10.1007/978-981-10-2579-2.pdf> Acesso em 17 de novembro de 2020.

11. Souza AE, Jordão AM, Saruhashi IT, Fritsch J, Ribeiro RT (2019) USO DE MARCADORES GENÉTICOS C-MYC, N-MYC, PROTEÍNA P-53, PROTEÍNA K-RAS E GENE HER-2 NEU PARA DIAGNÓSTICO DE TUMORES. Saúde e Desenvolv., v. 11, n. 6. Disponível em: <https://www.uninter.com/cadernosuninter/index.php/saude-e-desenvolvimento/article/view/1024> Acesso em 17 de novembro de 2020.

12. Ellisen LW (2015) Molecular genetics of cancer. ACP Medicine. Disponível em: <http://www.medicinanet.com.br/conteudos/acp-medicine/6631/genetica_molecular_do_cancer.htm> Acesso em 22 de novembro de 2020.

13. Poznak CV et al (2015) Use of biomarkers to guide decisions on systemic therapy for women with metastatic breast cancer: American Society of Clinical Oncology clinical practice guideline. J. Clin. Oncol.; 33: 2.695-2.704.4 Disponível em: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5478102/> Acesso em: 22 de novembro de 2020.

14. Araújo JHG (2014) Principais marcadores tumorais utilizados na prática clínica: uma revisão bibliográfica. Disponível em: <https://repositorio.ufpb.br/jspui/handle/123456789/566> Acesso em 18 de novembro de 2020.

15. Machado LFA (2017) Pesquisa de biomarcadores como fator prognóstico nos tumores da família do sarcoma de Ewing. Tese de Doutorado. Universidade de São Paulo. Disponível em: <https://www.iothcfmusp.com.br/wp-

content/uploads/2018/05/Tese_doutorado-LUCAS-MACHADO.pdf> Acesso em 18 de novembro de 2020.

16. Thakor AS, Gambhir SS (2013) Nanooncology: the future of cancer diagnosis and therapy. CA: a cancer j. for clinicians, v. 63, n. 6, p. 395-418, out. 2013. Disponível em: <https://acsjournals.onlinelibrary.wiley.com/doi/abs/10.3322/caac.21199> Acesso em 17 de novembro de 2020.

17. Singh P, Pandit S, Mokkapati VRSS, Garg A, Ravikumar V, Mijakovic I (2018) Gold nanoparticles in diagnostics and therapeutics for human cancer. International j. of molecular sciences, v. 19, n. 7, p. 1979, jun. Disponível em: <https://www.mdpi.com/1422-0067/19/7/1979> Acesso em 17 de novembro de 2020.

18. Almico T, Faro A (2014) Enfrentamento de cuidadores de crianças com câncer em processo de quimioterapia. Psicol., saúde & doenças, v. 15, n. 3, p. 723-737. Disponível em:<http://www.scielo.mec.pt/scielo.php?pid=S164500862014000300013&script=sci_arttext&tlng=en> Acesso em 22 de novembro de 2020.

19. Souza LC, Oliveira BLG (2017) Fatores psicológicos envolvidos no câncer infantil. Rev. Uningá, v. 51, n. 2. Disponível em: <http://revista.uninga.br/index.php/uninga/article/view/1344> Acesso em 19 de novembro de 2020.

20. David A, Windlin I, Gaspar KC (2013) O paciente oncológico e a terapêutica quimioterápica: uma contribuição da psicologia. Psicol. e Câncer. São Paulo: Casa do Psicólogo. Disponível em: <https://scielosp.org/article/icse/2017.v21n63/969-980/> Acesso em 17 de novembro de 2020.

21. Bonassa EMA (2012) Enfermagem em Terapêutica Oncológica. 4ª ed. São Paulo (SP): Editora Atheneu. Disponível em: <https://periodicos.ufpe.br/revistas/revistaenfermagem/article/download/10193/10751> Acesso em 17 de novembro de 2020.

22. Martínez AB, Corcuera MM, Font RF (2013) Efectos secundarios bucalesde la radioterapia y quimioterapia em el cáncer en la región cervicofacial. Rev.Med Clin (Barc);141:77-81. Disponível em: <https://scholar.google.com/scholar_url?url=https://medes.com/publication/82450&hl=ptBR&sa=T&oi=gsb&ct=res&cd=0&d=7135157934089884563&ei=N5e0X9CONYPumgGovrYo&scisig=AAGBfm2fPQYcGTgCGrLi44zByVaazQ0_Sw> Acesso em 17 de novembro de 2020.

23. Millsop JW, Wang EA, Fazel N (2017) Etiology, evaluation, and management of xerostomia. Clinics in Dermatology, v. 35, n. 5, p. 468-476. Disponível em: < https://scholar.google.com/scholar_url?url=https://www.sciencedirect.com/science/article/pii/S0738081X17301062&hl=pt-BR&sa=T&oi=gsb&ct=res&cd=0&d=5915997015540496533&ei=cJS0X5W_IIydmwGTqJf4Cw&scisig=AAGBfm2hbfeaOe7qI8DM573ct-uUu4EOaQ> Acesso em 17 de novembro de 2020.

24. Correia RA, Bonfim CVD, Ferreira DKDS, Furtado BMASM, Costa HVVD, Feitosa KMA, Santos SLD (2018). Quality of life after treatment for cervical cancer. Esc. Anna Nery, 22(4). Disponível em: <https://scholar.google.com/scholar_url?url=https://www.scielo.br/scielo.php%3Fpid%3DS1414-81452018000400225%26script%3Dsci_arttext&hl=pt-BR&sa=T&oi=gsb-ggp&ct=res&cd=0&d=7472142694287464028&ei=DJi0X_y2LqWGy9YPjqSC2Ak&scisig=AAGBfm22g5mCboxvoO6BqV9bvxABF77aIA> Acesso em 17 de novembro de 2020.

25. Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley J (2016) SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. J Cachexia Sarcopenia Muscle. 7(1):28-36. Disponível em: <https://onlinelibrary.wiley.com/doi/abs/10.1002/jcsm.12048> Acesso em 18 de novembro de 2020.

26. Beaudart C et al (2017) Validation of the SarQoL(R), a specific health-related quality of life questionnaire for Sarcopenia. J Cachexia Sarcopenia Muscle. 8(2):238-44 Disponível em: <https://onlinelibrary.wiley.com/doi/abs/10.1002/jcsm.12149> Acesso em 18 de novembro de 2020.

27. Jeevanandam J, Barhoum A, Chan YS, Dufrense A, Danquah MK (2018) Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. Beilstein j. of nanotechnol., v. 9, n. 1, p. 1050-1074, abr. Disponível em: <https://www.beilstein-journals.org/bjnano/content/pdf/2190-4286-9-98.pdf> Acesso em 17 de novembro de 2020.

28. Bayda S, Adell M, Tuccinardi T, Cordani M, RizzolioF (2020) The History of Nanoscience and Nanotechnology: From Chemical–Physical Applications to Nanomedicine. Molecules. Itália, v. 25, n. 1, p. 112, jan. 2020. Disponível em: <https://www.mdpi.com/1420-3049/25/1/112> Acesso em 17 de novembro de 2020.

29. Larrañeta E, Mccrudden MT, Courtenay AJ, Donnelly RF (2016) Microneedles: A New Frontier in Nanomedicine Delivery. Pharmaceutical res., v.33(5), p. 1055–1073, fev. Disponível em: <https://link.springer.com/content/pdf/10.1007/s11095-016-1885-5.pdf> Acesso em 17 de novembro de 2020.

30. Sbalqueiro G, Balvedi L, Bettiato R, Ribas J (2018) Uso da nanotecnologia para o desenvolvimento de fármacos. Rev. Saúde e Desenvolv., v. 12, n. 10, p. 242-252. Disponível em: <https://www.uninter.com/revistasaude/index.php/saudeDesenvolvimento/article/view/881> Acesso em 17 de novembro de 2020.

31. Yang Z, Ma Y, Zhao H, Yuan Y, Kim BY (2019) Nanotechnology platforms for cancer immunotherapy. Interdisciplinary Reviews: Nanomed. and Nanobiotechnology, v. 12, p. e1590, nov. Disponível em: <https://onlinelibrary.wiley.com/doi/abs/10.1002/wnan.1590> Acesso em 17 de novembro de 2020.

32. Liu Y, Hardie J, Zhang X, Rotello VM (2017) “Effects of engineered nanoparticles on the innate immune system.” Seminars in immunology, vol. 34, p. 25-32, dez. Disponível em: <https://www.sciencedirect.com/science/article/pii/S1044532317300040> Acesso em 17 de novembro de 2020.

33. Surendran SP, Ju LM, Park R, Jeong YY (2018) Bioactive nanoparticles for cancer immunotherapy. International j. of molecular sciences, v. 19, n. 12, p. 3877, nov. Disponível em: <https://www.mdpi.com/1422-0067/19/12/3877/htm> Acesso em 17 de novembro de 2020.

34. Costa AM, Silva VV (2017) Estratégias nanotecnológicas para diagnóstico e tratamento do câncer. Ver. Saúde e Meio Ambiente. Três Lagoas, v. 5, n. 2, p. 1-13, set. Disponível em: <https://core.ac.uk/download/pdf/235433129.pdf> Acesso em 17 de novembro de 2020.

35. Wu LP, Wang D, LI Z (2020) Grand challenges in nanomedicine. Materials Science and Engineering: C, v. 106, p. 110302, jan. Disponível em: <https://www.sciencedirect.com/science/article/pii/S092849311832577 3> Acesso em 17 de novembro de 2020.

36. Gmeimer WH, Ghash S (2013) Nanotechnology for câncer treatment. Nanotechnol. reviews. SN, v.3, n.2, p.111-122, ago. Disponível em: <https://www.degruyter.com/view/journals/ntrev/3/2/article-p111.xml> Acesso em 17 de novembro de 2020.

37. MIT, Escritório de Notícias do MIT. Instituto de Tecnologia de Massachusetts , 2018.

38. Quesada D (2017). Nano-informática y modelaciones para divulgar las nano-ciencias. Momento. Colombina, 54E, p. 28-37, mai. Disponível em: <https://revistas.unal.edu.co/index.php/momento/article/view/63268> Acesso em 17 de novembro de 2020.

39. Santos SG (2017) Relatórios de estágio e monografia intitulada" Nanoemulsões de aplicação no tratamento do cancro".Tese de Doutorado. Universidade de Coimbra. Disponível em: <https://estudogeral.sib.uc.pt/handle/10316/83666> Acesso em 17 de novembro de 2020.

40. Tinkle S (2014) Nanomedicines: addressing the scientific and regulatory gap. Annals of the New York Academy of Sciences, v. 1313, n. 1, p. 35-56, jan. Disponível em:<https://www.researchgate.net/profile/Raj_Bawa2/publication/261182396_Nanomedicines_Addressing_the_scientific_and_regulatory_gap/links/5be9e2e14585150b2bb23937/Nanomedicines-Addressing-the-scientific-and-regulatory-gap.pdf> Acesso em 17 de novembro de 2020.

41. Oliveira LC, Taveira EJF, Souza LG, Marreto RN, Lima EM, Taveira SF (2012) Aplicações das nanopartículas lipídicas no tratamento de tumores sólidos: Revisão de literatura. Brasil, v.1, p.1-7, mai. Disponível em: <https://rbc.inca.gov.br/revista/index.php/revista/article/view/581> Acesso em 17 de novembro de 2020.

42. Jaiswal M, Dudhe R, Sharma PK (2015) Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech, n. 5,2, p. 123-127. Disponível em: <https://link.springer.com/article/10.1007/s13205-014-0214-0> Acesso em 17 de novembro de 2020.

43. Caban S, Aytekin E, Sahin A, Capan Y (2014) Nanosystems for drug delivery. OA Drug Des. & Delivery. n. 2,1, p.1-7. Disponível em: <http://www.oapublishinglondon.com/abstract/1191#> Acesso em 17 de novembro de 2020.

44. Perecin CJ, Yoshioka AM, Oliveira AM, Chitta VA, Cerize NNP (2014) Nanopartículas superparamagnéticas encapsuladas com polímeros para aplicação no tratamento de câncer por hipertermia. In: XXIV, Congresso Brasiliero de Engenharia Biomédica, CBEB. São Paulo, v.1, p. 2703-2706, jan. Disponível em: <https://www.canal6.com.br/cbeb/2014/artigos/cbeb2014_submission_792.pdf> Acesso em 17 de novembro de 2020.

45. Winter A, Engels S, Goos P, Süykers MC, Gudenkauf S, Henke RP, Wawroschek (2020) Accuracy of Magnetometer-Guided Sentinel Lymphadenectomy after Intraprostatic Injection of Superparamagnetic Iron Oxide Nanoparticles in Prostate Cancer: The SentiMag Pro II Study. Cancers, v. 12, n. 1, p. 32, fev. Disponível em: <https://www.mdpi.com/2072-6694/12/1/32> Acesso em 17 de novembro de 2020.

46. Lucero P (2017) Evaluación de una terapia enzimática antitumoral en diferentes modelos celulares quimioresistentes. Disponível em: <http://193.147.134.18/bitstream/11000/3451/1/Lucero%20Calabuig%2C%20Paola%20TFGBiotec%202014-15.pdf> Acesso em 17 de novembro de 2020.