Nano Oncology: Overview of nanotechnology in cancer therapy

*Sofiya Bano[1], Archana Kispotta[2], Rukhmani Rai[3], Smithy Philip[4]
Department of Nanotechnology, Christian College of Engineering and Technology, Kailash Nagar, Bhilai-490026, Chhattisgarh, India
** [1]sofikgn786@gmail.com, [2]archanakispotta710@gmail.com, [3]rukhmanir1@gmail.com, [4]smithygphilip@gmail.com*

Abstract

Cancer is a highly complex disease as it entails multiple cellular physiological systems. The most common cancer treatments are chemotherapy, radiation, and surgery. The current challenges seen in cancer therapies today include lack of early disease detection, non-specific systemic distribution, inadequate drug concentrations reaching the tumour, and inability to monitor therapeutic responses. The traditional treatments possess serious side effects including damage of the immune system and other organs, lack of solubility, and inability to enter the core of the tumours which results in impaired treatment with reduced dose and also low survival rate.

Nanotechnology is one of the fastest growing fields in modern days and is having wide applications in medicine. The advantage of nanotechnology in cancer imaging and treatment is that it can be used for site-specific action without causing side effects. Nanotechnology is being applied to cancer treatment in two broad aspects: firstly the development of nanoparticles that carries drugs or imaging agents and then targeted to tumours and secondly the high throughput nanosensor devices for detecting the biological signatures of cancer. Cancer nanotechnology includes imaging, diagnostic, drug delivery and antimicrobial techniques. This review summarizes the report of the most innovative technologies in recent years and current status of nanotechnology in cancer therapy.

***Keywords**: nanotechnology, nanoparticles, cancer, drug-delivery, cancer therapy.*

1. Introduction

Nanotechnology refers to structures with a size range of 1-100 nm in at least one dimension. Advance in nanotechnology research, which involves investigating and manipulating matter at the atomic and molecular levels which result in drastic changes[3]. The field of medicine stands to be a significant benefactor in nanotechnology, with oncology already starting to reap the benefits of novel nanoscale technologies. These benefits have included advances in detection, imaging, and therapy of disease[5]. Targeted therapies are usually more effective than other convention treatments and exhibit lesser unwanted adverse effects. Since the non-specific and systemic drug delivery leads to rapid elimination of drug, administration of the highest tolerable doses of the drug is needed which is not economical and usually exhibits high toxicity. In recent years, accumulating studies have been shown the efficacy of nanosized materials for tumour targeting, diagnosis and therapy[4].

Cancer is one of the most fatal diseases in today's world which kills millions of people every year. The treatment of cancer therapy includes surgical removal, chemotherapy, radiation and hormone therapy. Chemotherapy, a very common treatment which delivers anticancer drug systemically to patients for quenching the uncontrolled proliferation of malignant cells. Cancerous cells have some unique properties that differentiate them from the healthy cells at molecular level. The most difficult task of cancer therapeutics is to distinguish the cancerous cells and the normal body cells[1]. Cervical cancer is the third most common malignancy disease among women. Although most cases of cervical cancer can be prevented by routine screening and treatment of pre-cancerous lesions[2]. Cancer is not a single cell disease but a multiple cell diseases with each organ or system developing a distinct set of diseases having the patronage of the entail cell like a parasite in the host cell[20]. To address these therapeutic requirements, nanosized molecular tools capable of distinguishing between malignant and non-malignant cells as well as delivering a lethal payload should be developed[13].

2. Drug delivery system

2.1 Drug Delivery Nanoparticle systems

Nanoparticles, nanospheres or nanocapsules can be prepared which possess unique properties and characteristics for drug delivery system[8]. A major challenge in cancer diagnostic in this century is to able to determine and find the exact relationship between cancer biomarkers and the clinical pathology as well as to find the non-invasively tumour to detect at an early stage for maximum therapeutic benefit[11].

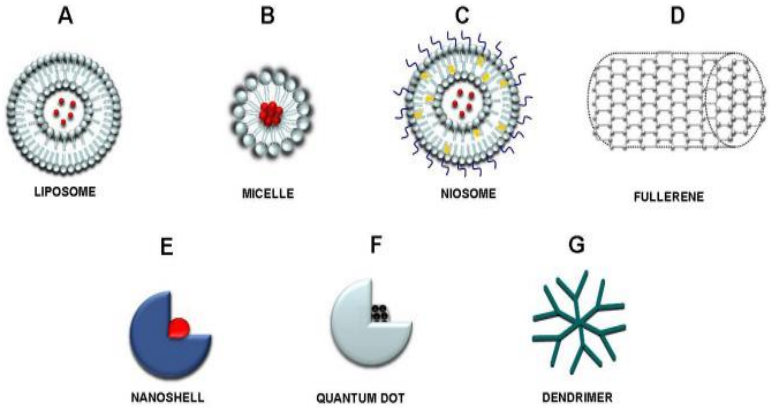

Figure 1. Drug delivery nanoparticle systems: (A) liposome (B) micelle (C) noisome (D) fullerene (E) nanoshell (F) quantum dot (G) dendrimer[9].

The Drug delivery systems are defined as supramolecular assemblies incorporating agents intended to treat a disease. There has been extensive research towards the development of new drug delivery system. Liposome and emulsions dominated the drug delivery field for some period[7]. Even though the conventional chemotherapeutic agents are still used on a large scale, nanoparticles are showing an increase in popularity, some of the newly developed nanoparticles possess better solubility and bioavailability. Nanoparticle therapeutics are usually formed by coalition between a therapeutic agent which is represented by small-molecule drugs, nucleic acids, antibodies, peptides, or maybe a drug carrier or proteins, such as lipids, metals or polymers[1]. Nanoparticles have been widely used because of their customised size, shape, and surface features. In order to exceed the limitations of the nanoparticles and utilizing their advantages, nanoparticle multi-target therapy is nowadays proposed, and in some cancer types (cervical cancer), it has already been reported to have superior effects. Fundamentally, this can be deduced and tested also for oral cancer [24].

Table 1. Various nanoparticles based delivery systems with their therapeutic and diagnostic uses in cancer therapy [11]

S.No.	Nanoparticle based delivery system	Therapeutic and diagnostic use
1	Liposome	Controlled and targeted drug delivery; targeted gene delivery
2	Nanoshells	Tumour targeting
3	Fullerene based derivatives	As targeting and imaging agent
4	Carbon nanotube	Drug gene and DNA delivery; tumor targeting
5	Dendrimers	Targeted drug delivery
6	Quantum dots	As targeting and imaging agent
7	Gold nanoparticles	Targeted drug delivery and imaging agent

8	Solid lipid nano particles(SLN)	Controlled and targeted drug delivery
9	Nanowires	As targeting and imaging agent
10	Paramagnetic nanoparticles	As targeting and imaging agent

2.2 Targeted drug delivery

Targeted drug delivery can be either active or passive, depending upon the therapeutic agents or carriers. Active is the one, in which the therapeutic agents are conjugated to a tissue or cell-specific ligand while in passive the therapeutic agent is incorporated into a macromolecule or nanoparticle that passively reaches the target organ[8].

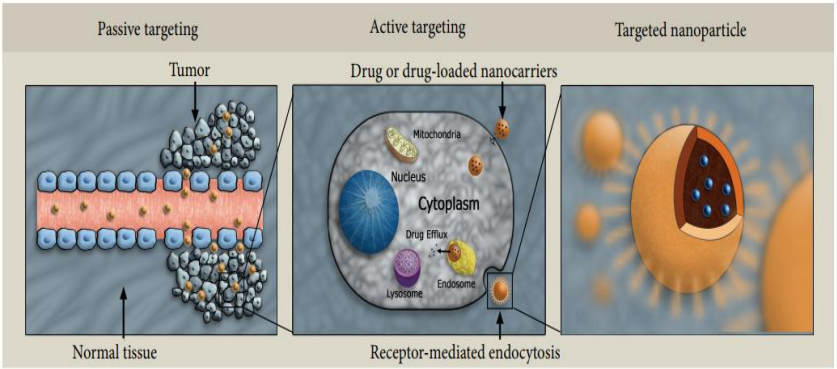

Figure 2: Active and passive targeting by nanoparticles [1].

3. Nanotechnology in Medicine: Nanomedicine

Nanotechnology offers great visions to enhanced and personalized treatment of disease. The hope is that personalized medicine will make it possible to develop the appropriate drug to the patient. The benefits of this approach are accuracy, efficacy, safety and speed. Some researchers use the term nanomedicine refers to the applications of nanoparticles currently under development; other researchers reserve the term nanomedicine to refer to longer range research that involves the use of manufactured nano-robots to make repairs at the cellular level. While nanomedicine potentially offers promising new value propositions and revenue streams, it also could completely displace certain classes of drugs.

For example, currently-employed chemotherapeutic agents are being substituted with novel nanoparticle reformulations. Today, commercial nanomedicine is at a nascent stage of development and its full potential years or decades away. Currently, the most advanced area of nanomedicines is the development and use of nanoparticles for drug delivery[12].

4. Conventional and modern method using nanotechnology

4.1 Conventional treatment

The general cancer therapies are limited to surgery, radiation, and chemotherapy. These methods cause serious damage to healthy tissues and there is also incomplete removal of cancerous cell. The traditional chemotherapy endures the lack of aqueous solubility of the drugs, lack of selectivity for the cancer cells and multidrug resistance reduces after taking the repeated administration of the same drug[21]. For the records, chemotherapeutic drugs are hydrophobic and hence lead to poor aqueous solubility and low bioavailability[23], which is overtaken by the usage of the albumin-based nano particles, nanocrystals, liposomal formulation, polymeric micelles.

Nanotherapeutics helps to overcome the multidrug resistance which is a trial in cancer chemotherapy that can be handled effectively by using solid lipid nanoparticles, mesoporous silica nanoparticles, nanoparticulated chemosensitizer, nanoparticulated poloxamer, polymeric nanoparticles, and magnetic nanoparticles[21]. The use of nanoparticals in the treatment of cancer increased the chances

of destroying the cancer tissues with minimal damage to healthy tissue and organs, detection of cancer and elimination of cancer cells before they form tumours.

4.2 Modern Treatment

The immune system has relevant tendency to identify abnormal changes in cell and has the capacity to destroy abnormal cells. This may prevent the development of many cancers but not all types of cancer cells. Some cancer cells escape the anti-cancer effect of the natural immune system by reducing the expression of tumour antigens on their surface, by inactivating the immune cells by expression of certain proteins, or modifying the cells in the surrounding microenvironment to release substances to suppress the immune response. There are various therapy for treating the different type of the cancer and tumours by imaging and detecting.

Therapies either trigger the activities of peculiar components of the immune system or oppose the signals produced by cancer cells that subdue the immune responses. Following list of the immunotherapies based on the nanoparticles drug delivery are:

Immune checkpoint modulator: The immune system tries to get rid of tumour cells via a response cycle that contains several steps, begins with the release of antigens from tumour cells at cell death, followed by the presentation of these antigens by antigen-presenting cells (APCs) to tumour cells that are then primed and activated against cancer-specific antigens in the lymph node[15]. CTLA4 inactivate the tumour cells because of that the strength of immune response reduces; ipilimumab binds to CTLA4 and prevents it from sending its inhibitory signal[25].

Adoptive cell transfer (ACT): Infiltrated T-cells from a patient's tumor are collected from samples of the tumor. The T-cells that show the greatest recollection of the patient's tumour cells in laboratory tests are selected, and large populations of these cells are grown in the laboratory. The cells are then activated by treatment with immune system signalling proteins called cytokines and infused into the patient's bloodstream[21].

Stem cell transplant: A stem cell transplant is prescribed as a treatment for some cancer types; it is also used to treat certain blood disorders. Previously, stem-cell transplants were referred to as "bone marrow transplants", as the stem cells were harvested from the bone marrow. The harvested marrow is filtered, stored in a special solution of bags and then frozen. When the marrow is to be used it is thawed and then put into the patient's blood through a vein just like a blood transfusion[21].

5. Work and Researches done in field of Cancer therapy

In the April 2006 PNAS publication "Nanoparticle-aptamerbioconjugates for cancer targeting", Langer and Farhrokzad from the MIT-Harvard CCNE tested the effect of aptamer-targeted nanoparticles for treatment of prostate cancer. The approach of using aptamers as targeted ligands, on drug-encapsulated nanoparticles, proved to be highly effective in targeting cancer cells and decreasing tumor size. Aptamers are DNA or RNA oligonucleotides that fold in tertiary conformations, which then are able to bind to targeting antigens[15]. They are advantageous because aptamers are extremely small in size and, therefore, do not have affect on particle's overall size. Also, aptamers are non-immunogenic and fairly stable with long circulation times in the body[14]. Aptamers have high affinity and specificity properties, which plays a significant role in targeting[14, 16]. The use of these docetaxel-encapsulated nanoparticle-aptamerbioconjugates demonstrated a decrease in tumor size from approximately 300 mm^3 to 120 mm^3[16].

In addition to reducing tumor size, these targeting methods had fewer side effects too on healthy cells within the body in comparison to current methods of chemotherapy. A number of projects within the Alliance are investigating methods to overcome the challenges in maintaining drug circulation and avoiding multi-drug resistance. Due to chemical compositions and lack of targeting, many current therapeutic agents are removed from the body's circulation by the reticuloendothelial system (RES) or immune system[17].

In June 2006 publication, Amiji and Langer addressed these challenges by developing poly(ethylene oxide)-modified poly(beta-amino ester) (PEO-PbAE) nanoparticles. They studied the efficacy and toxicity levels of paclitaxel when it was administrated through PEO-PbAE nanoparticles in mice, bearing human ovarian adenocarcinoma xenograft. The PEO-PbAE polymer nanoparticles were

significantly more efficient in drug delivery, reducing toxicity and decreasing tumor growth rates in comparison to the paclitaxel aqueous solution[17].

The interaction between the PbAE polymeric cores with the PEO modified surface gives particles a hydrophilic PEO component that decreases opsonization signal binding, and thus particles are less prone to phagocytes and macrophages. Particles were pH-sensitive, allowing drug release only at certain pH conditions, similar to pH levels unique in tumor cells. As a result the PEO-PbAE nanoparticles demonstrated the greatest drug efficacy. After four weeks the PEO-PbAE nanoparticle had reduced tumor volume to 22% of the original volume, where as the aqueous solution only had reduced tumor volume to 44% as these nanoparticles improve drug distribution system, they also found capable of decreasing chances of multi-drug resistance in long-term therapies.

In further research, Kommareddy and Amiji recently published their work on using poly(ethylene glycol) (PEG) surface modified thiolatedgelatin nanoparticles to test drug and gene efficacy on breast cancer cells. Studies demonstrated prolonged circulation due to the hydrophilic PEG-modified surfaces. Also, drug release was administrated through thiolated gelatin nanoparticles that are highly sensitive to reducing environments, similar to those found in tumor cells[18]. Through nanotechnology, nanoparticles can be modified in a numerous ways to prolong circulation, enhance targeted drug delivery system, increase drug efficacy, and gives enough resistance against multi-drug. Current therapies have limitations on early detection and imaging, which can be overcome by use of nanotechnology[19].

In July 2006, an article by Sathe et al. demonstrated the use of nanotechnology in cancer detection. Current detection methods are restricted in spectrum range, penetration depth, cell targeting, and signal/noise clarity[20]. The Nie team at the Emory/Georgia Tech CCNE has been focusing on the development of quantum dots to improve detection methods. In the study mentioned above, they developed dual-functioning beads comprised of quantum dots and iron oxide nanocrystals embedded in silica beads. These particles were able to target specific cells, due to the iron oxide crystals, and have high imaging qualities, due to the quantum dot component. Currently, they are determining ideal combinations of iron oxides and quantum dots that would give the best imaging qualities. Through nanotechnology, highly sensitive and specific imaging agents are being developed with biocompatible and multi-functional properties[13].

Cytimmune is one of the major companies doing research on nanomedicines in cancer treatment. Its main focus is on a discovery development and commercialization of multifunctional tumour targeted therapies[21].

Conclusion

Nanotechnology has great revolution in the field of cancer in many aspects and has significantly great impact in treatment pattern. It has made a great impact on selective recognization of the cancerous cells, targeted drug delivery, and overcoming limitations of the conventional chemotherapies. Many nanotechnology based formulations have already been launched in the market and many more are undergoing research and clinical trials. The side effects of the traditional chemotherapies can greatly be removed by active or passive targeting which can substantially increase the survival rate.

As cancer is one of the most serious fatal diseases, the contribution of nanotechnology is a positive movement in clinical practice for life saving approach. Ultimately, if the nanotechnology researchers can establish methods to detect tumors at a very early stage that is, before tumors begin to vascularize and metastasize, cancer will become a disease that will become amenable to complete cure via surgical resection.

Acknowledgements

We would like to thanks our Principal and the faculty members of Nanotechnology department for their expert advice and support.

References

[1] KumarBishwajitSutradhar and Md. Lutful Amin, "Nanotechnology in Cancer Drug Delivery and Selective targeting", ISRN Nanotechnology Volume 2014 (2014), Article ID 939378.

[2] FaridehOrdikhani, Mustafa Erdem Arslan, Raymundo Marcelo, Ilyas Sahin, Perry Grigsby, Julie K. Schwarz,and Abdel Kareem Azab,"Drug Delivery Approaches for the Treatment of Cervical Cancer", Pharmaceutics. 2016 ; 8(3): 23.Published online (2016), PMCID: PMC5039442 [PMC free article].

[3] Moslem Bahadori MD, FCCP, ForouzanMohammadi, "NANOMEDICINE", Iranian Journal of Pathology (2006).

[4] BehdokhtBahrami, Mohammad Hojjat-Farsangi, HamedMohammadi, EnayatAnvari, GhasemGhalamfarsa, Mehdi Yousefi, and FarhadJadidi-Niaragh, "Nanoparticles and targeted drug delivery in cancer therapy" (2017), Immunology Letters http://dx.doi.org/10.1016/j.imlet.2017.07.015.

[5] Frank Alexis, Eric M. Pridgen, Robert Langer, and Omid C. Farokhzad, "Nanoparticle Technologies for Cancer Therapy",HandbExpPharmacol. (2010);(197):55-86. [PubMed].

[6] Akin Aliosmanoglu1and IlkerBasaran, "Nanotechnology in Cancer Treatment", Journal of Nanomedicine & Biotherapeutic Discovery, (2012) 2:107.

[7] Sadhna Sharma and Amandeep Singh, "Nanotechnology Based Targeted Drug Delivery: Current status and Future Prospects for Drug Development", edited by Izet M. Kapetanovic, (2011).

[8] Rajesh Singh and James W. Lillard, Jr., "Nanoparticle-based targeted drug delivery", ExpMolPathol. 2009 Jun; 86(3): 215–223. (2009).

[9] Elisa Panzarini, Valentina Inguscio, Bernardetta Anna Tenuzzo, ElisabettaCarata and Luciana Dini, "Nanomaterials and Autophagy: New Insights in Cancer Treatment", Cancers (2013), 5, 296-319.

[10] Chetan C. Anajwala, Girish K. Jani, S.M. VijayendraSwamy, "Current Trends of Nanotechnology for Cancer Therapy", International journal of pharmaceutical Science and Nanotechnology, vol. 3 (3), (2010).

[11] Navedulhaque, Rafallah R. Khalel , N. Parvez , S. Yadav , N. Hwisa, M. S. Al-Sharif , B. Z. Awen and K. Molvi. "Nanotechnology in Cancer Therapy: A Review. Journal of Chemical and Pharmaceutical Research", (2010), 2(5): 161-168.

[12] Amiji M, Park K. "Prevention of protein adsorption and platelet adhesion on surfaces by PEO/PPO/PEO triblock copolymers". Biomaterials. (1992), 13(10):682-92.[PubMed].

[13] Omid C. Farokhzad, Jianjun Cheng, Benjamin A. Teply, Ines Sherifi, SangyongJon,Philip W. Kantoff, Jerome P. Richie and Robert Langer. "Nanoparticle-aptamer bioconjugates result in significant tumor reduction in vivo". PNAS (2006), 103 (16) 6315-6320.

[14] Ellington AD, Szostak JW. "In vitro selection of RNA molecules that bind specific ligands". Nature (1990) volume346, pages818–822.

[15] Farokhzad OC, Karp JM, Langer R. Nanoparticle-aptamer bioconjugates for cancer targeting. Expert Opin. Drug Delivery, (2006) ;3(3):311-24. [PubMed].

[16] Devalapally H, Shenoy D, Little S, Langer R, Amiji M. "Poly(ethylene oxide)-modified poly(beta-amino ester)nanoparticles as a pH-sensitive system for tumor-targeted delivery of hydrophobic drugs: part 3 Therapeutic efficacy and safety studies in ovarian cancer xenograft model". Cancer Chemotherapy and Pharmacology, (2007), Volume 59, Issue 4, pp 477–484.

[17] Kommareddy S, Amiji M. "Biodistribution and Pharmacokinetic Analysis of Long-Circulation Thiolated Gelatin Nanoparticles Following Systemic Administration in Breast Cancer-Bearing Mice". Journal Pharmaceutical Sciences, (2007), vol 96, issue 2, pg 397-407. [PubMed].

[18] Sathe TR, Agrawal A, Nie S. "Mesoporous Silica Beads Embedded with Semiconductor Quantum Dots and Iron Oxide Nanocrystals: Dual-Function Microcarriers for Optical Encoding and Magnetic Separation". Anal. Chemistry. (2006) 15;78(16):5627-32. [PubMed].

[19] Grodzinski P, Silver M, Molnar LK. "Nanotechnology for Cancer Diagnostics: Promises and Challenges". Expert Rev. Mol. Diagn. (2006) 6(3):307-18. [PubMed].

[20] William H. Gmeiner and Supratim Ghosh. "Nanotechnology for cancer treatment", HHS public access, (2015); 3(2):111-112. [PMC free article].

[21] Sebastian R . "Nanomedicine - the Future of Cancer Treatment: A Review". Journal of Cancer Prevention Current Reserch. Vol 8(8) (2017).

[22] Xu Wang, Yiqing Wang, Zhuo Georgia Chen and Dong M. Shin. "Cancer Research and Treatment". Journal of Cancer Research & Treatment, (2009) Mar; 41(1): 1–11.

[23] Alexandra Iulia Irimie, Laura Sonea, AncutaJurj, Nikolay Mehterov, Alina AndreeaZimta, LiviutaBudisan,CorneliaBraicu and IoanaBerindan-Neagoe. "Future trends and emerging issues for nanodelivery systems in oral and oropharyngeal cancer". International Journal of Nanomedicine. (2017); 12: 4593–4606. [PCM free article]

[24] Matthias Preusser, Michael Lim, David A. Hafler, David A. Reardon, and John H. Sampson. "Prospects of immune checkpoint modulators in the treatment of glioblastoma". Nat Rev Neurol. (2015); 11(9): 504–514. [PCM]

[25] Eileen S. Kim, Jennifer E. Kim, Mira A. Patel, Antonella Mangraviti, Jacob Ruzevick and Michael Lim. "Immune Checkpoint Modulators: An Emerging Antiglioma Armamentarium." Journal of Immunology Research. (2016), 11(9): 504–514. Article ID 4683607.