The Pharmaceutical and Chemical Journal, 2016, 3(3):12-16

Available online www.tpcj.org

Review Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Nanotechnology in Oral Cancer: Novel Approach Towards Detection and Drug Therapy

Saurabh Srivastava[1], Om Prakash Gupta[2], Kumud Nigam[3], Shaista Suhail[3], Shalini Gupta[3]

[1]Department of Oral & Maxillofacial Surgery, King George's Medical University, Lucknow, UP, India
[2]Department of General Surgery, Carrier Institute of Medical Sciences, Lucknow, UP, India
[3]Department of Oral Pathology & Microbiology, King George's Medical University, Lucknow, UP, India

Abstract Nanotechnology for oral cancer could be a use full tool for detection and drug therapy. By Possessing unprecedented potential for early stage detection, treatment of oral cancer, nanoparticles have been demonstrated over the last decade. In this review, we will summarize the current state-of-the-art of nanoparticles in biomedical applications such as detection, diagnosis and targeting over the oral cancer. Gold nanospheres, nanorods, nanoshells, nanocages, and surface enhanced nanoparticles will be discussed in detail regarding their uses in vivo imaging, cancer therapy, and drug delivery. The key feature of nanoparticle-based drug agents to target over ligands, therapeutic drugs, and other functionalities can all be integrated to allow for targeted molecular imaging and molecular therapy of oral cancer. The future of the nanotechnology for oral cancer looks brighter than ever yet many hurdles remain to be conquered. A multifunctional platform based on gold nanoparticles, with multiple receptor targeting, multimodality imaging, and multiple therapeutic entities, holds the promise for a "magic gold bullet" against oral cancer.

Keywords Nanotechnology, oral cancer, nanotube, drug therapy, cancer detection.

Introduction

More than 11 million people are diagnosed with oral cancer every year. It is estimated that there will be 16 million new cases every year by 2020 [1]. Cancer is a multifactorial disease brought on by a combination of causal and predisposing genetic factors, and which at a given moment and under favorable conditions may take effect in predisposed people [2]. Mortality from malignant neoplasm figures among the principles cause of death worldwide, and it is therefore a highly serious public health matter [3]. Oral squamous cell carcinoma is the most frequent tumor of oral cavity, statistically responsible for 90% of oral cancer world data diagnosed every year [4]. The main disorders that may lead to the development of oral cancer, pointed out by WHO experts working group recently defined are: leukoplakia, erythroplakia, palatal lesion of reverse cigar smoking, oral lichen planus, oral submucous fibrosis, discoid lupus erythematosus, hereditary disorders such as dyskeratosis congenital and epidermolisys bullosa [5]. The American National Cancer Institute (NCI), the Center for Disease Control and Prevention (CDC) and the American Cancer Society (ACS) have found increases in the incidence of oral cancer among specific segments of the population, including minorities, although oral cancer incidence and mortality rates in USA has declined. This study showed that although incidence rates of oral cancer have steadily decreased among white males, incidence rates among older black males have increased. Currently in The USA, cancer remains the second leading cause of mortality whereas oral cancer is the eighth cause of cancer death among males [5-6]. Oral cancer is a major problem in the Indian subcontinent where it ranks among the top three types of cancer in the country [7]. Age-adjusted rates of oral cancer in India is high, that is, 20 per 100,000 population and accounts for over 30% of all cancers in the country [8]. Oral cancer forms the sixteenth most common type of cancer worldwide with a crude incidence rate of 3.9. There are about 0.2 million new cases every year worldwide with 0.1 million deaths each year. On global comparison India shows high incidence rates of oral cavity cancers forming a major health burden. Age standardized

incidence rate in India is 7.5 per 100,000 population while in western Europe and USA it is 4.6 and 3.8 per 100,000 population respectively [9].

Table 1: Predictor factors for oral cancer and its potential to induce malignant disorders [3,9]

Predictive factors	Potential for malignant disorders
Age and Duration	The first five years of oral lesion is the most critical period for the malignance development. The older is the patient the worse is the prognosis.
Site	Lateral border of tongue and floor of mouth are the most critical sites for malignant transformation.
Size	Tongue carcinoma is more aggressive than any other oral site.
Gender and clinical appearance	Multiple lesions have four times more chances to become malignant than single anatomical lesion. Several studies point out a propensity of leukoplakia in female to become malignant when compared to male. Lesions containing nodular and red areas have been shown to be a greater risk of malignant transformation than the uniformly ones.

This cancer is any cancerous tissue growth which is present in the oral cavity. It mostly involves the tongue. It appears as skin lesions, lumps or ulcers. Tobacco, alcohol, genetic factors, the human papilloma virus and the consumption of spicy food are some of the main aetiological factors which are responsible for oral cancer [10]. Oral mucosa (tissue lining the mouth and gums), the floor of the mouth, the base of the tongue, and the oropharynx (area of the throat at the back of the mouth). There are several types of lesions (growths) that have the potential to become oral cancers. These include white lesions called leukoplakia (the most commonly diagnosed precancerous lesions in the mouth) and red, velvet-like lesions called erythroplakia. Smoking and the frequent consumption of alcohol typically cause these lesions. Of those that become cancerous, about 90 % are a type of cancer called squamous cell carcinoma. The complications of oral cancer and its treatment can have serious adverse effects on patients, their families, and society [11].

The treatment involves surgery, radiation therapy and chemotherapy [12]. People with early oral cancer may be treated with surgery or radiation therapy. People with advanced oral cancer may have a combination of treatments. For example, radiation therapy and chemotherapy are often given at the same time. Another treatment option is targeted therapy [13]. A chemotherapy drug may be used alone or combined with other drugs. Most common drugs use for chemotherapy are Cisplatin, 5-fluorouracil (5-FU. Carboplatin, Paclitaxel, Docetaxel, Methotrexate, Ifosfamide, Bleomycin. Often combining drugs can help tumors shrink better, but will cause more side effects. The most commonly used combination is cisplatin and 5-FU. This combination is more effective than either drug alone in shrinking cancers of the oral cavity and oropharynx. Chemotherapy is often given at the same time as radiation (known as chemoradiation). Cisplatin alone is usually the preferred chemo drug when given along with radiation. Some doctors prefer to give the radiation and chemo before surgery. However, the side effects can be severe and may be too much for some patients [14].

Applications of Nanotechnology in Oral cancer

Nanotechnology is a science which is used to manipulate the atoms and the molecules which lead to the production of structures in the nano-meter size, which range from 100 nm or even smaller, which attain their unique properties. The processes of the living organisms occur at a nano-meter scale, and the important biological units like the DNA proteins and the cell membranes are of this dimension. The nanoparticles which are used as drug delivery vehicles are generally <100nm in size and they consist of different bio-degradable materials such as natural or synthetic polymers, lipids or metals. The nanoparticles which are under extensive research to determine the roles that they can play in cancer detection and treatment [14-15]. The examples of cancer- related nanomodalities include liposomes, polymeric micelles, polymer-drug conjugates, carbon nanotubes, dendrimers, inorganic particulates such as quantum dots, paramagnetic nanoparticles, contrast agents for magnetic resonance imaging, etc. Materials at a nanoscale have several advantages compared to small molecule-based therapy such as higher payload capacity, prolonged blood circulation times, reduced toxicity to healthy tissues, and improved anti-tumor efficiency [16]. The nanoparticles are under research to develop a host of biomedical and biotechnological applications which include drug delivery, enzyme immobilization and DNA transfection (infection by transformation). For the past few years, quantum dots (QDs) have been an area of intense research. They have unique physical properties and they can be

exploited for the detection of cancerous tumours. Quantum dots have enough surface area to combine therapeutic agents and tumour specific modalities for the combined results of drug delivery, imaging and tissue engineering [17]. Presently, two main categories of nanoparticles are widely employed for biological applications: in-organic nanoparticles and polymeric nanoparticles [18]. Polymeric nanoparticles can encapsulate drugs and release them in a regulated fashion through surface erosion of the nanoparticles, diffusion of the drug through the polymer matrix, or swelling followed by diffusion [19].

Polymeric nanoparticlescoated with aptamers RNA based targeting moieties to guide them towards the tumour, where they bind, enter the cells and then dissolve to spill out their contents the anticancer drug docetaxel. The nanoparticles are also coated with polyethylene glycol (PEG) to aid their safe passage through the bloodstream and into the tumour cells [20].

Drug Delivery

Drug delivery using nanostructures offers considerable potential to accomplish this. For cancer therapy, the goal is to target cancerous cells while leaving healthy cells intact. With nanotechnology, it is possible to specifically target the cancerous cells and then activate the nano-structures to kill just that cells [20-21].

Quantum Dots: Semiconductor quantum dots are extremely small particles of cadmium selenide (CdSe) or zinc sulphide whose sizes are in the range of 1 to 10 nm. For biomedical applications, QD surfaces are modified further to target specific cells or molecules. QD–peptide conjugates have been used to target tumour vasculatures and homed to tumour vessels [22]. Antibody-conjugated QDs have been used for real-time imaging and tracking of molecules in living cells and have demonstrated high sensitivity and resolution [23-24].

Dendrimers: Dendrimers are a unique group of nanoparticles that are highly suitable for effective delivery of drugs, particularly for cancer treatment. Dendrimers can be synthesized by controlled, repeated polymerization reactions to engineer a desired shape and size. The main advantage of dendrimers is their exclusive branching point that is available for conjugation to multiple entities [25].

Future Perspective:

Nanotechnology is considered one of the greatest man-made engineering marvels in minuscule scale. The technology has grown exponentially in recent years, and it arguably has had the most impact on contemporary science and society since technologies of the Industrial Revolution. Demand for this cutting-edge technology in biomedical fields is growing by more than 17% annually, and is expected to reach approximately $53 billion by 2011 [26].

Hydrogels (macrogels), microgels and nanogels for topical application on oral pre-cancerous cells and oral cancerous cells incorporation with other therapy chemotherapy and radiation therapy. They are highly dispersible in aqueous solutions owing to the internal chemical or physical cross-linking of their macromolecular chains, which vary in size and structure. An ideal nanogel drug delivery carrier should have a few common features including, but not limited to a smaller particle size (10–200 nm), biodegradability and/or biocompatibility, prolonged blood circulation time, higher amount of drug or enzyme loading and/or entrapment and protection of molecules from the immune system of the body. There were many technology have been developed and more are under the stage of pre-clinical and developing stage for the treatment and detection of oral cancer by involving nanotechnology.

Summary: Nanotechnology is beginning to change the scale and methods of vascular imaging and drug delivery. Indeed, the NIH Roadmap's 'Nanomedicine Initiatives' envisage that nanoscale technologies will begin yielding more medical benefits within the next 10 years [27]. This includes the development of nanoscale laboratory-based diagnostic and drug discovery platform devices such as nanoscale cantilevers for chemical force microscopes, microchip devices, nanopore sequencing, etc [28-29]. The National Cancer Institute has related programs too, with the goal of producing nanometer scale multifunctional entities that can diagnose, deliver therapeutic agents, and monitor cancer treatment progress. These include design and engineering of targeted contrast agents that improve the resolution of cancer cells to the single cell level, and nanodevices capable of addressing the biological and evolutionary diversity of the multiple cancer cells that make up a tumor within an individual [30]. Thus, for the full in vivo potential of nanotechnology in targeted imaging and drug delivery to be realized, nanocarriers have to get smarter. Pertinent to realizing this promise is a clear understanding of both physicochemical and physiological processes [31]. These form the basis of complex interactions inherent to the fingerprint of a nanovehicle and its microenvironment [32-33]. Examples of which include carrier stability, extracellular and intracellular drug release rates in different pathologies, interaction with biological milieu, such as opsonization, and other barriers enroute to the target site, be it anatomical, physiological, immunological or biochemical, and exploitation of opportunities offered by disease states (e.g., tissuespecific receptor expression and escape routes from the vasculature) [34-35]. Inherently, carrier design and targeting strategies may vary in relation to the type, developmental stage, and location of the disease [36].

Conclusion

This review summarized recent developments in oral cancer detection methods with an emphasis on nanotechnology. Nanomaterials have unique features that are attractive, and can be applied to biosensing. The development of various nanomaterials and nanotechnology has enabled detection of oral cancer biomarkers with great precision and sensitivity that could not be achieved before. The low detection limit obtained by nanotechnology is expected to contribute immensely to the early detection and accurate prognosis of oral cancers. Since it is of huge importance to be able to diagnose oral cancer as early as possible, many studies are being conducted on developing sensing mechanisms that will push down the detection limit as far down as possible. As well, various new biomarkers can be discovered and verified with such sensitive tools. It is therefore highly anticipated that in the near future, nanotechnology shall help to detect oral cancer at an early stage and monitor the disease with much greater precision. It must be however noted that these new technologies must be validated critically before applying them for clinical diagnosis. Although detecting oral cancers at early stages is very attractive, factors such as probability of getting false positive/negative and impact of nanomaterials on human and environment should be fully understood.

References

1. Capilla MV, Olid MNR, Gaya MVO, Botella CR, Ruiz VB. Factors related to survival from oral cancer in an Andalusian population sample. Med Oral Pathol Oral Cir Bucal 2007; 12(7):518-23.
2. Moore SR, Johnson NW, Pierce AM, Wilson DF. The epidemiology of mouth cancer: a review of global incidence. Oral Dis 2000; 6(2):65-74
3. Chen PH, Shieh TY, Ho PS, Tsai CC, Yang YH, Lin YC, et al. Prognostic factor associated with the survival of oral and pharyngeal carcinoma in Taiwan. BMC Cancer 2007; 7:101.
4. González AP, López MA, Martínez LV. Comportamiento clínico y epidemiológico del cáncer de cavidad oral. Hospital Oncológico Provincial Docente María Curie. Instituto Superior de Ciencias Médicas Dr. Carlos Juan Finlay; 2005.
5. Kingsley K, O'Malley S, Ditmyer M, Chino M. Analysis of oral cancer epidemiology in the US reveals state-specific trends: implication for oral cancer prevention. BCM Public Health 2008; 8:87.
6. Napier SS, Speight PM. Natural history of potentially malignant oral lesions and conditions: an overview of the literature. J Oral Pathol Med 2008; 37:1-10.
7. Cho WSC. Contribution of oncoproteomics to cancer 2. biomarker discovery. Mol Cancer 2007; 6 : 25.
8. J. K. Elango, P. Gangadharan, S. Sumithra, and M. A. Kuriakose, "Trends of head and neck cancers in urban and rural India," Asian Pacific Journal of Cancer Prevention, vol. 7, no. 1, pp. 2006; 108–112.
9. R. Sankaranarayanan, K. Ramadas, G. Thomas et al., "Effect of screening on oral cancer mortality in Kerala, India: a clusterrandomised controlled trial," The Lancet, vol. 365, no. 9475, pp. 1927–1933, 2005.
10. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v 2.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.
11. National Institutes of Health Updated October 2010.
12. Logothetidis S. Nanotechnology in medicine: the medicine of tomorrow and nanomedicine. Hippokratia 2006; 10: 7-21.
13. Bonoiu A, Mahajan SD, Ye L, Kumar R, Ding H, Yong K-T, et al. MMP-9 gene silencing by a quantum dot-siRNA nanoplex delivery to maintain the integrity of the blood brain barrier. Brain Research. 2009; 1282: 142-55.
14. Shi J, Votruba AR, Farokhzad OC, Langer R. Nanotechnology in Drug Delivery and Tissue Engineering: From Discovery to Applications. Nano Letters. 2010; 10: 3223-30.
15. Karnik R, Gu F, Basto P, Cannizzaro C, Dean L, Kyei-Manu W, et al. Microfluidic Platform for Controlled Synthesis of Polymeric Nanoparticles. Nano Letters. 2008; 8: 2906-12.
16. Joseph K, Robert L. Responsive polymeric delivery systems. Advanced Drug Delivery Reviews. 2001;6: 19-50.
17. Alexis F, Rhee J-W, Richie JP, Radovic-Moreno AF, Langer R, Farokhzad OC. New frontiers in nanotechnology for cancer treatment. Urologic Oncology: Seminars and Original Investigations. 2008;26: 74-85.
18. Howarth M, Takao K, Hayashi Y, Ting A.Y. Targeting the quantum dots to the surface proteins in living cells with biotin ligases. Proc. Natl. Acad. Sci. USA 2005; 102: 7583-88

19. Andriy.Voronov, Coatings and Polymeric Materials Department, North Dakota State University, Fargo, ND
20. U.S. department of health and human services, National institutes of health, 2011; 15-16.
21. Kost J, Langer R. Responsive polymeric delivery systems. Advanced Drug Delivery Reviews. 2001; 46: 125-48.
22. American Cancer Society. Cancer Facts & Figures 2012. Atlanta, Ga: American Cancer Society; 2012.
23. Kojima, C.; Kono, K.; Maruyama, K.; Takagishi, T. Synthesis of polyamidoamine dendrimers having poly(ethylene glycol) grafts and their ability to encapsulate anticancer drugs. Bioconjug. Chem. 2000, 11, 910-917.
24. Robert Langer's ; Cancer nanotechnology: small, but heading for the big time; Nature Publishing Group; 2007; 6:175
25. Cancer Nanotechnology Plan, National Cancer Institute, July 2004, see http://nano.cancer.gov/about_alliance/cancer_nanotechnology_ plan.asp.
26. Ziober BL, Mauk MG, Falls EM, Chen Z, Ziober AF, Bau HH. Lab-on-a-chip for oral cancer screening and diagnosis. Head and Neck. 2008; 30: 111-121
27. Epstein JB, Zhang L, Rosin M. Advances in the diagnosis of oral premalignant and malignant lesions. Journal Canadian Dental Association. 2002; 68: 617-621
28. Mishra M, Mohanty J, Sengupta S, Tripathy S. Epidemiological and clinicopathological study of oral leukoplakia. Indian Journal of Dermatology, Venereology and Leprology. 2005; 71: 161-165.
29. Sankaranarayanan R. Screening for cervical and oral cancers in India is feasible and effective. National Medical Journal of India. 2005; 18: 281-284.
30. Sankaranarayanan R, Ramadas K, Thomas G, Muwonge R, Thara S, Mathew B, Rajan B; Trivandrum Oral Cancer Screening Study Group. Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomized controlled trial. Lancet. 2005; 365: 1927-1933
31. Akerman ME, Chan WCW, Laakkonen P, Bhatia SN, Ruoslahti E. Nanocrystal targeting in vivo. Proceedings of the National Academy of Sciences of the USA. 2002; 99: 12617-12621.
32. Gao X, Cui Y, Levenson RM, Chung LW, Nie S. In vivo cancer targeting and imaging with semiconductor quantum dots. Nature Biotechnology. 2004; 22: 969-976.
33. Hoffman, A.S. (2002) Hydrogels for biomedical applications. Adv. Drug Deliv. Rev. 54, 3–12.
34. Vinogradov, S.V. et al. (2002) Nanosized cationic hydrogels for drug delivery: preparation, properties and interactions with cells. Adv. Drug Deliv. Rev. 54, 135–147
35. The Freedonia Group. Nanotechnology in Health Care; US Industry Study with Forecasts to 2011, 2016, & 2021; Study #2168; The Fredonia Group: Cleveland, OH, USA, 2007.
36. Rathy Ravindran. Nanotechnology in cancer diagnosis and treatment: An overview. Oral and Maxillofacial Pathology Journal. 2011; 2: 101-106.