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Treatment of Prostate Cancer Using Nanotechnological Approaches- A Review

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ABSTRACT

Since tumor vasculature is more complicated, so the conventional drug delivery system finds difficult to provide a better therapeutic activity. In this regard, the advent nanomedicine, using the available chemotherapeutic drugs has emerged an approach to enhance the efficacy of the cancer treatment. Developments in nanoparticulate drug delivery system pave the way for the cancer drug delivery with improved bioavailability, specificity, low toxicity, and targetability. In the present review, we discussed the occurrence, prevalence, pathogenesis, and novel nanotechnological drug delivery systems adapted for the efficient treatment of prostate cancer.

INTRODUCTION

The life-threatening disease cancer is caused by abnormal cell growth without any controlled growth and invades nearby tissue, blood or lymph, which stimulates the growth of new blood vessels. The causative risk factors for cancer include smoking, tobacco, obesity, poor diet, lack of physical activity, and consumption of alcohol.In cancer, the genetic material (DNA) of the cell gets damaged or changed, due to mutations, which may affect normal cell growth and division. Benign tumors, in otherwords termed as non-cancerous, which can be removed from the body and it won't find its route to the other parts of the body. Whereas the malignant tumors are termed as cancerous this invades nearby tissues and also get spread to other parts of the body and ends with metastasis. The practical treatment options available for cancer treatments include chemotherapy and radiation therapy. The chemotherapeutic drugs work by stopping the growth of cancer cells either by killing or by preventing them from dividing. Radiation therapy utilizes high-energy external radiation source to kill the cancer cells and shrinks the tumors. But these treatments provided were not successful up to the mark.

Prostate Cancer

Prostate cancer is a most frequently diagnosed disease which affects the male reproductive system with cancerous tissues in the prostate, with alterations/changed shape of the prostate gland. Prostate cancer is the leading cause of cancer-related deaths globally. The symptoms associated with prostate cancer include frequent urination, interrupted urinary system and blood in urine.Typically prostate cancer is slow growing, but in few cases, it is metastatic [1].Prostate cancer is a malignant tumor, which can invade other parts of the body. Prostate cancer occurs due to alterations in zinc accumulation, alteration of metabolism, and citrate production. The pathogenesis of prostate cancer development depends on prostate differentiation and function, in addition to that of androgen receptor signaling. Androgen receptor is a protein comprising 919 amino acids in length but varies in the poly-glutamine, poly-glycine, and polyproline repeats of variable lengths [2]. Transactivation of androgen receptor leads to coregulatory proteins which differentially respond to altered microenvironmental conditions and may lead to cell growth and survival [2].

Incidence of Prostate Cancer

Prostate cancer is a major public health issue worldwide and the second most common cancer in men, In Asian countries, prostate cancer incidence rates varied from 2.0/100,000 in Iran, 20.3-100,000 in the Philippines during the year of 2002 [3]. The incidence rates of prostate cancer in India reveals the most of the registries, especially in Chennai and Bhopal and to the least extent in Mumbai [3].Approximately 70–80% of prostate cancer cases may lead to metastasis in the bone tissue [4].

Management of Prostate cancer

Previously multiple treatment options such as surgery, radionucleotide metabolic therapy (combined or not with hormonal therapy) and brachytherapy were utilized for the treatment of prostate cancer (Figure. 1). Real time" brachytherapy was applied recently for the treatment of prostate cancer [5]. Environmental elements, western dietary habits, and average life expectancy rise were the risk factors for prostate cancer development [6]. A web-based database termed as "Cancer of the Prostate Strategic Urologic Research Endeavor" (CaPSURE) was developed in 1995, for the longitudinal observation of prostate cancer patients in natural settings in the United States [6]. In Europe, the incidence of prostate cancer is increasing every year with 382,000 new cases and around 89,000 deaths every year [7].

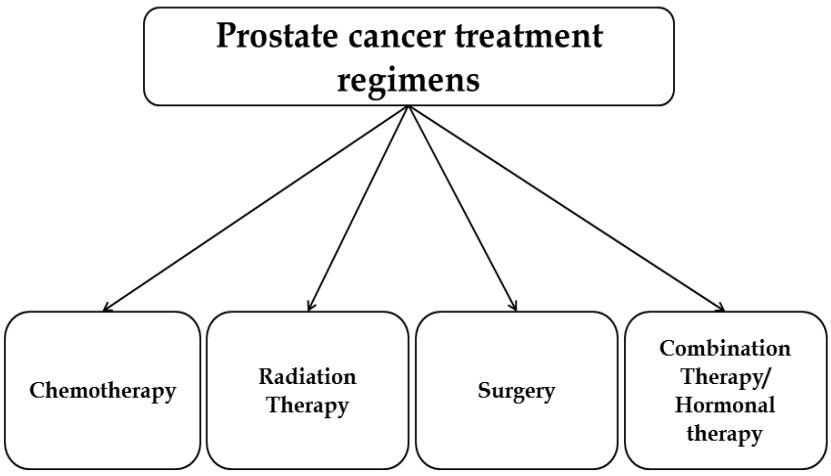

Figure. 1 Treatment regimens adopted for Prostate cancer

Nanotechnology and nano-based products

Nanotechnological products have evolved a great revolution in the 21st especially in the field of medicine, pharmaceuticals, chemicals, biologics, and information technology. The physicochemical properties of nano products offers surface area to mass ratios and high surface reactivity, these properties allow the materials to interact at the molecular level with specificity. Among these the advanced form, the nano micelles are nanosized aggregates of surfactant dispersed in a liquid colloid. Niosomes contains both the water-soluble and insoluble parts which assemble into closed bilayer nanostructures.Nanosponges were the complex structures, normally built up from long linear molecules again folded by crosslinking into spherical structures.The colloidal delivery agents for solubilizing the lipophilic bioactive compounds were termed as nanoemulsions.Depending on the core of the particle whether in oil or water, nanoemulsions can be termed as oil in water or water in oil forms. In the case of nanoparticles, the solubility of the particles in biological media should be considered during formulation development in order to achieve a better therapeutic effect at the diseased site. The release mechanism of nanoparticles is shown in Figure. 2. in case the problem of aggregation of nanoparticles should be addressed and rectified.

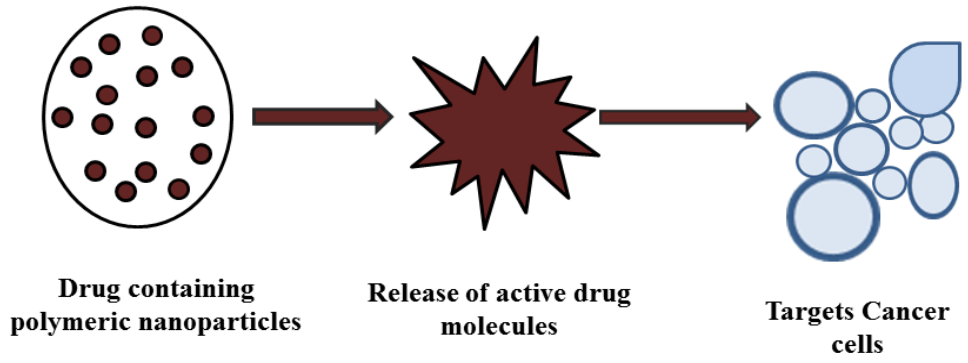

Figure. 2 Releasing mechanism of nanoparticles

Physicochemical characterization of nano products

The affordability of the nano products for its biological applications will be assured by its physicochemical characterization studies. The particle size and charge of nano products can be

checked by particle size analysis and zeta potential analysis. The morphology of the nano products can be checked by high resolution- transmission electron microscope. The amount of drug present in the nano products can be checked by analytical techniques such as HPLC or LC-MS/MS.The biological applications of different nano products were shown in Table. 1.

Table. 1: Nanoformulations and its biological applications

S No	Nano products	Particle size range (nm) and shape	Biological applications	References
1.	Nanoparticles (NSAIDs)	310 nm, spherical non-porous	Anti-inflammatory effect	8
2.	Nanoemulsions (Cinnamon oil nanoemulsion)	65- 254 nm, Spherical	Bactericidal effect	9
3	Nanomicelles (Clotrimazole)	17 nm	Breast cancer treatments	10

Nanotechnological approaches for prostate cancer treatment

Recently nanotechnology based drug delivery system was under research for the prostate cancer treatment using various formulation approaches such as nanoparticles, niosomes, nanomicelles, nanosponges, nanofilms, and nanoemulsions. Targeted drug delivery systems using functionalized nanoparticulates offers the possibility of achieving precise delivery of drugs to diseased cells without harming the normal cells.PEGylated PLGA- based nanoparticles grafted with RGD peptide-paclitaxel loaded nanoparticles has been reported for the targeting of tumor endothelium [11]. Doxorubicin functionalized gold nanoparticles for the treatment of cancer had been reported by Mirza et al [12]. The potential of transferrin-mediated curcumin solid lipid nanoparticles in enhancing anticancer effect in breast cancer cells [13]. Polyglutamic acid-paclitaxel- RGD peptide (polymeric-based drug conjugate) targets the tumor tissue exploiting enhanced permeability and retention effects providing enhanced anti-tumor activity with decreased toxicity when comparing to free paclitaxel-treated mice [14] with improved anti-angiogenic effect.

Nanoemulsions based drug delivery

Mishra et al; 2014 developed curcumin and etoposide loaded nanoemulsions for the treatment of prostate cancer, and they observed entrapment efficiency for both drugs as 98% with a globule size of less than 150 nm, zeta potential ranging −29.8 mV. The percent anti-cancer inhibition in case of etoposide and its combination with curcumin was found to be 55.92±1.2 and 41.13±2.4% respectively in prostate cancer cells. Moreover, curcumin provides a chemoprotective role in healthy cells [15].Nanodiamonds conjugated with the aspartic acid-glycine- glutamic acid-alanine (DGEA) peptide-loaded doxorubicin was prepared by Salaam et al., 2014 in order to address the toxicity and to afford the targetability at the α2β1 integrins receptors which were overexpressed in prostate cancers during metastasis stage. They found that the efficacy of 1 μg/mL and 2 μg/mL doxorubicin increased from 2.5% to 12% cytotoxicity and 11% to 34% cytotoxicity, respectively in human bone metastatic prostate cancer cells [16]. Along with nanoemulsions the niosomes also offering the best dosage form for cancer treatments, in this regimen the paclitaxel-loaded niosomes were prepared using Span 40 using the thin-film technique for cancer treatments and they observed the maximum amount of drug in the spleen tissue after intravenous injection to rats [17].

Nanoparticles and functionalization

Targeting of nanoparticles is an approach by which the drug will be brought in direct contact with the diseased site. The dual combination of a nanoparticulate system containing two anticancer agents such as cyclopamine and paclitaxel-loaded using glycerylmonooleate-chitosan solid lipid along with poly(glycolic-lactic) acid was developed by Shantanu et al; 2014 for prostate cancer treatment and they observed an enhanced cytotoxicity with sustained release pattern [18]. The anti-prostate cancer efficiency of different curcumin nanoparticles, such as cyclodextrin, hydroxyl propyl methyl cellulose, poly(lactic-co-glycolic acid), magnetic nanoparticles, and dendrimer-based curcumin nanoparticles produces its superior anti-prostate cancer efficiency in PC-3 cancer cells when using cellulose loaded curcumin nanoparticles [19].Gene expressions can be regulated during diseased state by binding of siRNA specifically to corresponding mRNA molecules. Poly(ethylenimine) (PEI)capped gold (Au) nanosphere conjugated anisamide (AA) has been reported in order to target the sigma receptor for the treatment of prostate cancer evaluated in PC3 prostate cancer cells, the results of their studies

concludes that the developed nanoformulation has the capacity to target prostate cancer cells [20]. The results of their cytotoxicity studies showed that Au-PEI and Au-PEI-AA formulations used may impact upon cellular toxicity.The potential of iron oxide magnetic nanoparticles (MNPs) conjugated with J591 antibody enhances the MRI imaging technology in prostate cancer preclinical mice xenografts models [21]. The synergistic effect of doxorubicin and zinc oxide nano complex has been used for multimodal cancer therapeutics and they observed an induced synergistic caspase-dependent apoptosis which results in an enhanced anticancer activity [22].

RNAi interference technology based nanoformulations

Recently advances have gained for the delivery of nanoformulations using RNAi technology. In this strategy, the small interfering RNAs (siRNA) has recently gained wide applications for cancer treatment due to its capacity to silence gene using a known sequence. The rapid degradation of naked siRNA in systemic circulation can be avoided using nanoparticulate based formulations and to offer an enhanced cellular effect.*In vivo* pH, sensitive delivery systems of siRNA loaded super-carbonate apatite nanoparticles have been used for the treatment of solid tumors. Intravenous administration of siRNA loaded super-carbonate apatite nanoparticles possess more accumulation in the cytoplasm of tumor cells at 4 h, with a quick endosomal escape and they also hold significant *In vivo* antitumor effect [23]. Adjuvant nanoparticles of siRNA combined with radiofrequency thermal ablation techniques have been also used for the treatments of cancer.

CONCLUSION

To conclude nano-based formulations possess small size, less toxicity, solubilizing the drug and targetability. However, owing to their tailorability it can be modified into light activated, pH sensitive, temperature activated and magnetic field activated. Thereby it may enhance the bioavailability at the maximal level when compared to conventional dosage forms. In the past, significant advances were made in overcoming the challenges of low solubility and bioavailability. Currently, technologies are available for sustaining/controlling the drug release from few hours to a few months using triple/penta block copolymers. However, toxicity to the healthy cells when compared to the diseased cells has to give priority before choosing a delivery system in prostate cancer treatments.Since the incidence of cancer has been increasing due to

risk factors such as changes in diet and lifestyle, tobacco consumption, and population aging the search for the novel treatments providing a complete cure without reoccurrence is an essential in the present scenario.

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