

Nanomaterials in Head & Neck Cancer Metastasis Treatment: A Mini-Review

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ABSTRACT

Head and Neck cancer (HNC) is a complex and heterogeneous disease associated with high incidence of disseminated metastasis. Traditional oncologic treatment resulted ineffective for a total regression of the disease. Nanomedicine is emerging as innovative and useful therapeutic approach able to overcome limitations of current treatments. A variety of Nanomaterials (NMs) are under investigation in preclinical and clinical trials to validate and guarantee the safety and effective use of NMs against Head and neck metastatic cancer.

Abbreviations: HNC: Head and Neck Cancer; NMs: Nanomaterials; AuNRs: Gold Nanorods; AuNPs: Gold Nanoparticles; SPION: Superparamagnetic Iron Oxide Nanoparticle

Mini Review

Head and Neck Cancer (HNC) is a complex multifactorial disease that originates in the epithelial layer of mucosa affecting oral cavity, pharynx and larynx. HNC is an invasive disease able to infiltrate surrounding lymph nodes with high incidence of ipsilateral and cervical lymph node metastasis (40%), and tissues with greater incidence in lungs (66%), bone (22%), liver (10%), skin, mediastinum and bone marrow [1]. Prognosis depends to several factors among which disease's stage, loco-regional relapses and incidence of distant metastasis. Actually a median survival of about 10 months is associated with diagnosis of distant metastasis [2]. Patients with HNC are treated with surgical ablation combined with radiotherapy and chemotherapy but patients showing HNC recurrence and spread metastasis are not responsive to these treatments. Cancer metastasis resistance is largely due to different and heterogeneous metastatic cells subpopulation in which they modify gene expression, growing rate, cell surface properties and functions, compared to primary tumor cells; these instability and consequent mutations are the causes of resistance against common drugs therapy. Moreover, drugs inability to reach sites of metastasis contributes to the poor outcome of current therapies [3].

Nanotechnology based therapy has emerged as promising oncology approach able to overcome limitations of current treatments. Nanomaterials (1-100nm) can act as carriers for drugs and targeting ligands to reach selectively cancer cells. Main properties that allow nanomaterials to exploit their favorable actions are: large surface area, structural surface properties and long circulation time; moreover due to their controlled drug load and selective delivery showed excellent biocompatibility, biodistribution and biodegradation resulting in lower systemic toxicity [4]. The incoming application of nanotechnology- based approaches in medicine are bringing advantageous opportunities for the detection, prevention and treatment of cancer metastasis due to their ability to direct specific response against defined target [3,5]. In this mini-review were summarized properties and applications of nanomaterials for treatment and detection of Head and Neck metastatic cancer and more recent studies under clinical trials validation.

Nanotechnology- Based Therapy

Nanomaterials (NMs) can be classified according to their material properties, shape and application. Concerning materials

used, NMs can be categorized in organic (gold and metals nanoparticles, quantum dots and fullerenes) and inorganic (liposomes, dendrimers and polymeric nanoparticles). NMs were primarily used as drug cover- protection to avoid premature degradation and/or clearance and at the same time prolong drug circulating time. Drug can be loaded inside the NMs structure (encapsulated drug) or surface absorbed/conjugated, depending on type of release desired [6]. NMs can exploit active or passive targeting strategy to perform their activity and reach desired site. Basically active targeting exploits the high affinity of ligand-receptor mechanism; by functionalizing the NMs surface with selective ligands; conversely passive targeting is based on NMs physico-chemical properties suitable to exploit EPR effect (Enhanced Permeability and Retention) that guarantees accumulation of NMs in the tumor site due to an increased vascular permeability [7]. Moreover NMs can act themselves as therapeutic agents exploit specific material properties. Exist NMs that are susceptible to external-induced physical triggers and endogenous- induced triggers to perform their activity. External-induced physical triggers NMs are sensitive to photo- thermal specific light wavelength or to magneto-thermal selective magnetic field. When these materials are excited by the external physical triggers, they release vibrational energy as heat to ablate malignant cells. Depending on the temperature induced (hyperthermia), it's possible caused cells apoptosis (42-46 °C) or cells necrosis (> 46 °C) [8].

The most used nanomaterials in hyperthermia treatments are: Gold Nanorods (GNRs), Gold Nanoparticles (GNPs) and Superparamagnetic Iron Oxide Nanoparticle (SPION) [9] These NMs are also used in clinic as contrast agents for imaging (magnetic resonance imaging-MRI) due to their ability to become detectable under magnetic field and distinguish diseased tissues from healthy ones [10]. Iron oxide NPs are used is Magnetic Resonance Imaging MRI to detect liver metastases, metastatic lymph nodes, inflammatory and degenerative diseases at an early stage when other contrast agents are unable to visualize them [11]. Instead Endogenous- induced triggers NMs are sensitive to endogenous environment changing such as pH, temperature, hypoxia and enzyme concentration. Using these environment variations NMs are able to achieve high drug concentration in the tumor region saving normal cells [12]. In vivo NMs biodistribution is correlated to their size and shape; remaining in the nanosize range, little dimension variations could influence NMs retention, uptake and pharmacologic activity [12]. Was reported that uptake of spherical gold nanoparticles with approx diameters of 50 nm was higher

than that of particles showing lower (14nm) or higher (74 nm) diameters. Concerning NMs shape, comparison between different gold nanomaterials (spherical nanoparticles, rod, wire, hollow) confirmed that different cellular up-take by endothelial cells was observed and more in specific, uptake of spherical nanoparticles was favored [13]. In Table 1 we choose some representative examples to have an overview of nanomaterials and drugs tested in preclinical studies for head and neck cancer and metastasis therapy [14].

Table 1: Nanomaterials and drugs used in Head and Neck cancer and metastasis therapy.

Nanomaterials (NMs)	Drug	Ref
Carbon-based nanovectors	Paclitaxel Cetuximab	[15]
Single wall carbon nanotube (SWNT)	Cisplatin along with epidermal growth factor (EGF)	[16]
Magnetic iron oxide (IO) NP	-	[17]
Magnetic nanoparticles	Folate-conjugated cisplatin (CDDP-FA-ASA-MNP)	[18]
Tenfibgen nanocapsules	Anti-CK2 α / α oligodeoxynucleotide	[19]
1,2-dioleoyl-sn-glycero-3-ethylphosphocholine-based cationic solid lipid nanoparticles (cSLN)	Small interfering RNAs (siRNA)	[20]
Poly (lactic-co-glycolic acid) (PLGA) nanoparticles	5-aminolevulinic acid (ALA)	[21]
Palmitoleyl (Pal-MTO) lipids	Mitoxantrone (MTO)	[22]
Cationic lipid nanoparticles	Pre-miR-107 (NP/pre-miR-107)	[23]
Dextran coated-Superparamagnetic iron oxide nanoparticles (DESPIONS)	Hyaluronic Acid (HA)	[24]
Silver Nanoparticles (AgNPs)	-	[25]
Gold nanoparticles (AuNPs)	Enhance X-ray irradiation	[26]
PEGylated liposome	rhenium-188 (188Re)	[27]
GE11-coniugated liposome	Resveratrol (RSV)	[28]

Nanotechnology in Clinical Trials

A fair number of nanotechnology drug formulations tested both for diagnostic and/or therapeutic purposes are under investigation in clinical trials for HNC and metastatic treatments in order to evaluate in vivo their effects for future approval in clinic applications [15-20]. In Table 2 are summarized only the most recent clinical trials focused on Head and Neck cancer metastasis found on clinicatrials.gov [21-23].

Table 2: Nanomaterials tested in clinical trials for Head and Neck metastatic cancer.

NCT Number	Interventions	Conditions	Status	Phase	Location	Last Update Posted
NCT02106598	Fluorescent cRG-DY-PEG-Cy5.5-C dots	Head and Neck Melanoma Real time image-guided intraoperative Mapping of Nodal Metastases	Recruiting	Phase 1 Phase 2	Memorial Sloan Kettering Cancer Center New York, New York, United States Weill Cornell Medical Center New York, New York, United States	February 25, 2021
NCT04862455	Hafnium Oxide-containing Nanoparticles NBTXR3	Metastatic Head and Neck Squamous Cell Carcinoma Recurrent Head and Neck Squamous Cell Carcinoma	Recruiting	Phase 2	M D Anderson Cancer Center Houston, Texas, United States	April 28, 2021
NCT02495896	Paclitaxel albumin-stabilized nanoparticle formulation	Head and Neck Squamous Cell Carcinoma	Active not recruiting	Phase 1	USC / Norris Comprehensive Cancer Center Los Angeles, California, United States Hoag Memorial Hospital Presbyterian Newport Beach, California, United States	April 5, 2021
NCT03817307	USPIO (ultra-small super-paramagnetic iron oxide)-enhanced MRI	Detection of Lymph Node Metastases in Head and Neck Carcinoma	Recruiting	NA	Radboudumc Nijmegen, Netherlands	October 9, 2020
NCT01927887	Nanoparticles (USPIO) MRI	Metastatic Medullary Thyroid Cancer Follicular Thyroid Cancer Lymph Node Metastasis	Completed	NA	Massachusetts General Hospital Boston, Massachusetts, United States	June 6, 2017
NCT01300533	BIND-014 (Docetaxel Nanoparticles for Injectable Suspension)	Advanced or Metastatic Cancer	Completed	Phase 1	Investigational Site #01 Scottsdale, Arizona, United States Investigational Site #02 Greenbrae, California, United States (and 4 more)	February 9, 2016

Note: NA: Not Applicable.

Conclusion

Many strategies are under investigation in order to improve HNC cancer metastasis treatments and therapies. Nanomaterials, thanks to their suitable properties such as small size, selective ligands functionalization, drug protection and vehiculation, suitable retention in the diseased site and modulated responses according to the applied stimulus (endogenous or exogenous), are becoming increasingly used both in therapy and diagnostic (theranostic application) [24-26]. NMs have the potential to enhance chemotherapy efficiency without increasing toxicity showing many encouraging results demonstrated by preclinical and clinical trials for HNC cancer and metastasis treatments. Despite these

new achievements, are still not enough for a complete eradication of metastatic cancer diseases and knowledge of cancer spreading mechanisms [27,28]. For a more in deep reading we suggest the review "Metastatic Disease in Head and neck cancer" that provide a complete and multidisciplinary update on distant metastases in Head and Neck oncology [29].

Conflict of Interest

None.

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