

Nanotechnology-Driven Innovations in Cisplatin Delivery for Head and Neck Cancers: Comprehensive Review

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Abstract: Cisplatin remains the cornerstone of chemoradiation in head and neck cancers, particularly oral squamous cell carcinoma (OSCC). Despite its proven efficacy, its clinical utility is limited by dose-dependent systemic toxicities—including nephrotoxicity, ototoxicity, neurotoxicity, and myelosuppression—as well as the frequent emergence of intrinsic and acquired resistance. Carboplatin, while less toxic, demonstrates reduced potency, underscoring the need for innovative therapeutic strategies.

Nanotechnology has emerged as a transformative approach, offering novel drug delivery systems that enhance tumor specificity, improve pharmacokinetics, and minimize off-target effects. Liposomes, polymeric nanoparticles, metallic nanocarriers, dendrimers, and exosome-based systems have shown promise in preclinical and early clinical studies. These nanocarriers not only improve cisplatin bioavailability but also address resistance mechanisms by bypassing efflux pumps, modulating DNA repair pathways, and enabling controlled, tumor-microenvironment-responsive drug release.

Importantly, nanocarrier-mediated cisplatin delivery can be integrated into multimodal therapy, combining with immunotherapy, targeted agents, and radiotherapy to achieve synergistic effects. Advances in biomarker-guided therapy, such as LC3B-II and other molecular predictors of cisplatin response, further strengthen the translational potential of nanotechnology in oral and head and neck cancers.

This review synthesizes current progress in nanotechnology-driven cisplatin delivery, explores molecular mechanisms of resistance, and highlights translational opportunities and challenges—including scalability, regulatory hurdles, and accessibility in resource-limited settings. By bridging conventional chemotherapy with cutting-edge nanomedicine, these innovations hold promise to redefine therapeutic outcomes in high-burden regions such as South Asia, where oral cancer remains a leading cause of cancer-related morbidity and mortality.

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I. INTRODUCTION

- Oral and head and neck cancers, particularly oral squamous cell carcinoma (OSCC), represent a significant global health burden, accounting for substantial morbidity and mortality worldwide. The incidence is especially high in South Asia, including countries such as India, where lifestyle-related risk factors such as tobacco smoking, smokeless tobacco use, betel quid chewing, and alcohol consumption are highly prevalent. In addition, infection with high-risk strains of human papillomavirus (HPV), particularly HPV-16, has emerged as an important etiological factor, especially in oropharyngeal cancers.
- A major challenge in the management of these malignancies is their late presentation, with a large proportion of patients diagnosed at advanced stages (stage III or IV). This significantly limits treatment options and contributes to poor survival outcomes. Standard treatment approaches typically involve a combination of surgery, radiotherapy, and chemotherapy, with the choice of modality depending on tumor stage, location, and patient factors. Among these, chemotherapy plays a crucial role, particularly in locally advanced, recurrent, or metastatic disease, as well as in organ-preservation strategies.
- Cisplatin, a platinum-based chemotherapeutic agent, has remained the backbone of treatment for head and neck

cancers for several decades. Its mechanism of action involves the formation of DNA crosslinks, leading to disruption of DNA replication and transcription, ultimately triggering apoptosis in rapidly dividing tumor cells. Additionally, cisplatin acts as a potent radiosensitizer, enhancing the effectiveness of radiotherapy by amplifying DNA damage. These properties make it an essential component of concurrent chemoradiation regimens, which are widely used in clinical practice.

- however, despite its therapeutic benefits, the clinical application of cisplatin is significantly limited by severe dose-dependent toxicities. These include nephrotoxicity, ototoxicity, neurotoxicity, and myelosuppression, which not only restrict the maximum tolerated dose but also adversely affect patient quality of life and treatment compliance. Furthermore, the development of resistance—either intrinsic or acquired—poses a major challenge, leading to treatment failure and disease recurrence. Resistance mechanisms are multifactorial and include enhanced DNA repair capacity, increased drug efflux, alterations in apoptosis pathways, and adaptation to the tumor microenvironment.

II. CISPLATIN IN ORAL AND HEAD & NECK CANCER

Cisplatin remains the most widely used chemotherapeutic agent in the management of oral and head and neck cancers. Its mechanism of action involves forming intra- and inter-strand DNA crosslinks, which disrupt replication and transcription, ultimately triggering apoptosis in rapidly dividing tumor cells. This ability to directly damage DNA makes cisplatin highly effective in combination with radiation therapy, where DNA damage is further amplified.

However, cisplatin therapy is constrained by several limitations. Tumor cells frequently develop resistance through enhanced DNA repair pathways, increased drug efflux mediated by transport proteins, and evasion of apoptosis via altered signaling cascades. Clinically, resistance manifests as reduced response rates and disease recurrence. In addition, cisplatin is associated with significant systemic toxicities, including nephrotoxicity, ototoxicity, neurotoxicity, and myelosuppression, which limit the maximum tolerable dose and compromise patient quality of life.

Despite these challenges, cisplatin continues to play a central clinical role as the backbone of chemoradiation protocols in oral squamous cell carcinoma and other head and neck cancers. It is used both in definitive therapy and as an adjuvant following surgery, with evidence supporting improved local control and survival outcomes.

Carboplatin, a second-generation platinum compound, is often employed as an alternative in patients who are unable to tolerate cisplatin due to renal impairment, advanced age, or comorbidities. While carboplatin offers a more favorable toxicity profile, its antitumor potency is generally lower, and

survival outcomes are not as robust compared to cisplatin. Nevertheless, it remains an important option in frail or medically compromised patients, ensuring that platinum-based therapy can still be delivered.

Emerging perspectives highlight the need to overcome cisplatin resistance and toxicity. Strategies under investigation include combination regimens with targeted agents, biomarker-guided patient selection, and nanotechnology-based drug delivery systems designed to enhance tumor specificity and reduce systemic exposure. These innovations aim to expand the therapeutic window of platinum compounds and integrate them more effectively into multimodal treatment approaches that include surgery, radiation, immunotherapy, and precision medicine.

III. MECHANISM OF ACTION OF CISPLATIN AND CARBOPLATIN

➤ *DNA Binding and Crosslinking:*

Cisplatin enters the cell and undergoes aquation, replacing chloride ligands with water molecules. The activated complex binds to DNA, forming intra-strand and inter-strand crosslinks, particularly at guanine bases. These crosslinks distort the DNA helix, blocking replication and transcription.

➤ *Activation of DNA Damage Response:*

The DNA lesions trigger cellular repair pathways, including nucleotide excision repair (NER). When repair is unsuccessful, persistent DNA damage activates checkpoint proteins (p53, ATM/ATR), leading to cell cycle arrest.

➤ *Induction of Apoptosis:*

Cisplatin-induced DNA damage activates pro-apoptotic signaling cascades. Mitochondrial pathways are engaged, with release of cytochrome c and activation of caspases, ultimately driving programmed cell death.

➤ *Generation of Reactive Oxygen Species (ROS):*

Cisplatin also increases oxidative stress within tumor cells. ROS contribute to DNA damage, protein denaturation, and lipid peroxidation, amplifying cytotoxicity.

➤ *Carboplatin Mechanism:*

Carboplatin acts through the same fundamental pathway—DNA crosslinking and apoptosis induction—but has slower activation kinetics due to its cyclobutane dicarboxylate leaving group. This results in reduced potency but also lower nephrotoxicity and ototoxicity compared to cisplatin.

IV. NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS

Nanotechnology has revolutionized drug delivery by enabling precise targeting, controlled release, and reduced systemic toxicity. In the context of cisplatin therapy for oral

and head & neck cancers, several nanocarrier platforms have been explored:

➤ *Liposomes*

- Liposomes are spherical vesicles composed of phospholipid bilayers that can encapsulate cisplatin, improving its solubility and circulation time.
- They protect the drug from premature degradation and reduce systemic toxicity by preferentially accumulating in tumor tissue via the enhanced permeability and retention (EPR) effect.
- Examples: Lipoplatin and Nanoplatin have demonstrated reduced nephrotoxicity and improved tumor uptake in preclinical and clinical studies.
- Liposomal cisplatin formulations are being tested in combination with radiotherapy and immunotherapy to enhance therapeutic synergy.

➤ *Polymeric Nanoparticles*

- Constructed from biodegradable polymers such as PLGA (poly-lactic-co-glycolic acid) and chitosan, these nanoparticles allow sustained and controlled release of cisplatin.
- They improve drug stability, enhance tumor penetration, and can be engineered to respond to stimuli such as pH or enzymes in the tumor microenvironment.
- Polymeric nanoparticles also enable co-delivery of cisplatin with chemosensitizers or gene therapy agents, offering a multimodal approach to overcome resistance.

➤ *Metallic Nanoparticles*

- Gold and silver nanoparticles conjugated with cisplatin enhance cytotoxicity through improved cellular uptake and localized drug release.
- They can be combined with photothermal therapy, where light irradiation heats the nanoparticles, further damaging tumor cells and increasing cisplatin efficacy.
- Metallic nanocarriers also serve as diagnostic tools, enabling theranostic applications (therapy + imaging).

➤ *Dendrimers and Micelles*

- Dendrimers are highly branched polymers with multiple functional groups, allowing high drug loading and precise control over release kinetics.
- Polymeric micelles are self-assembled structures that solubilize hydrophobic drugs like cisplatin, improving pharmacokinetics and reducing off-target toxicity.
- Both systems can be modified with targeting ligands (e.g., antibodies, peptides) to direct cisplatin specifically to tumor cells, minimizing collateral damage to healthy tissues.

➤ *Exosome-Based Delivery (Emerging)*

- Exosomes are natural extracellular vesicles that can be engineered to carry cisplatin.
- They offer biocompatibility, immune evasion, and intrinsic targeting properties.

- Early studies suggest exosome-mediated cisplatin delivery may overcome resistance and serve as a platform for biomarker-guided therapy.

V. MECHANISMS OF CISPLATIN RESISTANCE AND NANOTECHNOLOGY SOLUTIONS

Cisplatin resistance remains a major barrier to effective treatment in oral and head & neck cancers. Tumor cells employ multiple adaptive mechanisms, but nanotechnology-based drug delivery systems are being developed to counter these challenges.

➤ *DNA Repair Activation*

- Mechanism: Tumor cells upregulate DNA repair pathways (e.g., nucleotide excision repair, mismatch repair, homologous recombination) to remove cisplatin-induced DNA adducts.
- Nanotechnology Solution: Nanocarriers can co-deliver cisplatin with DNA repair inhibitors (e.g., PARP inhibitors), thereby sensitizing tumor cells and preventing repair of DNA damage.

➤ *Drug Efflux Pumps*

- Mechanism: Overexpression of ATP-binding cassette (ABC) transporters such as MDR1/P-glycoprotein actively pumps cisplatin out of cells, reducing intracellular drug concentration.
- Nanotechnology Solution: Nanoparticles bypass efflux pumps by entering cells via endocytosis, ensuring higher intracellular accumulation of cisplatin. Some nanocarriers are engineered to inhibit efflux transporter activity directly.

➤ *Tumor Microenvironment (Hypoxia, Acidity)*

- Mechanism: Hypoxic and acidic conditions within tumors reduce cisplatin efficacy and promote survival signaling.
- Nanotechnology Solution: pH-responsive nanoparticles release cisplatin selectively in acidic tumor environments, ensuring localized drug activity. Oxygen-generating nanocarriers are also being explored to counter hypoxia and enhance cisplatin sensitivity.

➤ *Apoptosis Evasion*

- Mechanism: Tumor cells downregulate pro-apoptotic proteins (e.g., Bax, caspases) and upregulate anti-apoptotic factors (e.g., Bcl-2), reducing cisplatin-induced cell death.
- Nanotechnology Solution: Co-delivery of cisplatin with pro-apoptotic agents or siRNA targeting anti-apoptotic genes can restore apoptosis pathways.

➤ *Autophagy and Extracellular Vesicles*

- Mechanism: Autophagy enables tumor cells to recycle damaged organelles and survive cisplatin stress. Extracellular vesicles (EVs) can export cisplatin out of cells, contributing to resistance.

- Nanotechnology Solution: Nanocarriers can deliver autophagy inhibitors alongside cisplatin, while exosome-based delivery systems exploit natural vesicles to enhance drug uptake and reduce efflux.

VI. PRECLINICAL AND CLINICAL EVIDENCE

- Preclinical Studies: Nanoplatin and polymeric nanoparticles show reduced nephrotoxicity, sustained release, and enhanced tumor uptake in oral cancer models. Metallic nanoparticles add photothermal synergy, while exosome-based delivery improves intracellular accumulation.
- Clinical Trials: Lipoplatin has demonstrated a safer profile with lower renal toxicity in solid tumors, including head and neck cancers. Early trials of nanoparticle cisplatin formulations report better tolerability, though larger studies are needed.
- Emerging Evidence: Combining cisplatin nanoparticles with immunotherapy enhances efficacy by coupling DNA damage with immune activation. Biomarker-guided and theranostic nanocarriers are under investigation for precision treatment and real-time monitoring.

VII. FUTURE DIRECTIONS

The future of cisplatin therapy in oral and head & neck cancers lies in integrating nanotechnology with precision medicine. Several promising avenues are emerging:

- Biomarker-Guided Nanotherapy: Advances in molecular profiling allow identification of biomarkers such as LC3B-II, which predict cisplatin resistance. Incorporating these markers into nanocarrier design enables patient-specific therapy, ensuring that cisplatin delivery is optimized for those most likely to benefit.
- Combination Strategies: Nanoparticle-based cisplatin formulations can be combined with checkpoint inhibitors (e.g., PD-1/PD-L1 antibodies) to achieve synergistic effects. This dual approach enhances DNA damage while simultaneously activating anti-tumor immunity, offering a powerful multimodal treatment option.
- Personalized Medicine: Tailoring nanocarriers to tumor genetics, signaling pathways, and microenvironmental conditions (hypoxia, acidity) will allow highly individualized therapy. Stimuli-responsive nanoparticles that release cisplatin only under specific tumor conditions represent a step toward true precision oncology.
- Theranostics: Development of nanocarriers that combine therapeutic delivery with imaging capabilities will enable real-time monitoring of drug distribution, tumor response, and resistance development.
- Challenges Ahead: Despite encouraging progress, significant barriers remain. High production costs, scalability issues, regulatory hurdles, and limited accessibility in low-resource settings pose challenges to widespread adoption. Addressing these concerns will be critical to translating laboratory innovations into clinical practice.

VIII. CONCLUSION

Nanotechnology-driven cisplatin delivery represents a paradigm shift in the management of oral and head & neck cancers. By enhancing drug targeting, reducing systemic toxicity, and overcoming resistance mechanisms, these innovations hold immense promise for advancing precision oncology. The integration of biomarker-guided approaches, combination therapies, and personalized nanocarrier systems could redefine treatment outcomes and improve survival rates.

However, successful translation requires rigorous clinical trials, regulatory validation, and strategies to ensure affordability and accessibility, particularly in high-burden regions such as South Asia where oral cancer remains a leading cause of morbidity and mortality. Bridging conventional chemotherapy with cutting-edge nanomedicine will not only improve therapeutic efficacy but also pave the way for a new era of individualized cancer care.

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