Head and Neck Cancer

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Definition

In head and neck cancer, early studies in nanotechnology have been designed to overcome the lack of the specificity of conventional chemotherapeutic agents to target cancer cells.

Nanoformulation will have a significant impact in the future of oncology treatment due to the potential to improve chemotherapeutic efficacy while reduce the toxicities by enhancing drug stability, solubility and bioavailability.

Further researches into higher-specificity tumor targets and more efficient drug delivery systems based on nanotechnology are needed in order to achieve the ultimate goal of personalized medicine.

1. Introduction

Head and neck cancer (HNC) is a complex multifactorial disease that originates in the epithelial layer of mucosa of the upper aerodigestive tract, including the oral cavity, pharynx and larynx showing microscopic evidence of squamous differentiation [1][2]. The main risk factors for HNC are tobacco smoke and alcohol consumption, as well as human papilloma virus (HPV) infection. Therapeutic decisions for patients with HNC are primarily based on clinical and pathological tumor stage [1]. It is estimated that 60% of the patients are diagnosed with advanced disease (stage III and IV) leading to low survival rates. In these cases, the treatment consists of surgical ablation followed by adjuvant radiation or chemoradiation (CRT) [3][4]. Despite recent advances in these therapeutic modalities, 50–60% of the patients develop regional relapses or distant metastasis within two years [5]. Patients with recurrent and/or metastatic disease have a median survival lower than 12 months [6], in part due to the limitations of conventional treatments, in particular the severe side effects that worsen quality of life [7].

Nanotechnology based therapy approaches have attracted great interest in oncology in recent years. Nanoformulations, a class of multifunctional materials with diameters of 1-100nm, can act as carriers for drugs and targeting ligands to optimized cancer therapy. The United States Food and Drug Administration (FDA) categorized nanomaterials based on the delivery vehicle or carrier as liposomal, polymeric, albumin-bounds, polymer-bounds, and inorganic particles [8]. These materials have been explored to overcome the biological barriers to cancer treatment due to their unique features such as a large surface area allowing conjugation to biologically active molecules, structural properties (optical, electronic, catalytic and magnetic) and a long time circulation in blood compared with small molecules. Furthermore, a plethora of nanomaterials has been developed to load sufficient drugs and accurately delivery to the tumor site with excellent biocompatibility, biodistribution and biodegradation resulting in lower systemic toxicity [9]. In HNC, early studies in nanotechnology have been designed to overcome the lack of the specificity of conventional chemotherapeutic agents to target cancer cells [10].

2. Development of Targeted Nanoparticles Systems for HNC Therapy

2.1. Interventions in HNC Using Chemotherapy Nanoformulations

Nanoparticles carrying different chemotherapy drugs have been identified in 9 HNC studies. Among the nanoparticles carrier chemotherapy (NCC) categories translated into clinical trials, the liposomes were the

most common complex observed, representing 6 among 9 papers, followed by 3 papers related to albumin-bound chemotherapeutics. Cisplatin (2/9), Doxorubicin (3/9) and Paclitaxel (4/9) were the chemotherapeutic agents used in these 9 studies. The posology, the administration mode and the timing of intervention were very heterogeneous among the studies. The concentrations of NCC solutions were not possible to calculate, as most of the articles did not use a standardized system to report their concentrations.

2.2. Tumor Response and Host Toxicity

Randomized clinical trials aiming to evaluate NCC for HNC therapy were not identified in the literature. The single arms clinical trials at Phases I and II showed small sample size (range 7–60) without control groups. It was not possible to evaluate survival outcomes with the Kaplan–Meier method and log-rank test, because these studies presented short period of follow-up (range 0.5–16 months) or the HNC patients underwent to definitive treatment after administration of NCCs.

2.3. Nanoformulation and Chemotherapeutic Agents Used in the Clinical Trials for HNC

2.3.1. Platinum-Based Chemotherapy

The platinum agents cisplatin and carboplatin are used both as single agents and to form the backbone for most combination regimens in HNC. Nanoparticles were combined with platinum-based chemotherapy in two studies: 1) Harrington *et al*. [10] treated ten patients with cisplatin combined with liposomes (200 mg/m^2) using two cycles every three weeks. Because of the lack of toxicity, the last eight patients received 260mg/m^2 every three weeks. Although the drug was well tolerated and the adverse effects were minimum, the partial response was only 11.1%. The high stability of the liposome may explain the lack of efficacy, once the slow drug release kinetics reduces the cisplatin bioavailability in the body. Thus, the drug concentration fails to exceed the threshold for therapeutic effects in patients. 2) Rosenthal *et al*. [11] treated 17 patients with cisplatin combined with liposomes concurrently with radiotherapy (60–72Gy in 6–7 weeks). The dose was escalated from 20–200mg/m^2 in six dose levels intravenously injected every two weeks. The estimated overall survival rate was 41% and disease-free survival was 25%. Among the adverse effects, liver toxicity or rash occurred in two patients. In addition, one patient showed elevated transaminases and neutropenia. Both studies observed low severe toxicities even at the highest cisplatin doses. It may be explained by the prolonged half-life of liposomal chemotherapy agents. Even though the first clinical trial [10] demonstrated a lack of efficacy, the second study[11] showed high therapeutic potential probably because of the association with radiotherapy.

2.3.2. Doxorubicin

Doxorubicin is an anthracycline drug for which the major side effect associated with its use is the cardiotoxicity. There are three clinical trials that used doxorubicin combined with NCC. 1) Harrington *et al*. [12] analyzed 18 patients after intravenous infusion of doxorubicin combined with liposomes. Consecutive groups of three patients received escalating doses starting at 10mg/m^2 and increasing through 15mg/m^2 to 20mg/m^2. The partial response to this treatment was observed in 57% of patients without severe side effects. 2) Caponigro *et al*. [13] analyzed 24 patients submitted to neoadjuvant therapy with radiation and/or chemotherapy using doxorubicin combined with pegylated liposome. The compound was administered at the initial dose of 30mg/m^2 and subsequently escalated by 5mg/m^2 per step. Partial response was 33% (95% CI: 16–55%), which is similar to the doxorubicin as a single agent. Three patients develop severe adverse effects (grade 3 and 4) with stomatitis, neutropenia, and 14 showed skin toxicity. 3) Faivre *et al*. [14] analyzed 24 patients who received doxorubicin conjugated with pegylated liposomes by intravenous infusion at an initial dose of 35mg/m^2, every three weeks. Four patients showed complete clinical response (17%; 95% CI 0.5–32%). The time observed for disease-free survival and overall survival were 3.5 and 4.6 months, respectively. Two patients showed severe adverse effects such neutropenia, however none of them had skin, digestive, cardiac or hepatic toxicities. This study shows that the high concentration of drugs increases severe adverse effects but not necessarily improve the efficacy of the

clinical response.

2.3.3. Paclitaxel

Paclitaxel (know as Taxol) is a microtubule-stabilizing drug that induces mitotic arrest, which leads to cell death. However, recent evidence demonstrates that intratumoral concentrations of single paclitaxel are too low to cause mitotic arrest and result in multipolar divisions instead. There are four clinical trials using paclitaxel associated with nanoparticles to increase drug efficacy. 1) Damascelli *et al*. [15] evaluated 29 patients undergone to three treatment cycles and four-weeks interval using paclitaxel conjugated to albumin nanoparticles administered by percutaneous catheterization of the neck vessels. The starting dose of 120mg/m^2 was progressively increased by 30mg/m^2 at each subsequent level. The dose-limiting toxicity was myelosuppression. Three patients had complete clinical responses and 19 partial responses. 2) In another Phase I clinical trial conducted by the same group, Damascelli et al. [16] analyzed 23 previously untreated HNC patients with paclitaxel conjugated albumin nanoparticles with the same posology. Eighteen patients (78%) had a clinical and radiologic response (complete: 26%; partial: 52%), three patients (13%) had stable disease and two cases (9%) showed disease progression. The adverse effects were hematologic (grade 3) in two patients (8.6%) and neurologic (grade 4) in two patients. 3) These scientists in 2007 expanded the study to 60 patients in a Phase II clinical trial [17], using an initial dose of 230mg/m^2 and subsequently a reduced dose of 150mg/m^2 of paclitaxel bounded albumin nanoparticles. Complete or partial responses were observed in 45 of 60 treated patients (75%). Seven patients (11.67%) had stable disease and eight (13.33%) showed disease progression. High-grade bone marrow depression was rare, however, the reduction in the dose eliminated this specific toxicity without losing efficacy. 4) Strieth *et al*. [18] performed a Phase I/II clinical trial and analyzed seven HNC patients previously exposed to surgery and/or radio-chemotherapy. They were treated with paclitaxel in a liposome formulation and, after three infusions of 0.55mg/kg or 1.1mg/kg, the tumor volume revealed stable disease in four cases and the disease progressed in only one patient. The applied doses in liposomal formulation are far below the doses of conventional paclitaxel usually given in clinical practice, which may also be a reason for the favorable safety profile. Mild adverse events were observed, such as fatigue, chills and hypertension. These clinical trials showed evidences that paclitaxel nanoformulation has lower systemic toxicity compared with the other clinical trials testing free formulations of paclitaxel. Unfortunately, none of these studies showed a proper control group.

3. Conclusions

In HNC, chemotherapy is usually used alongside surgery and/or radiotherapy in advanced cases generating severe side effects and poor quality of life. The most common chemotherapeutic agents used are platinum-based drugs (cisplatin or carboplatin) and combinations with taxanes (e.g., docetaxel) or 5-fluorouracil. However, conventional delivery methods of chemotherapeutic agents have several limitations: Firstly, some drugs have poor solubility and low bioavailability and contain toxic solvents in their formulation. Secondly, they have a short circulation time because of their physiological instability, degradation, and clearance. Thirdly, the non-specific distribution of the drugs limits the concentration achieved in the tumor and causes harmful side effects because of their unwanted accumulation in healthy tissues. A combination of chemotherapeutic agents improved therapeutic response for patients with advanced HNC but no effect on overall survival was observed.

Therefore, advanced drug delivery systems based on nanotechnology and a tumor-targeted strategy, hold considerable potential to enhance chemotherapeutic efficacy, representing a hot topic in cancer therapy for future investigations. Even though most approaches are still in the preclinical stages, they have shown tremendous potential to fulfill the need for viable alternative cancer therapies. Further researches into higher-specificity tumor targets and more efficient NCC are needed, including complex modifications to enhance the antitumor efficacy in order to achieve the ultimate goal of personalized medicine.

It was noticeable the studies limitations due to constraints on research design or methodology. These factors may impact the findings to demonstrate the efficacy of NCC for HNC tumor response due to the lack

of clinical studies with proper gold standard controls. Besides, the short-term follow-up and the use of co-concurrent therapies, such as radiotherapy, generate bias to determine the real impact of these strategies in the success of the treatment. However, in general, all the studies showed that nanotechnologies were not associated with increased severe adverse effects in HNC. We conclude that this topic demands future and well-designed experimental studies with proper randomized clinical trials.

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Keywords

nanoparticles;targeted therapeutics;head and neck cancer;selective drug delivery