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Current Status of Induction Chemotherapy in Locally Advanced Nasopharyngeal Carcinoma

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Abstract

Nasopharyngeal carcinoma (NPC) has a unique endemic distribution in the world, with the highest incidence rate in South China, Southeast Asia and North Africa. About 70% of newly diagnosed nasopharyngeal carcinoma patients suffer from locally advanced diseases. The current methods of radiotherapy and chemotherapy include synchronous radiotherapy and chemotherapy, induction chemotherapy, and adjuvant chemotherapy. Induction chemotherapy has better tolerance, so higher drug concentrations can be used to improve the survival rate of locally advanced nasopharyngeal carcinoma patients. Induction chemotherapy can eliminate micro metastatic diseases early. This article provides a review of the application of induction chemotherapy in the treatment of locally advanced nasopharyngeal carcinoma.

Keywords: locally advanced nasopharyngeal carcinoma, induction chemotherapy

1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor originating from the nasopharyngeal epithelium, predominantly occurring in the pharyngeal recess and posterior wall of the nasopharyngeal roof. Compared with other head and neck tumors, NPC exhibits unique geographical distribution characteristics and ethnic predisposition, with high-incidence areas in Hong Kong, Guangdong, and Guangxi regions of China (Torre L A, Bray F, Siegel R L, et al., 2015). Due to its occult anatomical location and biological features characterized by high invasiveness and metastatic potential, most cases are diagnosed as locally advanced disease at initial detection. Given the anatomical proximity of the nasopharynx to the skull base and the fact that the vast majority of NPC cases are poorly differentiated squamous cell carcinomas, radiotherapy is generally the primary treatment modality (Chen Y P, Chan A T C, Le Q T, et al., 2019; Lee A W M, Ng W T, Chan J Y W, et al., 2019; Lee V H, Lam K O, Chang A T, et al., 2018; Yoshizaki T, Ito M, Murono S, et al., 2012). While the application of concurrent chemoradiotherapy and intensity-modulated radiation therapy (IMRT) has significantly improved survival rates for early-stage NPC patients, therapeutic outcomes for locally advanced cases remain suboptimal, with a 5-year overall survival rate of approximately 50%. Previous studies have reported (Zhang L, Chen Q Y, Liu H, et al., 2013; Mao Y P, Xie F Y, Liu L Z, et al., 2009) that 15% to 54% of patients with locally advanced nasopharyngeal carcinoma (NPC) are prone to local recurrence, primarily influenced by tumor stage, cranial nerve involvement, and histological type. The 5-year distant metastasis rate ranges from 20% to 35%, reaching 60% to 80% in N3 patients (Au K H, Ngan R K C, Ng A W Y, et al., 2018; Lee A W, Tung S Y, Ngan R K, et al., 2011). Therefore, controlling the primary tumor and preventing distant dissemination remain critical challenges in the management of locally advanced NPC. Numerous phase III clinical trials (Wu X, Huang P Y, Peng P J, et al., 2013; Colevas A D, Yom SS, Pfister D G, et al., 2018; Chen Y, Sun Y, Liang S B, et al., 2013) have demonstrated that concurrent chemoradiotherapy (CCRT) can improve the overall survival (OS) and disease

control rate (DCR) in patients with locally advanced nasopharyngeal carcinoma (NPC). Currently, CCRT has been recommended by the National Comprehensive Cancer Network (NCCN) guidelines as the standard treatment strategy for stage III-IVb NPC.

Combining several cycles of systemic chemotherapy with concurrent chemoradiotherapy (CCRT) is a potential approach to address the high distant metastasis rate in locally advanced nasopharyngeal carcinoma (NPC). However, previous studies have indicated that sequential adjuvant chemotherapy following CCRT is associated with a high incidence of toxic side effects (approximately 60%) (Chen L, Hu CS, Chen XZ, et al., 2012), poor patient compliance, and no studies have demonstrated that adjuvant chemotherapy provides additional survival benefits beyond standard CCRT (Chen L, Hu CS, Chen XZ, et al., 2012; Chi KH, Chang YC, Guo WY, Leung MJ, Shiau CY, Chen SY, et al., 2002; Kwong DL, Sham JS, Au GK, Chua DT, Kwong PW, Cheng AC, et al., 2004; Chen L, Hu CS, Chen XZ, Hu GQ, Cheng ZB, Sun Y, et al., 2017). Consequently, sequential adjuvant chemotherapy after CCRT is not the optimal choice. In contrast to adjuvant chemotherapy administered after concurrent chemoradiotherapy (CCRT), induction chemotherapy delivered prior to CCRT has demonstrated superior benefits in multiple studies (Chen L, Hu CS, Chen XZ, Hu GQ, Cheng ZB, Sun Y, et al., 2017; Sun Y, Li WF, Chen NY, Zhang N, Hu GQ, Xie FY, et al., 2016; Cao SM, Yang Q, Guo L, Mai HQ, Mo HY, Cao KJ, et al., 2017). Compared to adjuvant chemotherapy, induction chemotherapy followed by CCRT offers better tolerability for patients with locally advanced nasopharyngeal carcinoma (NPC), ensures completion of planned chemotherapy cycles and drug dosages, and enables early eradication of micro-metastases. Consequently, the treatment strategy of induction chemotherapy followed by CCRT is clinically feasible and has been widely adopted in high-incidence regions of NPC in China.

2. Theoretical Basis of Induction Chemotherapy for Nasopharyngeal Carcinoma

Induction Chemotherapy (IC) refers to chemotherapy administered prior to radiotherapy, typically consisting of 2-3 cycles. It offers the following advantages: (1) Better patient compliance and tolerability: Before radiotherapy, patients are generally in better overall condition, enabling almost all patients to complete the full planned induction cycles. (2) Optimal drug delivery: Tumor vasculature has not yet developed fibrosis prior to radiotherapy, allowing chemotherapeutic agents to achieve sufficient concentrations at the tumor site (Imaizumi N, Monnier Y, Hegi M, et al., 2010; Gang W, Peng X U, Jinyi L., 2016). (3) Rapid symptom relief and psychological benefits: For patients with T3-4 tumors or lymph node metastases, IC can rapidly reduce tumor burden, alleviate clinical symptoms, create favorable conditions for radiotherapy, reduce psychological distress, and improve quality of life. (4) Radiotherapy optimization: Tumor volume reduction through IC enables smaller radiation fields, reduced radiation doses, minimized treatment-related side effects, and better protection of organs at risk. (5) Elimination of subclinical metastases: Chemotherapy helps eradicate subclinical metastatic lesions in the body, thereby improving distant metastasis-free survival rates (Ke L R, Xia W X, Qiu W Z, et al., 2017).

3. The Selection of Induction Chemotherapy Regimens

At present, the main induction chemotherapy regimens are based on platinum, such as TP regimen (paclitaxel-like drugs + platinum), PF regimen (5-fluorouracil + platinum), TPF regimen (paclitaxel-like drugs + 5-fluorouracil + platinum), GP regimen (gemcitabine + platinum), TPC regimen (paclitaxel-like drugs + platinum + capecitabine), etc. Usually, 2 to 3 cycles of treatment are administered.

3.1 PF Regimen

The PF regimen, a classic induction chemotherapy protocol for head and neck cancers, has been extensively studied. Zhang et al conducted a meta-analysis of 10 clinical trials, demonstrating that PF induction chemotherapy combined with radiotherapy significantly improved the 5-year overall survival rate (Na Z, Ping L I & Zhu-Mei L., 2010). A retrospective study by Qiu et al included 240 patients with locally advanced nasopharyngeal carcinoma (Qiu W, Huang P, Shi J, et al., 2015). The induction group consisted of 117 patients who received PF regimen as induction chemotherapy combined with intensity-modulated conformal radiotherapy, and 123 patients who received concurrent radiochemotherapy combined with cisplatin+5-FU adjuvant chemotherapy. The results indicate that there is no statistically significant difference in the 5-year overall survival rate and distant metastasis free survival rate between induction chemotherapy and concurrent chemoradiotherapy. However, the incidence of grade 3 and 4 gastrointestinal reactions and bone marrow suppression in the concurrent chemoradiotherapy group is significantly higher than that in induction hemotherapy. A retrospective study on PF induced chemotherapy showed (Boscolorizzo P, Tirelli G, Mantovani M, et al., 2015) that the 5-year distance control rate (DCR) and local control rate (LRC) were 82.2% and 80%, respectively 1%. The 5-year OS and disease-free survival (EFS) rates were 72 0 and 66 7%, this study also confirms the significant value of the PF scheme.

3.2 TP Regimen

The TP chemotherapy regimen typically consists of paclitaxel-based chemotherapeutic agents and platinum-based chemotherapeutic agents. In recent years, TP regimen has been commonly used in the treatment of nasopharyngeal carcinoma. In 2009, a phase II clinical trial (Hui E P, Ma B B, Leung S F, et al., 2009), which included 65 newly treated patients with locally advanced nasopharyngeal carcinoma. They were divided into TP Regimen (docetaxel + cisplatin) induction chemotherapy combined with concurrent chemoradiotherapy group and simple concurrent chemoradiotherapy group. The study confirmed that TP regimen induction chemotherapy can improve the progression free survival (PFS) and overall survival rate of locally advanced nasopharyngeal carcinoma patients. Xie et al compared TP induced chemotherapy with PF induced chemotherapy in 2015 (Yalin X, Jianming X, Oncology D O, et al., 2015). The research results showed that TP regimen induced chemotherapy could significantly prolong the median progression free survival time, and the difference was statistically significant (P=0.044), while there was no significant difference in the toxic side effects between the two. This also confirms that the TP regimen can be used as one of the induction chemotherapy options for locally advanced nasopharyngeal carcinoma.

3.3 TPF Regimen

He et al. confirmed that synchronous radiotherapy and chemotherapy after TPF induction chemotherapy can significantly improve 2-year OS and DFS in locally advanced nasopharyngeal carcinoma patients compared to concurrent radiotherapy and chemotherapy, with statistical significance (P<0.05) (H A J., 2011). Although the acute toxicity response rate of patients in the TPF induction chemotherapy group was higher, symptoms were mostly relieved after treatment. However, there were differences in the results of a randomized controlled study (Jin T, Qin W F, Jiang F, et al., 2019), which compared TPF induced chemotherapy combined with concurrent chemoradiotherapy and PF induced chemotherapy combined with concurrent chemoradiotherapy and confirmed that there was no statistically significant difference in 3-year OS and DFS between the two groups, and the incidence of grade 3-4 adverse reactions in the TPF induced chemotherapy group was significantly higher than that in the PF group. POSNER et al compared TPF induction chemotherapy with PF induction chemotherapy followed by sequential concurrent radiochemotherapy (POSNER M R, HERSHOCK D M, BLAJMAN C R, et al., 2007). The results showed that compared with patients receiving PF treatment, patients receiving TPF treatment had significantly improved OS and an increased incidence of severe (grade III and IV) bone marrow suppression. The study conducted by PENG H et al (2021) included 855 patients with locally advanced nasopharyngeal carcinoma. Among them, 395 cases (46.2%), 258 cases (30.2%), and 202 cases (23.6%) received TPF, TP, and PF induction chemotherapy regimens, respectively, and underwent a 10-year follow-up. The results demonstrated that, in terms of improving overall survival (OS) for stage III–IVa nasopharyngeal carcinoma patients, the TPF+CCRT and TP+CCRT groups exhibited superior 10-year OS compared to the PF+CCRT group.

3.4 GP Regimen

Gemcitabine, a cytidine analogue chemotherapeutic agent, has demonstrated favorable efficacy in nasopharyngeal carcinoma (NPC) in recent years. Studies by Zhao et al confirmed that the GP induction chemotherapy regimen (gemcitabine + platinum) improves overall survival (OS) and disease-free survival (DFS) compared to the PF regimen (5-fluorouracil + cisplatin) (Zhao L, Xu M, Jiang W, et al., 2017; Yang YQ, Qu XM, Z X, et al., 2018). Jamshed et al reported a 5-year overall survival rate of 71% for patients treated with GP induction chemotherapy combined with chemoradiotherapy (Jamshed A, Hussain R & Iqbal H., 2014). A 2017 phase II clinical trial (Wu M Y, Ou D, He X, et al., 2017) involving 112 patients with locally advanced NPC who received GP induction chemotherapy followed by intensity-modulated radiotherapy (IMRT) demonstrated 5-year survival rate and distant metastasis free rate of 82.1% and 89.0%, respectively. These findings further underscore the therapeutic value of the GP regimen combined with IMRT for locally advanced NPC.

3.5 TPC Regimen

Xiang et al. compared the efficacy of the TPC regimen (paclitaxel + platinum + capecitabine) versus the PF regimen (5-fluorouracil + cisplatin) for induction chemotherapy (Li WZ, Lv X, Hu D, et al., 2022). The results showed that the TPC regimen group achieved a significantly superior 3-year failure-free survival (FFS) rate compared to the PF regimen group. Additionally, the TPC regimen significantly reduced both distant metastasis risk and local recurrence risk relative to the PF regimen. Safety analysis revealed that the TPC regimen did not increase treatment-related toxicities compared to the PF regimen.

4. The Application of Induction Chemotherapy in Combination with Molecularly Targeted Agents

With the in-depth study of epidermal growth factor receptor (EGFR) and the continuous exploration of its signaling pathway, this signaling pathway is believed to be closely related to factors such as tumor proliferation and radiotherapy sensitivity. At present, drugs targeting EGFR mainly include gefitinib, rituximab, and cetuximab, among which rituximab has been approved for combined treatment with radiotherapy in stage III/IV

EGFR positive nasopharyngeal carcinoma patients.

A multicenter clinical study (Lu Y, Chen D, Liang J, et al., 2019) investigating Nimotuzumab combined with the PF regimen as induction therapy for locally advanced nasopharyngeal carcinoma found that, compared to TPF induction chemotherapy, there was no significant difference in the efficacy of primary nasopharyngeal lesions or overall response (primary lesions + cervical lymph nodes) between the two groups. However, the Nimotuzumab group demonstrated a higher cervical lymph node response rate (CR+PR) (81% vs. 60%, P=0.036). Additionally, Nimotuzumab reduced the incidence of adverse reactions and improved patients' tolerance to concurrent chemoradiotherapy (CCRT). In addition, multiple retrospective studies (Yang Z, Zuo Q, Liu R, et al., 2023; Jiang D, Cao J, Guo L, et al., 2023) have shown that receiving CCRT and NTZ treatment after induction chemotherapy can effectively improve the objective efficacy and 5-year progression free survival rate of locally advanced nasopharyngeal carcinoma patients compared to receiving only induction chemotherapy and CCRT.

5. The Application of Induction Chemotherapy in Combination with Immunotherapy Drugs

The importance of immunotherapy in the treatment of nasopharyngeal carcinoma is increasingly prominent. Its unique advantage lies in its ability to accurately target tumor cells, effectively recognize and attack tumors by activating or enhancing the patient's own immune system, thereby reducing damage to normal cells. In addition, immunotherapy can bring potential long-term survival benefits, providing a new treatment approach for patients who have failed traditional treatments such as radiotherapy and chemotherapy or have relapsed or metastasized, helping to overcome tumor drug resistance. Meanwhile, immunotherapy can also be combined with chemotherapy and radiotherapy to exert synergistic effects and improve overall treatment outcomes.

In the treatment of recurrent/metastatic nasopharyngeal carcinoma, PD-1 monoclonal antibody drugs have been widely used and recommended by guidelines in China. The results from Mai et al showed that the combination of trastuzumab and GP chemotherapy has significant efficacy, reducing the risk of patient death by 39%, achieving a 5-year OS rate of 52.0%, and being safe and controllable (Mai HQ, Chen QY, Chen D, et al., 2023). In addition, tislelizumab has been approved for first-line treatment of recurrent or metastatic nasopharyngeal carcinoma based on the results of a Phase III study (Yang Y, Pan J, Wang H, et al., 2023). This study demonstrated that compared to placebo combined with GP chemotherapy, tislelizumab plus GP chemotherapy significantly prolonged progression-free survival (PFS) in patients. A trend toward improved overall survival (OS) was also observed, while maintaining a safety profile comparable to placebo combined with chemotherapy.

In the treatment of locally advanced nasopharyngeal carcinoma, the application of PD-1 monoclonal antibodies has also shown progress. A study by Liu et al. (2024) first demonstrated that adding neoadjuvant and adjuvant immunotherapy based on the programmed death receptor-1 (PD-1) monoclonal antibody toripalimab to concurrent chemoradiotherapy (CCRT) significantly improved survival outcomes in high-risk locally advanced nasopharyngeal carcinoma patients. Compared to the placebo-plus-CCRT control group, the toripalimab-plus-CCRT group showed a markedly higher 2-year PFS rate (92.0% vs. 74.0%), reducing the risk of disease progression or death by 60%, along with a significantly improved 3-year overall survival rate (99.0% vs. 90.0%).

6. Prospect

Induction chemotherapy demonstrates superior overall survival (OS) and disease-free survival (DFS) compared to adjuvant chemotherapy in nasopharyngeal carcinoma. However, due to insufficient total sample size, variability in chemotherapy regimens, and individual heterogeneity, the optimal induction chemotherapy protocol remains inconclusive. Although the ideal regimen is yet to be defined, its therapeutic value in locoregionally advanced nasopharyngeal carcinoma remains undeniable. With the deepening of clinical research, emerging evidence is driving induction chemotherapy from standardized to personalized approaches. Future large-scale randomized phase III clinical trials are warranted to further clarify its role and establish the optimal induction chemotherapy strategy for locoregionally advanced nasopharyngeal carcinoma. In recent years, immunotherapy has demonstrated significant potential in nasopharyngeal carcinoma treatment. Neoadjuvant immunotherapy enhances therapeutic response rates and survival outcomes by activating anti-tumor immune responses prior to radiotherapy, while reducing post-radiotherapy risks of recurrence and metastasis. Recent studies reveal that combining neoadjuvant immunotherapy with chemotherapy significantly improves complete response rates in patients with locoregionally advanced nasopharyngeal carcinoma, without substantially increasing treatment-related toxicities. Looking forward, neoadjuvant immunotherapy is poised to become a cornerstone of nasopharyngeal carcinoma management, offering enhanced therapeutic efficacy, reduced treatment-associated adverse effects, and improved quality of life for patients.

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