Progress and controversy for the role of chemotherapy in nasopharyngeal carcinoma

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Abstract

Since the publication of Intergroup Study 0099, representing a superiority of concurrent chemoradiotherapy with cisplatin followed by adjuvant chemotherapy to radiotherapy alone for the treatment of locoregionally advanced nasopharyngeal carcinoma, an efficacy of concurrent setting of cisplatin-based chemotherapy with radiotherapy has been repeatedly validated. In meanwhile, the role of adjuvant part of the protocol has been controversial. There is an increasing evidence for the positive role of neoadjuvant chemotherapy with following concurrent chemoradiotherapy whereas favorable contribution was not proven in the last century. This article reviews the role of chemotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma.

Key words: head and neck, radiation oncology, H & N-RadOncol, nasopharyngeal carcinoma

Introduction

Nasopharyngeal carcinoma (NPC) is a unique malignancy with respect to epidemiology, etiology and clinical presentation. Epidemiologically, Southern China and South-East Asia are endemic areas. Etiologically, Epstein–Barr virus (EBV) is a causative agent in most cases. Clinically, it is highly invasive and metastatic, but sensitive to both chemotherapy and radiotherapy (1,2). However, these representative features of NPC are mainly for undifferentiated type, categorized to WHO-II or -III NPC (2,3). Contribution of EBV to carcinogenesis of differentiated type, WHO-Type I NPC, is considered to have similar characteristics to generally accepted head and neck cancers and has been controversial. Thus, WHO-I NPC poses more locoregionally aggressive and less chemoradiosensitive properties.

Most of clinical trials are undertaken in endemic area where the proportion of WHO-I disease is near zero. First randomized trial that showed the superiority of chemoradiotherapy (CRT) to radiotherapy (RT) alone was published in 1998, and until recently, the CRT protocol used in this Intergroup Study 0099 (IGS 0099 CRT) has been a mainstay in NPC treatment scene. The Intergroup Study 0099 Trial, undertaken in non-endemic area for NPC, showed a benefit of adding chemotherapy to RT (4). However, there were controversies regarding the results of the trial and the plethora of studies has been conducted to approach the question.

In this review, we address the recent progress and controversies in the treatment of NPC in relation with IGS0099 study.

The role of chemotherapy in recent NPC treatment scene

The meta-analysis of chemotherapy in NPC (MAC-NPC) study of the MAC-NPC Collaborative Group is the only meta-analysis that used an individual patient data design (5). The MAC-NPC study included eight randomized trials, which had completed accrual before end of 2001 and thus excluded the more recent trials from Asia. The meta-analysis investigated in four trials with neoadjuvant chemotherapy [plus adjuvant chemotherapy (AC) in one trial], three trials with concurrent chemoradiotherapy (CCRT) (plus AC in two trials) and one trial with AC alone. The authors concluded an absolute survival benefit of addition of chemotherapy at 5 years was 6% (from 56 to 62%) (5).

Although advantage of NAC was sporadically reported from accumulation of prospective, retrospective studies and meta-analysis, it is
currently reasonable to conclude that most validated regimen is in the concurrent setting (5). Cisplatin has been a key agent and thus cisplatin-based regimen has been repeatedly investigated and shown to be effective (6,7).

After the pivotal IGS 0099 study, concurrent chemotherapy during the initial RT should be the treatment core. Either weekly (30–40 mg/m²) or 3-weekly (100 mg/m²) use of cisplatin was similarly effective. However, IGS 0099 CRT showed only 63% of patients completed all three course of concurrent 100 mg/m² cisplatin treatment, indicating considerable toxic effect of 3-weekly high-dose cisplatin in concurrent setting (7). Feasibility of IGS 0099 CRT was also investigated in several studies. Tan et al. (8) concluded that it was feasible in the Asian context. Contrary, Chua et al. (9) indicated that CCRT improves locoregional control, but failed to detect any impact on distant failure and survival, and suggested that we should be prudent in extrapolating the findings of the IGS to Chinese patients. Isobe et al. (10) concluded that physicians should act with discretion in applying the IGS 0099 CRT for locoregionally advanced Japanese NPC patients because of severe acute adverse events such as skin reactions, pharyngitis, dysphagia and poor compliance, which lead to unsatisfactory outcomes. A Singapore group explored the feasibility and efficacy of a CCRT protocol, similar to that used in the IGS, but the chemotherapy regimen was modified from the original 0099 CRT. Patients in CRT arm received concurrent cisplatin (25 mg/m²) on Days 1–4) on Weeks 1, 4 and 7 of RT whereas concurrent cisplatin of 100 mg/m² was infused on Days 1 of Weeks 1, 4 and 7 in original 0099 CRT. Similarly, adjuvant cisplatin was also modified to 20 mg/m² on Days 1–4 and fluorouracil (1000 mg/m²) on Days 1–4) every 4 weeks (weeks 11, 15 and 19). The median follow-up time was 3.2 years. The hazard ratio (HR) for disease-free survival was 0.57 [95% confidence interval (CI), 0.38–0.87; P = 0.0093]. The 2- and 3-year overall survival (OS) rates were 78 and 85% and 65 and 80% for RT alone and CRT, respectively. The HR for OS was 0.51 (95% CI, 0.31–0.81; P = 0.0061) (11).

Dose intensity

A total dose of cisplatin used in IGS 0099 CRT is up to 540 mg/m², of which 300 mg/m² was included in CCRT setting. CCRT is the most important and integral part of the treatment in patients with locoregionally advanced NPC, which is mostly accompanied with acute and late dose limiting toxicities. Thus, it is quite important to set appropriate dose intensity of chemotherapy during the concurrent CRT.

Loong et al. (12) reported that patients with Stage II or III NPC who received >5 cycles of cisplatin, which corresponds to cumulative dose of 200 mg/m², had a significantly better OS than those with ≤5 cycles. Interestingly, there are some reports that implicate the priority of cumulative dose of 200 mg/m² cisplatin in CCRT for head and neck squamous cell carcinoma as well as alternating CRT for locoregionally advanced NPC (13–15).

Radiation alone arm

Current practice of adding concurrent-AC to RT for treating advanced NPC is based on the Intergroup-0099 Study published in 1998. However, the outcome for the RT-alone group in that trial was substantially poorer than those in other trials (16).

Lee et al. conducted the same study as IGS 0099 with randomly assigned 176 patients on RT arm and 172 patients on CRT arm. Addition of chemotherapy significantly improved the 5-year failure-free rate (CRT vs. RT: 67 vs. 55%; P = 0.014) and 5-year progression-free survival (CRT vs. RT: 62 vs. 53%; P = 0.035). Cumulative incidence of acute toxicity increased with chemotherapy by 30% (CRT vs. RT: 83 vs. 53%; P < 0.001), but the 5-year late toxicity rate did not significantly increase (CRT vs. RT: 30 vs. 24%; P = 0.30). Deaths by disease progression were reduced by 14% (CRT vs. RT: 38 vs. 24%; P = 0.008), but 5-year OS was not improved (CRT vs. RT: 68 vs. 64%; P = 0.22; HR of CRT was 0.81, 95% CI of 0.58–1.13). They analyzed that it was attributable to the increase of deaths due to toxicity or incidental causes by 7% (CRT vs. RT: 1.7% and 8.1 vs. 3.4%, respectively; P = 0.015).

They concluded that the surprisingly poor outcome of the control arm of IGS may have resulted by chance, and that more randomized trials are essential to establish the role of combined chemotherapy and RT (17).

Adjuvant chemotherapy

The role of AC in NPC has been receiving negative review. Nevertheless, AC was included in IGS 0099 CRT, and there have been skeptical opinions for the role of adjuvant setting part of the regimen (18,19). A meta-analysis did not demonstrated any improvements in survival rates by the addition of AC (20). Chen et al. aimed to assess the contribution of AC to CCRT vs. CRT alone. They conducted an open-label Phase 3 multicenter randomized controlled trial for the patients with non-metastatic Stage III or IV (except T3-4N0) NPC at seven institutions in China. Patients were randomly assigned to the CCRT plus AC group (n = 251) and to the CCRT alone group (n = 250). Patients in both groups received 40 mg/m² cisplatin weekly up to 7 weeks, concurrently with RT. The CCRT plus AC group subsequently received 80 mg/m² adjuvant cisplatin and 800 mg/m² per day fluorouracil every 4 weeks for three cycles. The estimated 2-year failure-free survival rate was 86% (95% CI 81–90) in the CCRT plus AC group and 84% (78–88) in CCRT only group (HR 0.74, 95% CI 0.49–1.10; P = 0.13). It is not clear why they excluded T3-4N0 patients. But in this series, adjuvant cisplatin and fluorouracil chemotherapy did not significantly improve failure-free survival after CCRT in locoregionally advanced NPC. They concluded that longer follow-up was needed to fully assess survival and late toxic effects, but such regimens should not, at present, be used outside well-designed clinical trials (19).

NAC + CCRT

Advantage of NAC setting has not been established in combination with RT alone (21,22). But, the role of NAC in combination with CCRT has not yet been confirmed. Kong et al. conducted NAC + CCRT for 32 patients with Stage III NPC and 64 patients with non-metastatic Stage IV NPC. All patients received TPF (docetaxel 75 mg/m², cisplatin 75 mg/m² and 5-FU 2500 mg/m² every 3 weeks for three cycles), followed by cisplatin 40 mg/m² per week concurrently with either three-dimensional conformal RT or intensity-modulated radiation therapy (IMRT). With a median follow-up of 32.9 months, the 3-year OS rates were 94.8% (95% CI, 87.6–100%) and 90.2% (95% CI, 81.8–98.6%) for the Stage III group and the IVA/JVB group, respectively. The 3-year progression-free survival, distant metastasis-free survival and local progression-free survival rates were 78.2% (95% CI, 64.6–91.8%), 90.5% (95% CI, 79.7–100%) and 93.9% (87.1–100%), respectively, for Stage III group and 85.1% (95% CI, 75.1–95.1%), 88% (95% CI, 78.6–97.4%) and
100%, respectively, for Stage IVA/IVB group. Grade 3/4 neutropenia was observed for 64 patients (55.2%) and nausea for 23 patients (19.8%) (23). Similarly, taxane-based NAC was expected to have positive effect for the control of metastatic disease (24,25).

Moreover, for patients with intracranial invasion, replanning of delineation for tumor volume after NAC improves local disease control and reduce IMRT associated adverse events.

Using NAC and replanning intensity-modulated RT for NPC with intracranial invasion to protect critical normal tissue. Thus, revival of NAC, with the combination of CCRT, would be studied in many clinical trials (26).

However, a meta-analysis found no differences between NAC + CCRT and CCRT for OS, locoregional failure- and distant metastasis-free survival. Therefore, at present, it is unclear whether the addition of NAC to CCRT improves survival rates compared with CCRT (27).

**Alternating CRT**

Fuwa et al. (28) reported the treatment results of alternating CRT in Aichi Cancer Institute, characterized by a decreased total dose of CDDP (540 mg/m² in the Intergroup 0099 vs. 300 mg/m² in Aichi), a shorter treatment period (130 days in the Intergroup 0099 vs. 83 days in Aichi), a higher treatment completion rate (55%: 43 of 78 cases in the Intergroup 0099 vs. 80%: 70 of 87 cases in Aichi) and a higher 3-year OS rate (78% in the Intergroup 0099 vs. 92% in Aichi). Again, completion ratio of chemotherapy, representing total infusion dose of cisplatin and fluorouracil, influences the treatment outcome. Ueno et al. (15) reported the patients who received three courses of chemotherapy had better survival than those with one or two courses. Considering these results, a Phase II study in which 25 facilities participated was initiated in December 2003. The long-term therapeutic results are now under preparation.

**EBV status**

The detection of EBV DNA has been increasingly used for the diagnosis of NPC. For the detection of distant metastases, the use of serum EBV DNA has been shown to be more sensitive and reliable than other options (29,30). The quantities of EBV DNA copies before and after treatment are significantly related to the rates of overall-and disease-free survival (31,32). There was a study reporting that the levels of post-treatment EBV DNA when compared with pretreatment EBV DNA had a better prediction for progression-free survival (33). Many analyses for the prognostic value of EBV status, especially the role of circulating EBV-DNA in patients with NPC, were mainly in endemic area and most of papers state the prognostic value of EBV load. Studies on EBV DNA in non-endemic area also state diagnostic value but prognostic value (28). What is the difference? It could be attributable to the following reasons. First, WHO-I, supposed to be EBV-unrelated NPC, is much popular in non-endemic area. And the patients with WHO-I are less chemoradiosensitive (34–36). IGS 0099 study, executed in non-endemic area, comprises ~20% of NPC patients with WHO-I histology. That background might have some influence to the discrepancy that is featured around the world.

**Conclusion**

Currently, there is no doubt that CCRT with cisplatin-based regimens are most promising treatment procedure for improving OS in patients with locoregionally advanced NPC. Additional NAC, especially with concurrent chemotherapy in the combination of IMRT, is expected to improve the outcome of these patients whereas AC is not likely to improve. We have to wait upcoming clinical trials that elucidate the exact role of AC.

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**Conflict of interest statement**

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