MINI-REVIEW

Progress and Challenges in Chemotherapy for Loco-Regionally Advanced Nasopharyngeal Carcinoma

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Abstract

Incidence rates of nasopharyngeal carcinoma are high in Indonesia, Singapore and South-Eastern China. Chemoradiotherapy has been the standard regimen for locally advanced nasopharyngeal carcinoma according to guidelines from the National Comprehensive Cancer Network. Recently, advances in the management of nasopharyngeal carcinoma have transferred into better treatment outcomes. Most phase III clinical trials support the addition of concurrent chemotherapy to radiotherapy for the initial treatment of these patients. Studies evaluating effects and toxicity of concurrent chemotherapy with different regimens have been reported. However, the status of adding adjuvant chemotherapy or induction chemotherapy remains controversial. Recent studies have shown that adjuvant chemotherapy with two or three cycles may improve survival for nasopharyngeal carcinoma with stage N2-3 disease or with persistently detectable plasma EBV DNA after radiotherapy. This review examines the pertinent issues and latest studies concerning the management of loco-regionally advanced NPC, regarding concurrent chemotherapy, adjuvant chemotherapy, and induction chemotherapy in decades.

Keywords: Nasopharyngeal carcinoma - concurrent chemotherapy - adjuvant chemotherapy - induction chemotherapy

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Introduction

There were an estimated 84,400 incident cases of nasopharyngeal carcinoma (NPC) and 51,600 deaths in 2008. According to world area, incidence rates are high in South-Eastern Asia, including Malaysia, Indonesia, Singapore, and South-Eastern China (Jemal et al., 2011). Because the early clinical symptoms are not obvious, at least 60% of patients with NPC present with locally advanced disease, while about 5-8% present with distant metastases at diagnosis (Fong et al., 1996; Heng et al., 1999).

Radiation therapy is the main treatment for NPC. In 2006, Yi et al. (2006) reported on their experience in the treatment of NPC by radiotherapy alone in their institution during the last decade. Radiotherapy was given to this cohort by conventional technique in a routine dose of 70-72 Gy to the primary tumor and metastatic lymph nodes. For residual primary lesion, a boost dose of 8-24 Gy was delivered. The 5-year overall survival (OS) rates were reported to be about 95.5% and 87.7% for stageIand II NPC, while they were 76.9% and 66.39% for stage III and IV disease.

Besides, NPC is also sensitive to chemotherapy. Many studies have demonstrated that the additional use of chemotherapy to radiotherapy has significantly improved outcomes when compared to radiotherapy alone (Al-Sarraf et al., 1998; Lin et al., 2003; Kwong et al., 2004). This article examines the pertinent issues and latest studies concerning the management of loco-regionally advanced NPC, regarding concurrent chemotherapy, adjuvant chemotherapy, and induction chemotherapy.

Concurrent Chemotherapy

The Intergroup-0099 trial (Al-Sarraf et al., 1998) is the first phase III randomized controlled trial (RCT) comparing concurrent chemoradiotherapy (CCRT) versus radiotherapy (RT) alone in patients with locally advanced NPC. 69 in the radiotherapy group and 78 in the chemoradiotherapy group were eligible for primary analysis. The 3-year progression-free survival (PFS) rate and OS were 24% versus 69% (P<0.001), and 47% versus 78% (P=0.005), respectively. In the NPC-9901 trial (Lee et al., 2005), 384 NPC patients with T1-4N2-3M0 disease were randomly assigned to receive RT alone or CCRT plus AC. With a median follow-up of 2.3 years, the combined arm gained significant improvement in 3-year failure-free survival (FFS) (72% vs. 62%, P=0.005) and loco-regional control (92% vs. 82%, P=0.027). However, there were no significant differences in distant control and OS between them (76% vs. 73%, P=0.47; 78% vs.78%, P=0.97).

Zhang et al. (2005) performed a phase III study to evaluate the efficacy of concurrent weekly oxaliplatin with radiotherapy in patients with loco-regionally advanced NPC. Oxaliplatin 70 mg/m^2 was administered weekly for 6 cycles for 59 patients during radiotherapy, while 56 patients received radiotherapy alone. After a median

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follow-up of 24 months, CCRT with weekly oxaliplatin supplied significant improvement in OS, distant metastasis failure-free survival (DMFS), and relapse-free survival (RFS) rates. This study is the first phase III study to confirm the INT-0099 regimen in regions of endemic NPC in China. Further randomized trials including oxaliplatin are warranted.

Several RCTs also demonstrated the addition of concurrent chemotherapy to radiotherapy provided survival benefit for loco-regionally advanced NPC (Lin et al., 2003; Kwong et al., 2004; Chan et al., 2005; Wee et al., 2005; Kwong et al., 2006; Chen et al., 2013). In 2013, Chen et al. (2013) reported a study about the long-term survival and late toxicities of CCRT in patients with stage III-IVB NPC from endemic regions of China. In this trial, 158 received radiotherapy alone (the RT group) and another 158 received CCRT plus AC (the CRT group). The regimen of concurrent chemotherapy was cisplatin 40 mg/m2 weekly during radiotherapy. The regimen of AC was cisplatin 80 mg/m2 and fluorouracil 800 mg/m2 daily for 5 days every 4 weeks for 3 cycles. After a median follow-up of 70 months, the 5-year OS rate was 72% vs 62% for the CRT group and the RT group [HR (hazard ratio):0.69, 95% CI (confidence interval): 0.48-0.99; P=0.043]. What's more, FFS was significantly higher in the CRT group (P=0.020). Most late toxicities were similar. However, cranial neuropathy, peripheral neuropathy, and ear damage were significantly higher in the CRT group. The addition of concurrent chemotherapy and AC to radiotherapy supplied survival benefits to patients with stage III-IVB NPC.

Lee et al. (2011) conducted a combined analysis of the NPC-9901 and the NPC-9902 trials to evaluate the efficacy of the Intergroup-0099 regimen and the contributing factors. 218 patients with stage III-IVB NPC were randomly assigned to radiotherapy alone and 223 patients were assigned to CCRT followed by AC (the CRT group). After a median follow-up of 6.1 years. Comparison by intention-to-treat showed that the CRT group gained significant improvement in overall failure-free rate (FFR), loco-regional-FFR and cancer-specific survival (P≤0.019); but the improvements for distant-FFR and OS were statistically insignificant (P≥0.14). However, comparison based on actual treatment showed that an additional improvement in 5-year OS was achieved in the CRT group (P=0.037). Multivariate analyses showed that the dose of cisplatin during the concurrent phase had

Table 1. Studies on CCRT+/-AC in the Treatment of Patients with Loco-regionally Advanced Nasopharyngeal Carcinoma

Study	No. of patients	Group	Chemotherapy		Results			
			Concurrent	Adjuvant	Endpoints	CCRT+/-AC	RT alone	P
Al-Sarraf, 1998	147	CCRT+AC RT alone	Cisplatin, q3wks for 3 cycles	Cisplatin and 5-fluorouracil, q4wks for 3 cycles	3-y OS 3-y PFS	78.00% 69.00%	47.00% 24.00%	0.005 <0.001
Lin,2003	284	CCRT RT alone	Cisplatin and 5-fluorouracil, q4wks for 2 cycles	\	5-y OS 5-y PFS 5-y DMFS 5-y LRFS 5-y NRFS	72.30% 71.60% 78.70% 89.30% 96.80%	54.20% 53.00% 69.90% 72.60% 92.10%	0.0022 0.0012 0.0577 0.0009 0.1716
Kwong,2004 Kwong,2006	217	CCRT±AC RT±AC	UFT(uracil and tegafur) every day for 35-40 days	Cisplatin and fluorouracil q3wks for 6 cycles	3-y OS 5-y FFS 5-y LFFS 5-y DMFS	86.50% 67.70% 78.20% 84.10%	76.80% 54.30% 71.20% 70.70%	0.06 0.04 0.22 0.02
Lee,2005	348	CCRT+AC RT alone	Cisplatin, q3wks for 3 cycles	Cisplatin and 5-fluorouracil, q4wks for 3 cycles	3-y OS 3-y FFS 3-y LFFS 3-y DMFS	78.00% 72.00% 92.00% 76.00%	78.00% 62.00% 82.00% 73.00%	0.97 0.027 0.005 0.47
Zhang,2005	115	CCRT RT alone	Oxaliplatin weekly for 6 cycles	\	2-y OS 2-y RFS 2-y DMFS	100.00% 96.00% 92.00%	77.00% 83.00% 80.00%	0.01 0.02 0.02
Wee,2005	221	CCRT+AC RT alone	Cisplatin, q3wks for 3 cycles	Cisplatin and 5-fluorouracil, q4wks for 3 cycles	3-y OS 3-y DFS	80.00% 72.00%	65.00% 53.00%	0.0061 0.0093
Chan,2005	350	CCRT RT alone	Cisplatin weekly for 6-7 cycles	\	5-y OS 5-y PFS	70.30% 60.20%	58.60% 52.10%	0.065 0.16
Lee,2011	441	CCRT+AC RT alone	Cisplatin, q3wks for 3 cycles	Cisplatin and 5-fluorouracil, q4wks for 3 cycles	5-y OS 5-y FFS 5-y LFFS 5-y DMFS	70.00% 66.00% 87.00% 74.00%	64.00% 57.00% 80.00% 69.00%	0.14 0.019 0.014 0.34
Chen,2013	316	CCRT+AC RT alone	Cisplatin weekly for 7 cycles	Cisplatin and 5-fluorouracil, q4wks for 3 cycles	5-y OS 5-y FFS 5-y LFFS 5-y DMFS	72.00% 72.00% 89.00% 80.00%	62.00% 62.00% 85.00% 71.00%	0.043 0.02 0.112 0.058

*Notes: CCRT:Concurrent chemoradiotherapy;AC:Adjuvant chemotherapy;RT:Radiotherapy;OS:Overall survival;PFS:Progression-free survival;DMFS:Distant metastasis failure-free survival;LRFS:Local relapse-free survival;NRFS:Nodal relapse-free survival;LFFS: Loco-regional failure-free survival;RFS:Relapse-free survival;DFS:Disease-free survival; FFS:Failure-free survival

significant impact on locoregional-FFR and OS, while that of fluorouracil during the adjuvant phase was significant for distant-FFR. What's more, the 5-year loco-regional-FFR for patients who received 0-1, 2 and 3 concurrent cycles were 79%, 88% and 88%, respectively; the corresponding distant-FFR by adjuvant cycles were 68%, 78% and 77%, respectively. These results demonstrated that the concurrent phase was important for loco-regional control and survival. And additional chemotherapy using fluorouracil-containing combination contributed to improving distant control.

Data of nine studies on CCRT+/-AC in the treatment of loco-regionally advanced nasopharyngeal carcinoma were shown in Table 1.

In Baujat et al's meta-analysis (Baujat et al., 2009), 8 trials with 1753 patients were included. The pooled HR of death, tumor failure or death, loco-regional failure, and distant failure between the CCRT+/-AC group and the RT alone group were 0.60 (95% CI 0.48 to 0.76), 0.63 (95% CI 0.51 to 0.78), 0.81 (95% CI 0.55 to 1.18), and 0.69 (95% CI 0.49 to 0.97), respectively. There were significant differences in survival in favor of CCRT+/-AC when compared to RT alone. Other Meta-analysis also confirmed that CCRT with or without AC provided survival benefit for loco-regional advanced NPC (Langendijk et al., 2004; Zhang et al., 2010). In order to evaluate the efficacy of CCRT compared with RT alone in the treatment of NPC in endemic geographic areas, Zhang et al. (2010) conducted a meta-analysis of CCRT vs. RT alone in NPC treatment which included studies only done in endemic area. Seven trials including 1608 patients were included. At last, risk ratios (RRs) of 0.63 (95% CI, 0.50 to 0.80), 0.76 (95% CI, 0.61 to 0.93) and 0.74 (95% CI, 0.62 to 0.89) were observed for 2, 3 and 5 years OS respectively in favor of the CCRT group.

It is essential to evaluate the efficacy and safety of different regimens of concomitant chemotherapy. Chitapanarux et al. (2007) performed a single centre, randomized non-inferiority trial to compare CCRT with carboplatin versus cisplatin in patients with loco-regionally advanced NPC. 101 were randomized to cisplatin arm and 105 to carboplatin arm. With a median follow-up of 26.3 months, 59% of patients in the cisplatin arm and 73% in the carboplatin arm completed the planned CCRT. There were more renal toxicity, leucopenia, and anemia in the cisplatin group, and more thrombocytopenia in the carboplatin arm. The 3-year disease free survival (DFS) rates and OS rates were 63.4% vs 60.9% (P=0.96), and 77.7% vs 79.2% (P=0.99) for cisplatin and carboplatin groups, respectively. This trial showed that the tolerability of carboplatin was better than that of cisplatin. Moreover, the treatment efficacy of carboplatin arm was not inferior to the standard regimen in the treatment of loco-regional advanced stage NPC. An ongoing phase III trial will report whether the effectiveness of nedaplatin versus cisplatin with IMRT chemoradiotherapy in treating patients with loco-regionally advanced NPC (NCT01540136). In 2014, Xu et al. (2014) reported the survival and toxicity in patients with locoregionally advanced NPC treated with IMRT and concurrent nedaplatin plus paclitaxel or fluorouracil (NP or NF). They found the two groups received comparable survival results and toxicities were acceptable. Chen et al. (2014) also conducted a meta-analysis to evaluate effects of two different regimens of concomitant chemotherapy for NPC. One arm used taxanes and platinum, while the other arm used 5-fluorouracil and platinum. The results showed that the former regimen brought significant improvement in complete remission and less incidence rate in adverse reactions, while no significant differences were found in the long term effectiveness.

It is also imperative to compare the efficacy and toxicity of concomitant chemotherapy with different dose delivery. In Jagdis et al's trial (Jagdis et al., 2014), 73 patients with NPC were analyzed. 45 patients received cisplatin 40 mg/m^2 intravenously weekly for 7 weeks during radiotherapy, while another 28 patients received cisplatin 100 mg/m^2 intravenously days 1, 22, and 43. At last, the two groups achieved similar deliverability, toxicity profiles, and overall survival.

Adjuvant Chemotherapy

Update to now, there were 3 RCTs comparing RT+AC vs RT alone for loco-regional advanced NPC. In Rossi et al's trial (Rossi et al., 1988), 116 patients with loco-regional advanced NPC after curative radiotherapy were randomized to no further therapy and 113 patients to a combination of vincristine, cyclophosphamide, and Adriamycin (VCA) for six monthly cycles. The addition of VCA to RT didn't provide significant benifit in RFS (RT, 55.8%, RT + VCA, 57.7%, P=0.45) and OS (RT, 67.3%, RT + VCA, 58.5%, P=0.13). Another trial were performed in Taiwan (Chi et al., 2002), in which 77 patients with stage IV, M0 advanced NPC were randomized to receive radiotherapy alone, and 77 received radiotherapy with 9 weekly cycles of chemotherapy. The regimen of AC was cisplatin20 mg/m^2, 5-fluorouracil 2,200 mg/m^2, and leucovorin 120 mg/m^2. With a median follow-up of 49.5 months, the 5-year OS and RFS rates were 60.5% vs. 54.5% (P=0.5) and 49.5% vs. 54.4% (P=0.38) for the RT alone group and the combined group, respectively. In 2004, Kwong et al. (2004) reported a factorial study, in which 108 received CCRT or RT without AC, 111 received CCRT or RT with AC. The regimen of concurrent chemotherapy was uracil and tegafur, while AC comprised alternating cisplatin, fluorouracil, vincristine, bleomycin, and methotrexate for six cycles. Three-year OS between the CCRT/RT+AC group versus the CCRT/RT group were 80.4% versus 83.1% (P=0.69). Five-year FFS between the CCRT/RT+AC group versus the CCRT/RT group were 60.8% versus 61.3% (P=0.99) (Kwong et al., 2006). These studies showed that the additional of AC to CCRT might not essential. No survival benefits were found in these three trials.

According to guidelines from the National Comprehensive Cancer Network (NCCN), CCRT with or without AC is recommended as the standard regimen for locally advanced NPC (category 2). However, it is unclear whether the addition of AC to CCRT was essential. In order to solve this problem, several RCTs have been conducted. The largest sample of them was the trial registered with ClinicalTrials.gov, number NCT00677118

(Chen et al., 2012). All patients were non-metastatic stage III or IV (except T3-4N0) NPC. They were assigned to receive CCRT plus AC or CCRT alone. After a median follow-up of 37.8 months, no survival benefits were found in 2-year OS, FFS, DMFS, and loco-regional failure-free survival (LFFS) in the CCRT plus AC group. Stomatitis was the most commonly reported grade 3 or 4 adverse event during CCRT or AC.

In a retrospective analysis conducted by Maeng et al (Maeng et al., 2012), a total of 148 patients with locally advanced NPC were included to compare clinical outcomes between CCRT followed by AC and CCRT alone. The estimated 5 year survival rates were 78.3% vs 69.1% for the CCRT group and the CCRT+AC group, respectively (P=0.223). For the patients with stage I-III or IVa-b at diagnosis, the PFS and OS were not statistically significant. This study showed that for all stages of NPC, AC after CCRT did not affect the survival or recurrent rate.

Data of five studies on AC in the treatment of loco-regionally advanced nasopharyngeal carcinoma were shown in Table 2.

In 2013, Ouyang et al (OuYang et al., 2013) conducted a meta-analysis in which five RCTs with 1187 patients were eligible to evaluate efficacies of AC for NPC. They found that patients receiving additional AC had lower loco-regional recurrence rate (P=0.03; RR 0.71, 95% CI 0.53-0.96). But no benefit of OS and distant metastasis rate were achieved from AC.

In previous RCTs, the rates of patients receiving sufficient cycles of AC have been low, and this might have influenced the reported efficacy of AC. For example, in Chen's trial (2012), 91/251 patients (36.3%) did not receive AC or discontinued AC due to refusal or adverse events. In 2013, 181 with newly diagnosed, locally advanced NPC who received CCRT followed by AC were retrospectively analyzed. With a median follow-up of 40 months, compared those without adjuvant chemotherapy or who had received one cycle, patients receiving two to three cycles of adjuvant chemotherapy achieved significant higher rate in OS (Lin et al., 2013). In 2014, we reported the value of AC as the addition to CCRT for NPC (Liang et al., 2014). 130 patients were treated with CCRT plus 2-3 cycles of AC. And another 130 patients were treated with CCRT alone who were matched according to age, gender, WHO histology, T stage, N stage, and the technology used for radiotherapy. After a mean follow-up period of 42.1 months, there was a borderline significant benefit from concurrent chemoradiotherapy plus adjuvant chemotherapy for patients with N2-3 disease [HR 0.35 (95% CI: 0.11-1.06), P=0.052].

Besides, the regimen of AC in published studies was mostly cisplatin and fluorouracil. Perhaps this combination might not be an effective combination for eradicating micro-metastases in NPC. In 1992, Jacobs et al reported that compared to cisplatin and fluorouracil as single agents for advanced squamous cell carcinoma of the head and neck, the combination of cisplatin and fluorouracil didn't show benefit in survival (Jacobs et al., 1992). New drugs needed to be explored to be the regimen of AC. Paclitaxel, docetaxel, gemcitabine, and capecitabine are newer cytotoxic agents that have shown activity in NPC and non-nasopharyngeal head and neck cancers (Airoldi et al., 2002; Posner et al., 2007; Chua et al., 2008; He et al., 2012). In He et al's trial, a total of 54 patients with loco-regionally advanced NPC were treated with cisplatin and gemcitabine for two cycles as neoadjuvant chemotherapy, and two cycles of the same regimen were administered as AC. After a median follow-up of 30 months, the 3-year loco-regional control, metastasis-free rate and OS were 94.9%, 86.2% and 87.7%, respectively (He et al., 2012).

Table 2. Studies on AC in the Treatment of Patients with Loco-regionally Advanced Nasopharyngeal Carcinoma

Study	No. of patients	Group	Chemotherapy		Results			
			Concurrent	Adjuvant	Endpoints	With AC	Without AC	P
Rossi,1988	229	RT+AC RT alone	\	Vincristine, cyclophos-phamide,and adriamycin for 6 monthly cycles	4-y OS 4-y RFS	58.50% 57.70%	67.30% 55.80%	0.13 0.45
Chi,2002	154	RT+AC RT alone	\	Cisplatin, 5-fluorouracil and leucovorin for 9 weekly cycles	5-y OS 5-y RFS 5-y LRFS 5-y DMFS	54.50% 54.40% 49.40% 59.60%	60.50% 49.50% 51.30% 58.40%	0.5 0.38 0.95 0.68
Kwong,2004 Kwong,2006	217	CCRT/RT+AC CCRT/RT alone	UFT (uracil and tegafur) every day for 35-40 days	Cisplatin and fluorouracil every 3 weeks for 6 cycles	3-y OS 5-y FFS 5-y LFFS 5-y DMFS	80.40% 60.80% 80.00% 75.10%	83.10% 61.30% 69.40% 79.80%	0.69 0.99 0.08 0.26
Chen,2012	508	CCRT+AC CCRT alone	Cisplatin for 7 weekly cycles	Cisplatin and fluorouracil every 4 weeks for 3 cycles	2-y OS 2-y FFS 2-y LFFS 2-y DMFS	94.00% 86.00% 98.00% 88.00%	92.00% 84.00% 95.00% 86.00%	0.32 0.13 0.1 0.12
Maeng,2012	148	CCRT+AC CCRT alone	Cisplatin	Cisplatin and 5-fluorouracil	5-y OS 5-y OS(I-III) 5-y OS(IVa-b) 5-y PFS(I-III) 5-y PFS(IVa-b)	69.10% \ \ \ \	78.30% \ \ \ \	0.22 0.27 0.54 0.11 0.06

*Notes: AC:Adjuvant chemotherapy;RT:Radiotherapy;CCRT:Concurrent chemoradiotherapy;OS: Overall survival;RFS:Relapse-free survival;LRFS:Local relapse-free survival;DMFS:Distant metastasis failure-free survival; FFS:Failure-free survival;LFFS: Loco-regional failure-free survival;PFS:Progression-free survival

What's more, it would be confirmed that whether NPC patients staged N2-3M0 need AC consisting of paclitaxel and platinum after CCRT (NCT01694576). In 2011, Xu et al (Xu et al., 2011) reported a retrospective study comparing treatment outcomes of different chemotherapy sequences during radio-chemotherapy for stage N3 NPC. All patients with NPC were restaged according to the American Joint Committee on Cancer (AJCC) 2002 stage classification system. The technology of radiotherapy was two-dimensional radiotherapy (2DRT). CCRT regimen was delivered to in 37 patients, and CCRT+AC in 15 patients. With a median follow-up of 54months (3-117months), the rates of 5-year OS and 5-year DMFS between the CCRT+AC group and the CCRT alone group were 71% versus 51%, and 80% versus 54%, respectively. The CCRT+AC regimen was more effective than CCRT alone for N3 disease. However, the shortage of this study was that it was not a RCT and the sample was small. Large and multicenter RCTs are required to assess whether CCRT followed by AC is superior to CCRT alone for loco-regionally advanced NPC with N3 disease.

In addition, plasma EBV DNA after primary radiotherapy or chemoradiotherapy predicted poor survival and might be a biomarker of subclinical residual disease. AC might improve survival for those patients. In order to explore it, Chan et al. (2012) used EBV DNA to select high risk NPC for adjuvant CT while low risk NPC only received clinical follow-up. They concluded that delivery of 6 cycles of AC was feasible with acceptable toxicity after full dose RT or CCRT, while the survival results need to be further verified. In Twu et al's trial, 85 patients with persistently detectable plasma EBV DNA after 1 week of curative radiotherapy plus induction/ concurrent chemotherapy were analyzed. 33 were administered adjuvant chemotherapy consisting of oral tegafur-uracil (2 capsules twice daily) for 12 months. 52 patients didn't receive adjuvant chemotherapy. There were no significant differences in age, sex, pathologic type, performance status, T classification, N classification, and overall stage between the two arms. After a median follow-up of 70 months, data showed that adjuvant chemotherapy can reduce distant failure (P=0.0034) and improve overall survival (P<0.0001).

Table 3. Studies on IC in the Treatment of Patients with Loco-regionally Advanced Nasopharyngeal Carcinoma

SStudy	No. of patients	Group	Chemotherapy			Results			
			Induction	Concurrent	Adjuvant	Endpoints	With IC	Without IC	P
Chan,1995	77	IC+RT+AC RT alone	Cisplatin and 5-fluorouracil for 2 cycles	\	Cisplatin and 5-fluorouracil for 4 cycles	2-y OS 2-y DFS	80.00% 68.00%	80.50% 72.00%	0.29 0.45
Cvitkovic, 1996	339	IC+RT RT alone	Bleomycin,epirubicin a nd cisplatinum for 3 cycles	\	\	OS DFS	\ 67.30%	\ 45.30%	>0.05 <0.01
Chua,1998	334	IC+RT RT alone	Cisplatin and epirubicin for 2-3 cycles	\	\	3-y OS 3-y RFS	78.00% 48.00%	71.00% 42.00%	0.57 0.45
Hareyama, 2002	80	IC+RT RT alone	Cisplatin and 5-fluorouracil for 2 cycles	\	\	5-y OS 5-y DFS 5-y LFFS 5-y DMFS	60.00% 55.00% 65.00% 74%	48.00% 43.00% 68.00% 56%	>0.05 >0.05 >0.05 >0.05
Ma,2001	456	IC+RT RT alone	Cisplatin,bleomycin and 5-fluorouracil for 2-3 cycles	\	\	5-y OS 5-y RFS 5-y DMFS	63.00% 59.00% 79.00%	56.00% 49.00% 75.00%	0.11 0.05 0.4
Chua,2005	784	IC+RT RT alone	Cisplatin, bleomycin, and fluorouracil, or cisplatin and epirubicin for 2-3 cycles	\	\	5-y OS 5-y RFS 5-y DMFS	61.90% 50.90% 74.00%	58.10% 42.70% 70.00%	0.092 0.014 0.088
Hui, 2009	65	IC+CCRT CCRT	Docetaxel and cisplatin, q3wk for 2 cycles	Cisplatin, qwk for 8 cycles	\	3-y OS 3-y PFS	94.10% 88.20%	67.70% 59.50%	0.012 0.12
Ruste, 2011	30	IC+CCRT CCRT+AC	Cisplatin and 5-fluorouracil, q4wks for 3 cycle.	Cisplatin, q3wks for 3 cycle.	Cisplatin and 5-fluorouracil, q4wks for 3 cycles	3-y OS 3-y PFS	25.40% 63.00%	36.00% 25.00%	0.89 0.18
Fountzilas, 2012	141	IC+CCRT CCRT	Cisplatin,epirubicin, and paclitaxel, q3wks for 3 cycles.	Cisplatin,qwk for 6-7 cycles	\	3-y OS 3-y PFS	66.60% 64.50%	71.80% 63.50%	0.65 0.71

*Notes: CCRT:Concurrent chemoradiotherapy;AC:Adjuvant chemotherapy;RT:Radiotherapy;OS:Overall survival;PFS:Progression-free survival;DMFS:Distant metastasis failure-free survival;LRFS:Local relapse-free survival;NRFS:Nodal relapse-free survival;LFFS: Loco-regional failure-free survival;RFS:Relapse-free survival;DFS:Disease-free survival; FFS:Failure-free survival

Induction Chemotherapy

The role of induction chemotherapy (IC) exists controversy in the treatment of loco-regional advanced NPC. In Cvitkovic et al's trial (Cvitkovic et al., 1996), 168 were assigned to radiotherapy alone and 171 to IC+RT. The regimen of IC consisted of 3 cycles of bleomycin, epirubicin, and cisplatin (BEC). With a median follow-up of 49 months, there was a significant improvement in DFS favoring the IC+RT arm ($P<0.01$). However, several studies showed no benefit of survival was achieved from IC (Chan et al., 1995; Chua et al., 1998; Ma et al., 2001; Hareyama et al., 2002). In 2002, Hareyama et al (Hareyama et al., 2002) reported a RCT comparing two courses of IC with cisplatin and 5-fluorouracil followed by RT and RT alone. With a median follow-up of 49 months, no benefits were found in OS, DFS, DMFS, and LFFS.

Update to now, the study with the most large samples on IC for loco-regionally advanced NPC was reported by Chua et al (Chua et al., 2005). A total of 784 patients were included for analysis, with an equal number of patients in the IC+RT group and the RT alone group. IC consisted of two to three cycles of cisplatin, bleomycin, and fluorouracil, or cisplatin and epirubicin. The results showed that the 5-year RFS rate and the 5-year disease-specific survival rate between the IC+RT group and the RT alone group were 50.9% versus 42.7% ($P=0.014$), and 63.5% versus 58.1% ($P=0.029$), respectively, while the 5-year OS rate was 61.9% versus 58.1% ($P=0.092$). They conclude that the addition of IC to RT could provide improvement in disease-specific survival and significant decrease in relapse for advanced-stage NPC.

According to guidelines from NCCN, IC followed by CCRT was recommended as standard treatment for locally advanced NPC (category 3). In 2009, Hui et al (Hui et al., 2009) reported a randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced NPC. The 3-year PFS were 88.2% vs 59.5% for the group with IC and the group without IC (P=0.12), while the 3-year OS were 94.1% vs 67.7% (P=0.012). Acute toxicities, late radiotherapy toxicities and quality of life scores were comparable in both arms. Other trials showed that patients with NPC gained no survival benefits form the addition of IC to CCRT (Ruste et al., 2011; Fountzilas et al., 2012). In a phase II study, 72 patients were assigned to receive IC plus CCRT, while 69 patients received CCRT alone. The regimen of IC was cisplatin 75 mg/m2, epirubicin 75 mg/m2 and paclitaxel 175 mg/m2 (CEP) every 3 weeks for three cycles They found that IC with CEP followed by CCRT did not significantly improve response rates and/or survival compared to that of CCRT alone (Fountzilas et al., 2012).

Data of nine studies on IC in the treatment of loco-regionally advanced nasopharyngeal carcinoma were shown in Table 3.

In 2004, Thephamongkhol et al (K.Thephamongkhol et al., 2004) reported a meta-analysis in which 101 RCTs were included. Compared to RT alone, IC followed by RT could significantly improved 5-year DFS and OS rates with an odds ratio of 0.65 (95% CI, 0.51-0.84) and 0.63 (95% CI 0.51-0.79), respectively. In another meta-analysis(Langendijk et al., 2004), 10 randomized clinical studies including 2,450 patients were identified. After pooled analysis, no significant beneficial effect on the OS was found for IC (HR, 0.87; 95% CI, 072 to 1.04), while significant benefits in DMFS and LFFS were gained by the additional of IC to RT. In Ouyang et al's study (OuYang et al., 2013), six trials including 1418 patients were pooled to evaluate efficacies of neoadjuvant chemotherapy for NPC. At last, HR of death for IC was 0.82 (95% CI 0.69-0.98, $P=0.03$). Significant benefit in DMFS ($P=0.00$; RR 0.69, 95% CI 0.56-0.84) was also found from IC. But no decrease in LFFS ($P=0.49$; RR 0.90, 95% CI 0.66-1.22) was observed. In 2013, we performed the first analysis to compare the efficacy and toxicity of IC followed by CCRT versus CCRT with or without AC for loco-regionally advanced NPC (Liang et al., 2013). 11 studies with 1096 patients were included. RRs of 0.99 (95%CI 0.72-1.36), 0.37 (95%CI 0.20-0.69), 1.08 (95%CI 0.84-1.38), 0.98 (95%CI 0.75-1.27) were observed for 3 years OS, 3 years PFS, 2 years LFFS and 2 years DMFS. There were no treatment-related deaths in either group in the 11 studies. Risk ratios of 1.90 (95%CI 1.24-2.92), 2.67 (95%CI 0.64-11.1), 1.04 (95%CI 0.79-1.37), 0.98 (95%CI 0.27-3.52) were found for grade 3-4 leukopenia, grade 3-4 thrombocytopenia, grade 3-4 mucous membrane, and grade 3-4 hepatic hematologic and gastrointestinal toxicity, the most significant toxicities for patients. This study demonstrated that the addition of IC to CCRT with or without AC could only provide significant benefit in terms of PFS.

In the last few years, several new drugs have shown promising activity against advanced NPC. Two phase II trials had explored the use of cisplatin plus gemcitabine (GP) as IC before radiotherapy in loco-regionally advanced NPC and excellent results were achieved (Yau et al., 2006; He et al., 2012) . In Yau et al's trial (Yau et al., 2006), 33 patients with stage IVA-B NPC were treated with 3 cycles of GP followed by CCRT. The technology of radiotherapy was conventional radiotherapy. The overall response rate to IC was >90%. At a median follow-up of 2.9 years, the 3-year OS and DFS rates were 76% and 63%, respectively. In another trial, 54 patients with stage IIB-IVB NPC received 2 cycles of GP as IC and 2 cycles of AC. The technology of radiotherapy was IMRT. The overall response rate to IC was 88.6%. The 3-year LFFS, DMFS and OS were 94.9%, 86.2% and 87.7%, respectively (He et al., 2012). Two ongoing clinical trials shall present the efficacy and safety of GP as IC followed by CCRT in treatment of loco-regionally advanced NPC (NCT01417390 and NCT01872962).

Conclusions

Based on the above data, a clear role for concurrent chemotherapy followed by AC has shown statistically significant improvement in survival for locally advanced NPC. Studies comparing effects of concomitant chemotherapy with different regimens need to be conducted. Compared to CCRT alone, CCRT with AC didn't provide significant survival benefit for NPC.

However, large and multicenter RCTs are required to assess whether loco-regionally advanced NPC with N2-3 disease or with persistently detectable plasma EBV DNA after radiotherapy plus concurrent chemotherapy could gain significant survival benefit from the addition of AC to CCRT. There exists controversy whether IC followed by CCRT is superior to CCRT alone in survival for loco-regionally advanced NPC. It is essential to design larger RCTs with long follow-up periods to evaluate survival benefit from the addition of IC to CCRT.

Conflicts of Interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work.

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