REVIEW
ONCOLOGY

Diseases & Research

Clinical Progress of Adjuvant Chemotherapy in Locoregionally Advanced Nasopharyngeal Carcinoma

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Abstract: Concurrent chemoradiotherapy (CCRT) is the foundational standard-of-care for patients with locoregionally advanced nasopharyngeal carcinoma (LANPC). Adding adjuvant chemotherapy (AC) or induction chemotherapy (IC) to CCRT has been shown to benefit LANPC patients. During recent five years, large numbers of prospective randomized controlled clinical trials have demonstrated the superior efficacy of IC+CCRT than CCRT alone in LANPC patients. However, prospectively designed studies concerned with AC are limited. The efficacy of CCRT+AC in treating LANPC remains unclear. For better understanding and more properly clinical usages of AC, we reviewed the studies of CCRT+AC in the treatments for LANPC patients. In summary, adding AC to CCRT is a feasible therapeutic strategy for patients with EBV positive LANPC.

Keywords: Nasopharyngeal carcinoma; Adjuvant chemotherapy; Concurrent chemoradiotherapy.

Introduction

Radiotherapy (RT) is the mainstay in the treatment of nasopharyngeal carcinoma (NPC). However, the efficacy of single RT is limited and needs to be improved. Since the 1990s, adjuvant chemotherapy (AC) had been added to the treatment of NPC. Survivals are prolonged by concurrent chemoradiotherapy (CCRT) plus AC compared with RT alone. With the application of induction chemotherapy (IC), researchers pay higher attention to the explorations of IC followed by CCRT. In trials of IC, patients with locoregionally advanced NPC (LANPC) benefit more from IC+CCRT versus CCRT. There is still controversy over the administration of IC or AC for LANPC. Here, for better usage of AC, we intend to comprehensively review the studies of AC in treating LANPC patients.

1. Additional Adjuvant Chemotherapy For Locoregioally Advanced Nasopharyngeal Carcinoma In National Comprehensive Cancer Network Guidelines

According to the National Comprehensive Cancer Network (NCCN) guideline (Head and Neck Cancers, Version 1. 2021), patients with stage Ⅱ-IVa nasopharyngeal carcinoma are recommended to receive (1) clinical trials, (2) induction chemotherapy (IC) followed by systemic therapy/RT, (3) concurrent systemic therapy/RT followed by AC, or (4) concurrent systemic therapy/RT not followed by AC[1].

The recommendations of both IC+CCRT and CCRT+AC are category 2A, while CCRT is category 2B. It seems that the NCCN guideline prefers IC+CCRT and CCRT+AC other than CCRT in the treatment of LANPC.

For IC+CCRT, numerous data have demonstrated the improvement of all survival outcomes versus CCR T alone in LANPC patients. Zhang and his colleagues showed that additional gemcitabine and cisplatin IC significantly improved 3-year failure-free survival (FFS) (85.3% in the IC+CCRT group vs 76.5% in the CCRT group) and overall survival (OS) (94.6% in the IC+CCRT group vs 90.3% in the CCRT group) in patients with LANPC[2]. Our published meta-analysis also indicated the superiority of IC+CCRT compared with CCRT alone (5-year OS hazard ratio [HR] 0.77, 95% CI 0.62–0.94, p = 0.01)[3].

However, the efficacy of adding AC to CCRT in LANPC remains unclear. Therefore, the different categories of the recommendation of CCRT+AC and CCRT by NCCN guideline might not be reasonable and convincing.

2. Regimens of adjuvant chemotherapy

After searching the PubMed database, we found that platinum, including cisplatin, carboplatin, and nedaplatin, combined with fluorouracil or tegafur had also been used in the AC trials. In the following tables, we reviewed six prospective and five retrospective studies to further manage the adjuvant chemotherapeutic regimens. The AC strategies were listed. The details are as Table 1 and Table 2.

Here, we noticed that the combination of cisplatin and fluorouracil is the main adjuvant treatment for LANPC. Other AC strategies included single-agent cisplatin and docetaxel plus cis-

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Received 10 January 2021; Revised 1 April 2021; Accepted 12 May 2021; Available Online 16 May 2021
DOI: 10.54457/DR.202101001

platin[14, 15]. While we found in Qiu's study, the dosage of fluorouracil was 4 g/m^2 daily for 5 days[12]. We consider that might be a typing mistake as such a high dose is unconventional. In the cancer center of our hospital (Wuhan Union Hospital), the most adopted AC is taxane plus platinum-based chemotherapy. Since IC+CCRT has been certificated to be superior to CCRT[3], we suggest whether IC regimens could also be used as AC regimens in LANPC patients. In a recently published study, LANPC patients received the same IC and AC regimens combined with CCRT. The detailed drugs comprised paclitaxel plus cisplatin, docetaxel plus cisplatin/ nedaplatin, docetaxel plus cisplatin and fluorouracil, and gemcitabine plus cisplatin/nedaplatin[16]. However, patients failed to benefit from IC+CCRT+AC against IC+CCRT. Therefore, more clinical studies are needed to confirm our hypothesis whether IC regimens exert comparable effects when used as AC modalities.

Table 1. Adjuvant chemotherapy in prospective studies.

Study	Regimens
Al-Sarraf, 1998[4]	cisplatin (80 mg/m^2) and fluorouracil (1000 mg/m^2 daily for 4 days) every 4 weeks for 3 cycles
Chan, 2005[5]	cisplatin (80 mg/m^2) and fluorouracil (1000 mg/m^2 daily for 4 days) every 4 weeks for 3 cycles
Dechaphunkul, 2011[6]	carboplatin (AUC 5) and fluorouracil (1000 mg/m^2 daily for 4 days) every 3 weeks for 2 cycles
Chen, 2012/2017[7, 8]	cisplatin (80 mg/m^2) and fluorouracil (800 mg/m^2 daily for 5 days) every 4 weeks for 3 cycles
Chen, 2013[9]	cisplatin (80 mg/m^2) and fluorouracil (800 mg/m^2 daily for 5 days) every 4 weeks for 3 cycles
Lee, 2017[10]	cisplatin (80 mg/m^2) and fluorouracil (1000 mg/m^2 daily for 4 days) every 4 weeks for 3 cycles

Table 2. Adjuvant chemotherapy in retrospective studies.

Study	Regimens
Liang, 2014[11]	(1) cisplatin (75–100 mg/m^2) every 3 weeks; (2) cisplatin (80 mg/m^2) and fluorouracil (1000 mg/m^2 daily for 5 days) every 3 weeks for 2-3 cycles
Qiu, 2016[12]	cisplatin (80 mg/m^2) and fluorouracil (4 g/m^2 daily for 5 days) every 3 weeks for 2 cycles
Liu, 2019[13]	cisplatin (80 mg/m^2) and fluorouracil (800–1000 mg/m^2 daily for 4 days) for 1 to 4 cycles
Chen, 2020[14]	(1) nedaplatin (75 mg/m^2) and tegafur (1 g on days 1 to 3) or fluorouracil (300 to 500 mg/m^2 for 3 to 5 days) every 3 weeks for 2–3 cycles; (2) docetaxel 75 mg/m^2 and cisplatin (75 mg/m^2) every 3 weeks for 2-3 cycles
Tang, 2020[15]	(1) cisplatin (80 mg/m^2) and fluorouracil (800 mg/m^2 daily for 5 days) every 3 weeks for 3 cycles; (2) cisplatin (100 mg/m^2) every 3 weeks for 3 cycles

3. Adjuvant chemotherapy benefit locoregionally advanced nasopharyngeal carcinoma patients

In terms of AC, although the NCCN guideline prefers adding AC to CCRT, the results in the cited articles fail to indicate the superiority of CCRT+AC compared to CCRT.In Al-Sarraf's study, locoregionally advanced nasopharyngeal carcinoma patients were treated CCRT plus cisplatin and fluorouracil AC versus RT alone[4]. Data showed that CCRT+AC significantly improved the progression-free survival (PFS) (69% vs 24%) and OS (76% vs 46) rates. However, Al-Sarraf's study could not demonstrate the advantage of combining CCRT and AC. Another cited paper was published in 2005 by Chen. Similarly, the phase Ⅲ study found that CCRT followed by adjuvant cisplatin and fluorouracil prolonged OS time. The 5-year OS was 58.6% for the RT group and 70.3% for the CCRT+AC group[5]. Based on these two studies and the other two prospective studies, we only convince that CCRT+AC is better than RT but no CCRT in treating LANPC patients. However, we still question the benefits brought by AC. In 2012, Chen and his colleagues published a phase Ⅲ multicenter randomized controlled trial comparing CCRT+AC with CCRT in LANPC. For 2-year data, they failed to found the improvement of (FFS) by adding adjuvant cisplatin and fluorouracil to CCRT. Consistently, long-term results did not demonstrate the significant survival benefit of CCRT+AC against CCRT alone[7, 8].

For retrospective studies, Liang in 2014 found that LANPC patients received no significant survival benefit from the combination of CCRT and AC in comparison with CCRT (OS hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.37–1.57). In subgroup analysis, CCRT+AC might provide a borderline significant benefit for patients with N2-3 stage disease[11]. In another retrospective study published by Qiu in 2016, they compared CCRT+AC with IC+RT. Data showed that the survival outcomes of the two groups were comparable (5-year OS: 78.0% in IC+RT vs 78.7% in CCRT+AC)[12]. The studies mentioned above seem to suggest that CCRT+AC could be a treatment strategy for LANPC, rather than adding AC to CCRT is necessary. To further explore the efficacy of the addition of AC to CCRT, we have reviewed the published meta-analyses. In 2013, Ouyang meta-analyzed the efficacy of CCRT+AC versus CCRT alone. The analysis showed that NPC patients received additional AC had lower locoregional recurrence rate (Risk ratio 0.71, 95% CI 0.53-0.96, p = 0.03)[17]. In the next year, Chen conducted a Bayesian network analysis to compare CCRT+AC, CCRT alone, and RT alone in LANPC. Although the authors indicated the superiority of CCRT+AC and CCRT against RT for all survival outcomes, no statistically significant differences were found between CCRT and CCRT+AC[18]. The Bayesian network analysis reminds clinicians and researchers to discuss the omission of AC for reducing toxicities without shortening survival time. Similarly, another two

Bayesian network analyses published by Yan and Yu also found that AC failed to improve survival outcomes following CCRT[19, 20].

The above studies were all published before 2020. In last year, we found two newly reported retrospective studies. Chen showed that CCRT+AC did not improve survival outcomes, but was associated with higher rates of toxicities against CCRT alone in stage Ⅱ NPC patients. However, in the subgroup analysis in Tang's study, compared with IC+CCRT, CCRT+AC significantly reduced the risk of locoregional recurrence in the T4 subgroup[15].

In our recently published study (Head&Neck, 2021 accepted), CCRT+AC did not show significantly better survival responses compared to CCRT but had comparable responses compared to IC+CCRT. Moreover, CCRT+AC had the highest survival rates in comparison with CCRT and IC+CCRT. We still consider the advantages of AC in benefiting LANPC patients. The most important might be to find out the precise patient population who would benefit from adding AC to CCRT.

4. The population of patients who benefited from adjvant chemotherapy

In the NCCN guideline, patients with T0 (Epstein–Barr virus [EBV] positive)-T1, N1-3 disease, and patients with T2-T4, N0-3 share the same treatment strategies. The T0 and EBV positive patients tracked our attention, which is underlined by the NCCN guideline. Because the guideline explained that the EBV DNA load may reflect prognosis and change in response to therapy. However, no cited articles could show us the reasons.

EBV is one of the most common viruses in humans and strongly correlated with NPC. When EBV copy numbers reduce to the normal level after systemic therapy, this phenomenon predicts a better prognosis for NPC patients. However, the importance of EBV is much more than that.

To study the dynamic changes in plasma EBV DNA after RT in NPC, Hui conducted a clinical trial of AC versus observation in NPC patients who had detectable plasma EBV DNA at 6-weeks post-RT. Patients with complete clearance of post-RT plasma EBV DNA had superior 5-year PFS to patients without post-RT plasma EBV DNA clearance (85.5% vs 23.3%), comparable to patients with initially undetectable post-RT plasma EBV DNA (77.1%), irrespective of AC or observation. The authors concluded that NPC patients with detectable post-RT plasma EBV DNA who experienced subsequent plasms EBV DNA clearance had superior survival comparable to patients with initially undetectable postRT plasma EBV DNA[21]. On the other hand, we consider that patients without post-RT plasma EBV DNA clearance might receive subsequent AC to reduce the incidence of recurrence or relapse.

In the retrospective study reported by Liu, LANPC patients were divided into three groups according to the N stage and EBV load: (1) low-risk group: N0–1, and EBV DNA<4, 000 copies/mL; (2) intermediate-risk group: N0–1, and EBV DNA ≥ 4, 000 copies/mL; N2–3, and EBV DNA<4, 000 copies/mL; (3) Highrisk group: N2–3, and EBV DNA≥4, 000 copies/mL. However, the results failed to show any significant improvements in all endpoints after adding AC to CCRT[13].

The ongoing clinical trial NRG-HN001 might help us to find out the suitable population who need to receive AC. This trial comprises two sections, phase Ⅱ and phase Ⅲ. In the phase Ⅱ study, patients with detectable plasma EBV DNA are treated with cisplatin plus fluorouracil (Arm 1) and gemcitabine plus paclitaxel (Arm 2). While in the phase Ⅲ study, patients with undetectable plasma EBV DNA were enrolled in Arm 3 (cisplatin and fluorouracil) and Arm 4 (observation). We are eager for the results of NRG-HN001.

Conclusions

For patients with LANPC, CCRT, IC+CCRT, and CCRT+AC are effective therapeutic strategies. Although IC+CCRT benefits the most according to published data, CCRT and CCRT+AC have their preferred populations. CCRT alone might be recommended to early-stage LANPC. In terms of adding AC to CCRT, patients with EBV positive LANPC might be the accurate population. The ongoing and future clinical trials are warranted to confirm our conclusions.

Abbreviations

AC, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; CI, confidence interval; EBV, Epstein–Barr virus; FFS, failure-free survival; HR, hazard ratio; IC, induction chemotherapy; LANPC, locoregionally advanced nasopharyngeal carcinoma; NCCN, National Comprehensive Cancer Network; NPC, nasopharyngeal carcinoma; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

Funding

This study was supported by the Hubei Provincial Natural Science Foundation (Grant number: 2020CFB397 to Bi-Cheng Wang), the Independent Innovation Foundation of Wuhan Union Hospital (Grant number: 2019-109 to Bi-Cheng Wang).

Conflict of interest

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Acknowledgement

We thank the members in the SNOWELL STUDIO (Bi-Cheng Wang's workgroup) for helping to improve the manuscript.

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