Chapter

Chemotherapy in Nasopharyngeal Carcinoma

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Abstract

Nasopharyngeal carcinoma is a unique disease entity among head and neck cancers due to its epidemiology and clinical behavior. Non-keratinizing or undifferentiated carcinoma is the most common histological type in endemic areas. Radiotherapy is the treatment for early-stage disease. With the widespread use of IMRT, loco-regional control has improved significantly in locally advanced diseases. But distant metastasis continues to be the most common pattern of failure. To address this issue, chemotherapy has been incorporated into radiotherapy in various settings; as concurrent, induction, and adjuvant. The initial trials of concurrent chemotherapy incorporated adjuvant chemotherapy also and the magnitude of benefit contributed by each treatment was not clear. Later trials proved that adjuvant chemotherapy was not beneficial. Induction chemotherapy when added to concurrent chemoradiation resulted in improvement in Failure Free Survival, Overall Survival, and Distant Metastasis Free Survival. Thus, induction chemotherapy followed by concurrent chemoradiation became the standard of care for locally advanced disease (stage III and IVA). The role of chemotherapy in stage II disease is still evolving. Metastatic nasopharyngeal carcinoma is treated by platinum doublet chemotherapy, Cisplatin-gemcitabine is the standard regimen.

Keywords: Nasopharyngeal carcinoma, locally advanced, metastatic, concurrent chemotherapy, induction chemotherapy, adjuvant chemotherapy

1. Introduction

Nasopharyngeal carcinoma (NPC) is unique from other head and neck cancers due to its difference in epidemiology, etiology and propensity for distant metastasis. It is endemic in Southern China, South East Asia, North Africa, and Artic region. Non-keratinizing or undifferentiated carcinoma is the most common histological type in endemic areas. Radiotherapy is the backbone of treatment owing to the complex anatomical location and high radiosensitivity. Higher local control and survival are reported for early-stage disease with radiotherapy alone [1]. But around 70% of patients present with locoregionally advanced disease and outcomes with radiotherapy alone are poor [2]. Many strategies have been tried to improve outcomes in locoregionally advanced NPC; the incorporation of chemotherapy and the use of modern radiotherapy techniques. IMRT when compared with two-dimensional

radiotherapy showed significantly better locoregional control and survival with a lower incidence of radiation- induced toxicities [3, 4]. IMRT is mainly aimed at reducing the toxicities in the early stages whereas it improves loco-regional control (LRC) in advanced stages. After the widespread use of IMRT, distant metastasis remains the predominant pattern of failure. Hence chemotherapy was added to radiotherapy in various settings; as concurrent, induction, and adjuvant. Patients with metastatic disease are treated by palliative chemotherapy or palliative radiotherapy.

2. Evolution of chemoradiation in NPC

Stage I disease is treated by radical radiotherapy. Locally advanced disease (stage III and IVA) was treated by radiotherapy till the early '90s. Chemo-radiation was first studied in the landmark intergroup trial by Al Saraaf et al [5]. This trial compared chemoradiation followed by adjuvant chemotherapy versus radiotherapy (RT) alone in stage III and IV NPC (N = 147). The radiotherapy dose was 70Gy, delivered by conformal technique. There was a significant improvement in PFS and OS with the addition of chemotherapy. The 3-year PFS rate was 69% versus 24% (P < .001) and the 3-year OS was 78% versus 47% (P = .005) in the chemoradiation and radiotherapy arms respectively. But this trial was conducted in a non-endemic area and 22% of patients had keratinizing SCC. Hence the results could not be extrapolated to endemic areas.

Four randomized trials were conducted in a similar fashion in the endemic population, one each from Singapore and China and two from Hongkong. Wee et al randomized patients (N = 221) with stage T3-4NxM0 or TxN2-3 M0 NPC with WHO type II or III histology to radiotherapy alone or chemoradiotherapy followed by adjuvant chemotherapy [6]. Patients on chemoradiotherapy received concurrent cisplatin (25 mg/m2 on days 1 to 4) on weeks 1, 4, and 7 of RT and adjuvant cisplatin (20 mg/m2 on days 1 to 4) and fluorouracil (1,000 mg/m2 on days 1 to 4) every 4 weeks (weeks 11, 15, and 19) for three cycles after completion of RT. RT dose was 70Gy in 7 weeks by conventional technique. The 3-year survival rate was 65% and 80% for RT alone and CCRT, respectively (HR 0.51 (95% CI, 0.31 to 0.81; P = .0061). There was a 17% decrease in cumulative incidence of distant metastasis in the chemotherapy arm (p = 0029).

Two parallel RCTs from Hongkong namely NPC 9901 and NPC 9902 were done for advanced regional disease and advanced local disease respectively in the endemic population [7, 8]. In NPC 9901, patients with nonkeratinizing/undifferentiated NPC staged T1–4N2-3 M0 were randomized to chemo-RT followed by adjuvant chemotherapy or RT alone (N = 348). There was a significant improvement in LRC and failure free survival (FFS) but at the expense of significantly higher rates of acute and late toxicities. The update also showed significant improvement in 5 year FFS (67% vs 55%, P = .014) and PFS (62% vs 53%, P = .035) in favor of chemotherapy [9]. There was an increase in acute toxicities (CRT vs RT: 83% vs 53%; P < .001), but late toxicities were not different. OS did not show any benefit, probably due to the increased rates of noncancer death in the chemotherapy arm. NPC 9902 included Stage T3-4N0-1M0, nonkeratinizing or undifferentiated carcinoma of the nasopharynx (N = 189). There were 4 arms; RT with conventional fractionation alone, RT with accelerated fractionation alone, RT with conventional fractionation + concurrent /adjuvant chemotherapy (CF + C), and RT with accelerated fractionation + concurrent/ adjuvant chemotherapy (AF- + C). There was a significant improvement in FFS in the AF + C compared to the CF arm (94% vs. 70% at 3 years, p = 0.008), but the difference was not significant between the AF arm and the CF + C. There was no significant difference in OS between the 4 arms.

Acute toxicities were significantly more in both the chemo-RT arms. The late toxicity was more in the AF + C arm compared to the CF arm($p = 0.05$).

Another prospective trial with a similar design was conducted in the endemic population of China by Chen et al [10]. RT dose was 70Gy in 7 weeks by conventional technique. The chemotherapy arm received concurrent cisplatin (40 mg/m2 on Day 1) weekly during RT, followed by cisplatin (80 mg/m2 on Day 1) and fluorouracil (800 mg/m2 on Days 1–5) every 4 weeks (Weeks 5, 9, and 13) for three cycles after completion of RT. The 2 year overall survival rate (89.8% vs. 79.7%, $p = 0.003$), failure-free survival rate (84.6% vs. 72.5%, $p = 0.001$), distant failure-free survival rate (86.5% vs. 78.7%, $p = 0.024$), and locoregional failure-free survival rate (98.0% vs. 91.9%, $p = 0.007$) was better in the chemotherapy arm. But acute toxicities were more in the chemotherapy arm (62.6% vs. 32%, $p = 0.000$).

Different trials used different concurrent cisplatin schedules. A randomized phase 3 trial was conducted by Liang et al to identify the ideal concurrent regimen. Weekly cisplatin 40 mg/m2 was shown to have efficacy similar to 3 weekly cisplatin 100 mg/m2 but at the expense of increased hematological toxicities [11].

The chemoradiation trials showed improvement in failure-free survival and distant metastasis-free survival with the addition of chemotherapy at the expense of increased acute toxicities. But overall survival benefit was not consistent among trials. A meta-analysis of 7 randomized trials done in endemic population by Zhang et al showed significantly better 5 years OS in favor of the CCRT treatment groups with a relative risk (RR) of 0.74 [0.62–0.89]. Locoregional recurrence (RR of 0.67,95% CI, 0.49 to 0.91) and distant metastasis (RR of 0.71;95% CI, 0.58 to 0.88) was significantly lower in the chemo-RT arm [12].

A meta-analysis with ten RCTs was done by Langendijk et al (4 neoadjuvant trials, 3 concurrent +/−adjuvant trials, and 2 adjuvant trials) to identify the additional benefit of chemotherapy when added to radiation [13]. There was an absolute survival benefit of 4% at 5 years with chemotherapy. Among the three chemotherapy timings, concomitant chemotherapy was associated with an absolute survival benefit of 20% at 5 years (HR of 0.48 (95% CI, 0.32 to 0.72). There was a significant reduction in locoregional recurrences with the addition of chemotherapy. The RR for locoregional recurrence was 0.47 ($p < 0.0001$) with concomitant chemotherapy and 0.74 ($p = 0.005$) with induction chemotherapy. But there was no benefit with adjuvant chemotherapy for locoregional control. The addition of chemotherapy demonstrated significant benefit in reducing distant metastasis also($p < 0.001$).

The MAC NPC collaborative group meta-analysis included trials 8 trials that used chemotherapy in induction, concurrent or adjuvant setting [14]. There was an absolute survival benefit of 6% at 5 years with the addition of chemotherapy to RT which corresponds to an 18% reduction in the HR of death (HR 0.82; $p = 0.006$). The concomitant schedule showed more benefit (HR = 0.60) than induction (HR = 0.99) and adjuvant (HR = 0.97) regimens. There was an absolute EFS benefit of 10% at 5 years with the addition of chemotherapy. Chemotherapy decreased the risk of locoregional failure (p 0.003; HR, 0.76) and distant failure ($p = 0.001$; HR, 0.72) irrespective of the timing of chemotherapy. Chemotherapy was more efficient against WHO type 1 disease than against WHO type 2 or 3 diseases ($p = 0.003$ for OS and $p = 0.0001$ for EFS). The survival outcomes were favoring the chemotherapy arms even after excluding WHO type 1 patients ($p = 0.03$).

The updated MAC NPC meta-analysis included 19 trials and with a median follow-up of 7.7 years [15]. There was an absolute survival benefit of 6.3% at 5 years by the addition of chemotherapy to radiotherapy. The addition of chemotherapy resulted in significant improvement in PFS, LRC, distant control, and cancer mortality. The outcome was analyzed separately for concurrent chemotherapy with or without adjuvant chemotherapy. The benefit of chemotherapy was dependent

on the timing of chemotherapy. HR was 0·65 (0·56–0·76) for concomitant plus adjuvant chemotherapy, and 0·80 (0·70–0·93) for concomitant with out adjuvant chemotherapy. There was no significant benefit with induction chemotherapy alone or adjuvant chemotherapy alone.

A meta-analysis of 28 RCTs on the association of chemoradiotherapy regimens and survival done by Zhang et al showed that concurrent chemoradiotherapy (CCRT) was significantly associated with improved OS, PFS, DMFS, and LRFS compared with radiotherapy. The addition of induction chemotherapy resulted in improvement in OS ([HR 0.84; 95%CI 0.74–0.95), PFS (HR 0.73; 95% CI, 0.64–0.84), DMFS (HR, 0.67; 95% CI, 0.59–0.78), and LRFS (HR, 0.74; 95% CI, 0.64–0.85). The addition of adjuvant chemotherapy was not associated with survival benefits [16].

3. Role of adjuvant chemotherapy after concurrent chemoradiation

The above-mentioned five chemoradiation trials used adjuvant chemotherapy also. Hence the benefit of adjuvant chemotherapy when added to chemoradiation is not clear. Moreover, with the advancements in radiation techniques, the local control has increased significantly and distant metastasis remains the common mode of failure. This prompted investigators to test the value of adjuvant chemotherapy when added to chemoradiation. Chen et al randomized stage III and IV nonmetastatic non-keratinizing NPC patients to concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone. Cisplatin 40 mg/m2 weekly was used as the concurrent regimen. Adjuvant chemotherapy consisted of 3 cycles of cisplatin 80 mg/m on day 1 and 5FU 800 mg/m^2 per day on days 1–5. After a median follow-up of 37·8 months, the 2 year FFS was 86% in the adjuvant chemotherapy group compared to 84% in the CCRT group(p = .13). There was no significant difference in Overall survival, Distant failure-free survival, and loco-regional failure-free survival [17]. The update also showed similar results [18]. The outcomes in the two arms were similar irrespective of the radiotherapy technique (2D vs 3Dvs IMRT). All three cycles of adjuvant chemotherapy were completed by only 63% of patients in the adjuvant arm.

Adjuvant chemotherapy after concurrent chemoradiation is associated with significant toxicities and poor compliance without any survival advantage. There is no evidence to recommend routine use of adjuvant chemotherapy in locally advanced NPC.

4. Adjuvant chemotherapy-risk adjusted treatment

EBV is related to NPC in endemic areas. EBV DNA load has been correlated with the prognosis of NPC in many studies [19, 20]. Hong Kong 0502 trial included patients with detectable plasma EBV DNA after curative radiotherapy. Patients were randomized to adjuvant chemotherapy with cisplatin-gemcitabine or observation [20]. After a median follow-up of 6.6 years, there was no significant difference in the 5-year relapse-free survival (RFS) rate between the two arms (49.3% versus 54.7%; HR 1.09, P = 0.75).

5. Induction chemotherapy in NPC

Concurrent chemo-RT with advanced radiotherapy techniques have increased the locoregional control in locally advanced NPC. But distant metastasis continued

Author (year)	Control	Intervention	Median follow up	DFS/FFS (Intervention vs. control arm in %)	OS	DMFS
Yang et al [22] (2019) N = 476	CCRT (cisplatin 80 mg/m^2)	CDDP+5FU infusion X 2 cycles ➔CCRT	82.6 months	5 year DFS 73.4 vs. 63.1 P = 0.007	5 year OS 80.8 vs. 76.8 P = 0.040	5 year DMFS 82.8 vs. 73.1 P = 0.014
Li et al [24] (2019) N = 480	CCRT (Cisplatin 100 mg/m^2)	Docetaxel 60 mg/m^2 D1, cisplatin 60 mg/m2D1,5FU 600 mg/m^2 D1–5 X 3 cycles➔CCRT	71.5 months	5 year FFS 77.4 vs. 66.4 P = 0.019	5 year OS 85.6vs 77.7 P = 0.042	5 year DMFS 88vs 79.8 P = 0.030
Zhang et al. [25] (2019) N = 480	CCRT (cisplatin 100 mg/m^2)	Cisplatin 80 mg/m^2 D1, gemcitabine 1 g/m^2 D1, D8 X 3 cycles➔ CCRT	42.7 months	3 year Recurrence Free Survival 85.3 vs. 76.5 P = 0.001	3 year OS 94.6 vs. 90.3 HR 0.43(0.24–0.77)	3 year DMFS 91.1 VS 84.4 HR 0.43(0.25–0.73)
Frikha et al [26] (2018) N = 83	CCRT Weekly cisplatin 40 mg/m^2	Docetaxel 75 mg/m^2, cisplatin 75 mg/m^2,5Fu 750 mg/m^2 D 1–5 X 3 cycles ➔ CCRT	43.1 months	3 year PFS 73.9 vs. 57.2 P = 0.042	3 year OS 86.3 vs. 68.9 P = 0.059	3 year DMFS HR 0.53 P = 0.18
Hong et al. [27] (2018) N = 479	CCRT (cisplatin 80 mg/m^2)	MEPFL regimen (mitomycin 8 mg/m^2 D1, Epirubicin 60 mg/m^2 D1, Cispaltin 60 mg/m^2 D1,5FU 450 mg/m^2 D8. caLV 30 mg/m^2 D8) X3 cycles➔CCRT	72 months	5 year DFS 61 vs. 50 P = 0.0264	5 year OS 72 vs. 68 P = 0.624	5 year DMFS 76 vs. 71 P = 0.28
Tan et al. [28] (2015) N = 180	CCRT (cisplatin (40 mg/m^2 weekly)	Paclitaxel 70 mg/m^2, carboplatin AUC(2.5),Gemcitabine 1 g/m^2 D1,D8X 3 cycles➔ CCRT	3.2 years	3 year DFS 74.9 vs. 67.4 P = 0.362	3 year OS 94.3 vs. 92.3 P = 0.494	3 year DMFS 83.8 vs. 79.9 P = 0.547
Jin et al. [29] (2019) N = 276	Cisplatin 100 mg/m^2 D1,5FU 800 mg/m^2 D1–5➔CCRT (cisplatin 80 mg/m2)	Docetaxel 75 mg/m2 D1, Cisplatin 75 mg/m2 D1,5FU 600 mg/m2 D1–4 X 3 cycles➔ CCRT	36 months	3 year PFS 84.5 vs. 77.9 P = 0.380	3 year OS 91.1vs 91.1 P = 0.082	—

(CCRT- Concurrent Chemoradiotherapy, OS-Overall Survival, DFS-Disease Free Survival, FFS- Failure Free survival, DMFS- Distant Metastasis Free Survival, HR-Hazard Ratio)

Table 1.
Phase 3 trials of induction chemotherapy in locally advanced nasopharyngeal carcinoma.

to be a major problem and hence adjuvant chemotherapy was tried. But it failed to show benefit and the compliance to chemotherapy after chemoradiation was poor. Induction chemotherapy was tried to decrease the rates of distant metastasis, to increase survival, and to reduce radiotherapy toxicities by decreasing treatment volumes.

Six randomized trials on induction chemotherapy have been published; three from China, one each from Europe, Taiwan, and Singapore. These trials used different induction regimens, radiotherapy techniques, and dosage schedules. The three Chinese trials showed improvement in DFS, OS, and DMFS with the addition of induction chemotherapy [21–25]. But GORTEC, Taiwan, and Singapore trials did not show any advantage in terms of DMFS or OS [26–28]. All these trials reported significantly higher rates of acute toxicities with induction chemotherapy. Jin et al tested TPF against PF as induction therapy in locally advanced NPC and reported similar outcomes with better tolerance and compliance in the PF arm [29]. The details of induction chemotherapy trials are given in **Table 1**.

Three meta-analyses of induction chemotherapy have been published. Tan et al included 6 RCTs and five observational studies with 2802 patients. Induction chemotherapy was associated with significantly improved PFS (HR 0.69, P = 0.0003) and OS (HR 0.77, P = 0.03,) at the expense of increased toxicities. There was a statistically significant 37% reduction in the hazard for the development of distant metastases (HR 0.63, P = 0.001) in favor of induction chemotherapy [30]. Individual patient data pooled analysis of 4 randomized trials from endemic areas by Chen et al reported an absolute benefit of 9.3% in 5 year PFS with the addition of induction chemotherapy to CCRT (P = 0.0009). Induction chemotherapy also improved OS (HR = 0.75; p = 0.04) and reduced distant failure (HR0.68; P = 0.008) [31]. Meta-analysis of 8 randomized trials with 2384 patients by Mane et al reported a significant benefit in OS (HR 0.68, P = 0.001) and PFS (HR 0.657, P < 0.001) with the addition of induction chemotherapy to CCRT, but acute toxicities were more with induction chemotherapy [32].

Induction chemotherapy before chemoradiation is associated with improvement in PFS, OS, and DMFS. TPF did not show any advantage over PF and the optimal induction regimens are cisplatin-infusion 5FU and cisplatin-gemcitabine.

6. Chemotherapy in stage II NPC

Radical radiotherapy is the treatment for stage I disease. Stage III and IVA are managed by induction chemotherapy followed by chemoradiation or chemoradiotherapy with or without adjuvant chemotherapy. But the treatment of stage II disease is controversial. Stage II is a heterogeneous group with T2N0M0, T1N1M0, and T2N1M0disease. A phase 3 trial done by Chen et al in the conventional RT era randomized stage II patients into RT or CCRT [33]. Chemo-RT resulted in better 5 year OS, PFS and Distant metastasis-free survival at the expense of increased acute toxicities. IMRT resulted in improvement in OS by reducing local and regional recurrence with decreased toxicities and better quality of life compared to 2D RT. The benefit of concurrent chemotherapy in the IMRT era is doubtful. Many comparative studies were done to study the effect of the addition of chemotherapy to IMRT. But most of the studies are retrospective in nature. A randomized phase 2 trial by Huang et al showed no significant difference in OS, LFFS, RFFS, DFS, and DMFS after a median follow-up of 75 months. There was a detrimental effect on bone marrow function with chemo-RT [34]. Two retrospective studies from endemic areas showed no improvement in survival with the addition of chemotherapy to IMRT [35, 36]. Propensity score matching analysis in intermediate-risk NPC

by Zhang et al showed no survival benefit (OS, FFS) by adding concurrent chemotherapy to IMRT [37]. Two meta-analyses of stage 2 trials have been published. Xu et al included 2D and IMRT studies [38]. CRT had significantly higher OS (HR 0.67, P = 0.04) and LRRFS (HR = 0.61, P = 0.0003) compared to RT alone, but there was no difference in DMFS. Acute toxicities were more in the chemo-RT arm. Subgroup analysis showed that IMRT alone achieved equivalent OS(P = 0.14), LRRFS(P-0.06) and DMFS(P = 0.89) compared to CRT. Liu et al published a meta-analysis of seven trials that compared IMRT alone with IMRT plus concurrent chemotherapy [39]. There was no benefit with the addition of chemotherapy to IMRT in terms of OS, PFS, DMFS, or LRRFS. Moreover CCRT was associated with increased rates of grade 3–4 leukopenia.

The benefit of adding chemotherapy to intensity-modulated radiotherapy in stage II disease is doubtful and is still under investigation.

7. Chemotherapy in metastatic NPC

Being a chemosensitive tumor, chemotherapy is the mainstay of treatment for metastatic NPC. Single-agent chemotherapy was used previously. Standard chemotherapy agents used now are platinum doublets with gemcitabine, 5FU, or paclitaxel [40, 41]. Higher response rates are associated with combination regimens than monotherapy. Cisplatin-5FU continuous infusion regimen resulted in a response rate of 55–65% [42]. Paclitaxel when added to carboplatin resulted in response rates as high as 75% [43]. A Randomized phase 3 trial from China compared Cisplatin gemcitabine (GP) with cisplatin 5FU(FP) in recurrent and metastatic NPC [44]. Gemcitabine plus cisplatin prolonged progression-free survival in patients with recurrent or metastatic NPC. The updated results showed an improvement in OS with Cisplatin -gemcitabine regimen (HR 0.723 (95% CI, 0.578 to 0.904; P = .004). The median OS was 22.1 months with GP versus 18.6 months with FP [45]. Triplet regimens tried in metastatic settings resulted in higher response rates and increased median OS, but with increased toxicities [46]. There is no head-on comparison with the standard doublets and triplet regimens are not recommended for first-line therapy.

These patients eventually progress on platinum-based chemotherapy due to the development of platinum resistance. The selection of second line treatment depends on the chemotherapy agent used in first line. The common second-line agents are 5-FU (including capecitabine), taxanes (paclitaxel, docetaxel), irinotecan, vinorelbine, and gemcitabine [47–50] The response rates are inferior compared to the first-line agents.

8. Future directions

The role of adjuvant chemotherapy according to risk-adapted approach is evolving. Two trials of adjuvant chemotherapy according to post-treatment plasma EBV DNA measurements (NRG-HN001- NCT02135042 and NCT02363400) are underway [51, 52]. The benefit of concurrent chemotherapy in stage II NPC is not clear. NCT02610010, NCT02116231, and NCT02633202 are ongoing randomized phase2/3 trials evaluating the same [53–55]. There is no proven role for targeted therapy or immunotherapy in locally advanced or metastatic NPC [56, 57]. A phase 3 trial (NCT02633176) comparing cisplatin, docetaxel plus cetuximab with cisplatin and docetaxel induction chemotherapy followed by concurrent chemoradiation in previously untreated metastatic NPC is underway [58]. PD-1 antibody Camrelizumab

is being compared with best supportive care after Chemoradiotherapy in Locoregionally Advanced NPC in a phase 3 trial [59]. Camrelizumab in combination with chemotherapy is tested against chemotherapy alone in recurrent and metastatic NPC in another randomized phase 3 trial [60].

9. Conclusion

Stage I NPC is treated by radical radiotherapy. Stage II disease is treated by IMRT alone or concurrent chemoradiation. Stage III and stage IVA disease are treated by induction chemotherapy followed by concurrent chemoradiation or concurrent chemoradiation +/−adjuvant radiotherapy. Metastatic NPC is usually treated by chemotherapy using platinum doublets, cisplatin-gemcitabine is the standard regimen.

Conflict of interest

The authors declare no conflict of interest.

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