World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/esps/
wjco@wjgnet.com
doi:10.5306/wjco.v4.i2.47

World J Clin Oncol 2013 May 10; 4(2): 47-51
ISSN 2218-4333 (online)
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BRIEF ARTICLE

Combined chemo-radiotherapy in locally advanced nasopharyngeal carcinomas

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Received: February 14, 2013 Revised: March 30, 2013
Accepted: April 13, 2013
Published online: May 10, 2013

Abstract

AIM: To provide efficacy and safety data about the combined use of radiotherapy and chemo-radiotherapy in nasopharyngeal carcinoma (NPC).

METHODS: We reviewed data of 40 patients with locally advanced NPC treated with induction chemotherapy followed by concomitant chemo-radiotherapy (CCRT) (22/40 patients) or CCRT alone (18/40) from March 2006 to March 2012. Patients underwent fiberoscopy with biopsy of the primitive tumor, and computed tomography scan of head, neck, chest and abdomen with and without contrast. Cisplatin was used both as induction and as concomitant chemotherapy, while 3D conformal radiation therapy was delivered to the nasopharynx and relevant anatomic regions (total dose, 70 Gy). The treatment was performed using 6 MV photons of the linear accelerator administered in 2 Gy daily fraction for five days weekly. This retrospective analysis was approved by the review boards of the participating institutions. Patients gave their consent to treatment and to anonymous analysis of clinical data.

RESULTS: Thirty-three patients were males and 7 were females. Median follow-up time was 58 mo (range, 1-92 mo). In the sub-group of twenty patients with a follow-up time longer than 36 mo, the 3-year survival and disease free survival rates were 85% and 75%, respectively. Overall response rate both in patients treated with induction chemotherapy followed by CCRT and in those treated with CCRT alone was 100%. Grade 3 neutropenia was the most frequent acute side-effect and it occurred in 20 patients. Grade 2 mucositis was seen in 29 patients, while grade 2 xerostomia was seen in 30 patients. Overall toxicity was manageable and it did not cause any significant treatment delay. In the whole sample population, long term toxicity included grade 2 xerostomia in 22 patients, grade 1 dysgeusia in 17 patients and grade 1 subcutaneous fibrosis in 30 patients.

CONCLUSION: Both CCRT and induction chemotherapy followed by CCRT showed excellent activity in locally advanced NPC. The role of adjuvant chemotherapy remains to be defined.

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Key words: Nasopharyngeal carcinoma; Induction chemotherapy; Concurrent chemoradiotherapy; Adjuvant chemotherapy; Locally advanced disease

Core tip: Clinical data of 40 patients (33 males, 7 females) with locally advanced nasopharyngeal carcinoma (NPC) treated at two participating institutions from March 2006 to March 2012 were reviewed. Patients received either induction chemotherapy followed by concomitant chemo-radiotherapy (CCRT) (22/40 patients) or CCRT alone (18/40). Patients underwent fiberoscopy with biopsy of the primitive tumor, and a computed tomography scan of the head, neck, chest and abdomen with and without contrast. Cisplatin was used both as induction and as concomitant chemotherapy, while 3D conformal radiation therapy was delivered to the nasopharynx and node areas (total dose, 70 Gy). A complete response rate of approximately 95% was achieved both in patients treated with induction chemotherapy followed by CCRT and in those treated with CCRT alone. In the sub-group of twenty patients with a follow-up time longer than 36 mo, the 3-year survival and disease free survival rates were 85% and 75%, respectively. These results showed that both CCRT and induction chemotherapy followed by CCRT have excellent activity in locally advanced NPC. The role of adjuvant chemotherapy remains to be defined.

Perri F, Della Vittoria Scarpati G, Buonerba C, Di Lorenzo G, Longo F, Muto P, Schiavone C, Sandomenico F, Caponigro F. Combined chemo-radiotherapy in locally advanced nasopharyngeal carcinomas. *World J Clin Oncol* 2013; 4(2): 47-51 Available from: URL: http://www.wjgnet.com/2218-4333/full/v4/i2/47.htm DOI: http://dx.doi.org/10.5306/wjco.v4.i2.47

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a rare malignancy that arises from the epithelium of the nasopharynx. It is particularly frequent in Southeast Asia and can be classified into three histological types, namely nonkeratinizing squamous cell carcinoma, keratinizing squamous cell carcinoma and undifferentiated carcinoma[1,2]. NPC presents several features that differentiate it from other head and neck carcinomas, such as its prognosis and its association with the Epstein-Barr virus (EBV)[3]. While radiotherapy alone is associated with a 5-year disease free survival (DFS) of 95/100% in patients with early stage disease (T1,2aN0M0), locally advanced disease requires combined use of chemotherapy and radiotherapy[4-6]. Two large meta-analysis studies showed superiority of concurrent chemo-radiotherapy (CCRT) compared to radiotherapy alone[7,8]. The role of adjuvant chemotherapy remains controversial. A significant survival advantage was reported for CCRT followed by adjuvant chemotherapy with respect to radiotherapy alone in some trials[9,10], but it was not confirmed by others[11]. Neoadjuvant chemotherapy also appears to be a feasible option, since it may control subclinical metastatic foci, especially patients with locally advanced disease (T4b and/or N2/3). Although several phase Ⅱ and Ⅲ trials of induction chemotherapy followed by radiotherapy have been carried out, no conclusive evidence in favor of its efficacy is presently available[12-15].

In this retrospective analysis, we reviewed data of 40 patients with locally advanced NPC treated with induction chemotherapy followed by CCRT or CCRT alone .

MATERIALS AND METHODS

Patients selection

Data regarding patients with a histologically confirmed diagnosis of locally advanced NPC (T2bN0M0-T4bN3M0) and treated with chemotherapy and radiotherapy from March 2006 to March 2012 at the participating Institutions, were retrieved from reviewed charts. Patients underwent fiberoscopy with biopsy of the primitive tumor, and computed tomography (CT) scan of head, neck, chest and abdomen with and without contrast. A 18-fluoro-2-deoxy-*D*-glucose positron emission tomography (FDG-PET) scan was performed in selected patients according to the physician's judgment.

Treatment plan

Patients were treated with the either induction chemotherapy followed by CCRT (22 patients) or with CCRT alone (18 patients). Several cisplatin-based regimens were used for induction chemotherapy (Table 1). After induction chemotherapy, a CT scan of head, neck, chest and abdomen and a fiberoscopy were performed for re-staging. Patients receiving CCRT were treated with cisplatin (100 mg/m^2 on days 1, 22 and 43) and 3D conformal radiation therapy, which was administered concurrently in cycle 1.

The nasopharynx and other relevant anatomic regions were included in the treatment plan. Gross tumor volume (GTV), clinical target volumes (CTVs), planning target volume and planning organ at risk volumes were defined for each patient according to the reports 50 and 62 of the International Committee on Radiation Units and Measurements. The CTV-T included the GTV-T, the posterior third of the nasal cavity, the maxillary sinuses, the inferior sphenoidal body, the clivus and the pterygoid fossae. CTV-N was defined as the volume encompassing GTV-N (if macroscopic nodal metastases were present) and bilateral cervical lymph node stations (levels Ib-V), the medial supraclavicular fossae and retro/parapharyngeal spaces. In order to account for set-up errors and patient movements, two sets of planning target volumes were also defined by adding a 5 mm margin to each corresponding CTV. A total dose of 70 Gy was planned. The treatment was performed using 6 MV photons of the linear accelerator administered in 2 Gy daily fraction for five days weekly. In all patients, an electron beam boost (8-10 MeV) was administered to limit the dose to spinal cord. Late toxicity was graduated according to the Radiation Therapy Oncology Group guidelines for toxicity.

Response assessment

Patients underwent a fiberoscopy and a FDG-PET scan 60-90 d after radiotherapy, while a CT scan of head,

Table 1 Patients characteristics

Characteristic	Patients
Total	40
Male	33
Female	7
Age, yr, median (range)	60 (24-82)
Stage	
Ⅱb	3
Ⅲ	18
Ⅳa	15
Ⅳb	4
ECOG performance status	
0	36
1	4
2	0
Treatment performed induction CT followed by	
CCRT[1]	22
CCRT[2]	18
Total	40
Induction chemotherapy scheme	
PF[3]	9
TPF[4]	3
TP[5]	9
BMC[6]	1
Total	22
Total radiation dose delivered	
70 Gy	36
68 Gy	3
66 Gy	1
Histology squamous cell	
G1	1
G2	2
G3	4
Undifferentiated	33

[1]Induction chemotherapy followed by concomitant chemo-radiotherapy; [2]Concurrent chemoradiotherapy; [3]Cisplatin (100 mg/m^2 every 3 wk) and 5-fluorouracil (5-FU) (1000 mg/m^2 per day, 4-d continuous infusion every 3 wk); [4]Docetaxel (75 mg/m^2 every 3 wk), cisplatin (75 mg/m^2 every 3 wk) and 5-FU (750 mg/m^2 per day, 4-d continuous infusion every 3 wk); [5]Docetaxel (75 mg/m^2 every 3 wk) and cisplatin (75 mg/m^2 every 3 wk); [6]Bleomycin (25 mg/m^2 on days 1 and 8 of a 21-d cycle), methotrexate (35 mg/m^2 weekly) and cisplatin (80 mg/m^2 every 3 wk). ECOG: Eastern Cooperative Oncology Group; CT: Computed tomography.

neck, chest and abdomen with and without contrast was performed 45-50 d after completion of radiotherapy. The response evaluation criteria in solid tumors criteria were used to define response.

This retrospective analysis was approved by the review boards of the participating institutions. Patients gave their consent to treatment and to anonymous analysis of clinical data.

RESULTS

Patients characteristics

Forty patients (33 males and 7 females) were included in this analysis. Median age was 60 years (range, 24-82 years). The majority of patients had an undifferentiated carcinoma (33 patients, 82.5%) and a stage Ⅲ-Ⅳ disease (37 patients, 92.5%). Patients' characteristics are detailed in Table 1.

Table 2 Results *n* (%)

Treatment performed	Results
ORR	40 (100)
Total (all group)	
Induction chemotherapy followed by	
CCRT[1] group	22 (100)
CCRT[2] group	22 (100)
CR rate	
Induction chemotherapy followed by	38 (95)
CCRT[1] group	21 (95.5)
CCRT[2] group	17 (94.4)
3-yr OS	
Total (all group)	17 (85)
3-yr DFS	
Total (all group)	15 (75)

[1]Induction chemotherapy followed by concomitant chemoradiotherapy; [2]Concurrent chemoradiotherapy. ORR: Overal response rate; CR: Complete response; OS: Overall survival; DFS: Disease free survival.

Response rate

All patients were evaluable for response after completion of the planned treatment. In patients receiving induction chemotherapy followed by CCRT, overall response rate (ORR) to induction chemotherapy was 90.9% (20/22), with a complete response (CR) rate of 36.4% (8/22). In this sub-group, after completion of chemoradiotherapy, ORR was 100% with a CR rate of 95.5% (21/22). In the CCRT only group, an ORR of 100% was obtained, with a CR rate of 94.4% (17/18).

Survival

Median follow-up time was 58 mo (range, 1-92 mo). At the time of the analysis, no patient had been lost to follow-up, six had died for the disease, twenty-eight were disease free, and the remaining six patients were alive with recurrent/persistent disease.

In the sub-group of 20 patients with a follow-up period > 3 years (12 treated with induction chemotherapy followed by CCRT, 8 treated with CCRT only), the 3 year overall survival and DFS rate were respectively 85% (17/20) and 75% (15/20). These results are detailed n Table 2.

Toxicity

Grade 3 neutropenia was the most frequent acute side-effect and it occurred in 20 patients. Grade 2 mucositis was seen in 29 patients, while grade 2 xerostomia was seen in 30 patients. Overall toxicity was manageable and it did not cause any significant treatment delay. In the whole sample population, long term toxicity included grade 2 xerostomia in 22 patients, grade 1 dysgeusia in 17 patients and grade 1 subcutaneous fibrosis in 30 patients.

DISCUSSION

NPC is highly chemo and radiosensitive, and an excellent disease control can be achieved using combined modal-

ity chemoradiation even in patients with locally advanced disease[1,2]. Presently, the benefit of adding neoadjuvant/adjuvant chemotherapy remains to be defined. Three large phase Ⅲ trials confirmed the superiority of CCRT followed by adjuvant cisplatin and 5fluorouracil *vs* radiotherapy alone[9-11]. Interestingly, a combined analysis of two large studies (NPC-9901 and the NPC-9902) revealed that the dose of cisplatin during the CCRT had a significant impact on locoregional control[16,17]. Despite patients included in this retrospective study did not receive adjuvant chemotherapy, a CR rate of approximately 95% a 3-year DFS rate of approximately 75% were obtained. These results are in line with published data and highlight the need of further phase Ⅲ trials to assess the role of adjuvant therapy.

One possible way to select better patients suitable for an adjuvant approach may be assessment of plasma EBV DNA levels. In fact, several data showed that EBV DNA levels correlated significantly with tumor load, recurrence rate and survival[18,19]. An early post-CCRT detection of high EBV DNA levels may be an indication to administer adjuvant chemotherapy.

One strategy to further improve the efficacy of chemotherapy is to use induction chemotherapy followed by radiation therapy alone or CCRT. Induction chemotherapy is generally better tolerated than adjuvant chemotherapy and might provide early eradication of distant micro-metastases[3], especially in patients with locally advanced disease (T4 and/or N2/3). In addition, induction chemotherapy could shrink the primary tumor to give wider margins for irradiation. In several phase Ⅱ clinical trials, induction cisplatin-taxane containing chemotherapy followed by radiotherapy or chemo- radiotherapy has been employed, with a median ORR of 94% and a 3-year DFS of 81%[20-22]. These results are in line with those reported here. One interesting strategy may include selection of NPC patients who are more likely to benefit from chemotherapy. Human papilloma virus positivity, high Ki-67 value, absence of p53 mutation are strongly related to chemo and radiosensitivity in head and neck squamous cell carcinomas[23,24]. These factors should be explored in NPC also.

Patients included in this retrospective analysis received 3D conformal radiation therapy. Of note, intensity-modulated radiation therapy (IMRT) can improve dose conformity for complex tumor targets and is able to obtain a better protection of adjacent organs[25,26]. It is likely that IMRT will become the standard technique employed for head and neck malignant tumors.

In conclusion, our study confirms that concurrent chemoradiotherapy represents the standard treatment for patients with locally advanced NPC. The role of adjuvant chemotherapy following CCRT is not well defined and requires to be investigated in phase Ⅲ trials. Assessment of EBV DNA titers in patients treated with CCRT may be helpful to select patients requiring adjuvant chemotherapy.

COMMENTS

Background

Nasopharyngeal carcinoma (NPC) is a rare malignancy that has several distinct features with respect to other head and neck tumors. While radiotherapy alone is associated with a 5-year disease free survival of 95/100% in patients with early stage disease (T1, 2aN0M0), locally advanced disease requires combined use of chemotherapy and radiotherapy.

Research frontiers

Adjuvant and neoadjuvant chemotherapy may have a role for the treatment of locally advanced NPC.

Innovations and breakthroughs

Three large phase Ⅲ trials confirmed the superiority of concurrent chemotherapy and radiotherapy followed by adjuvant chemotherapy *vs* radiotherapy alone in NPC.

Applications

Results obtained in this retrospective review confirm the effectiveness of combined use of chemotherapy and radiotherapy in locally advanced NPC. The role of adjuvant chemotherapy remains to be ascertained.

Terminology

Epstein-Barr virus is a virus of the herpes family that is best known as the cause of infectious mononucleosis, but it is also associated with human malignancies, such as NPC and lymphomas. Intensity-modulated radiation therapy is an advanced type of radiation therapy that uses multiple small radiation beams of varying intensities to radiate a tumor in a precise way. It is considered to be more accurate than 3D conformal radiation therapy.

Peer review

The article is a retrospective study about the efficacy of induction chemotherapy in the context of chemoradiotherapy for locally advanced NPC and serves to confirm what has been published in several large studies and in some meta-analysis.

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