

Original article

Neoadjuvant Docetaxel, Cisplatin and Fluorouracil followed by Concurrent Cisplatin Intensity Modulated Radiation Therapy in Treatment of Locally Advanced Nasopharyngeal Carcinoma

E. Ibrahim¹ and H. Zagloul²

¹Medical Oncology and ²Radiation Oncology Departments, King Fahad Specialist Hospital and Dammam, Saudi Arabia

Aim of the Study: To assess the tolerability, toxicity and efficacy of neoadjuvant Docetaxel, Cisplatin and Fluorouracil (TPF) followed by concurrent Cisplatin and radiotherapy (RT) in patients with locoregionally advanced nasopharyngeal carcinoma (NPC).

Patients and Methods: Twenty patients with locally advanced nasopharyngeal carcinoma who presented to the Oncology Centre at King Fahd Specialist Hospital, Dammam in Saudi Arabia received induction chemotherapy with 2 cycles of TPF chemotherapy: Docetaxel: 75 mg/m², Cisplatin: 75 mg /m² and continuous infusion of 5-Fluorouracil: 750 mg / m² CI for 96 hours followed 3-4 weeks later by concurrent weekly Cisplatin (40 mg /m²) and IMRT (Intensity Modulated Radio Therapy) (GTV:70 Gy over 35 fractions).

Results: Response to neoadjuvant chemotherapy was as follows: 6 patients (30%) and 12 patients (60%) achieved complete remission (CR) and partial remission (PR), respectively. One patient (5%) had no response to induction chemotherapy and one patient (5%) died post first cycle of chemotherapy. At last follow up, 17 patients (85%) were in complete remission while 2 patients (10%) had progressive disease. The most common acute toxicity of TPF was grade 3-4 neutropenia (40%). The most common acute toxicity of Cisplatin plus RT was grade 3-4 mucositis (60%). At last follow up (May 2012) seventeen patients (85%) were alive and free of disease.

Conclusions: Neoadjuvant Docetaxel, Cisplatin and Fluorouracil (TPF) followed by concurrent Cisplatin and radiotherapy (RT) in patients with locoregionally advanced nasopharyngeal carcinoma (NPC) was feasible and resulted in complete remission rate of 85% with acceptable toxicity profile.

Key words: nasopharyngeal carcinoma, neoadjuvant chemotherapy, and radiotherapy.

Corresponding Author: Ehab Ibrahim

E-mail: ehabhas@hotmail.com

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INTRODUCTION

Radiotherapy is the primary treatment modality for all locally and regionally confined stages of nasopharyngeal carcinoma (NPC). Whereas the control of early-stage disease with radiotherapy is usually successful, the response of locally and regionally advanced NPC to radiation is poor because of local relapse and distant metastases¹⁻⁴.

Diagnosis is made by biopsy and workup which includes careful examination, documentation of the size and location of the neck nodes; evaluation of cranial nerve function and hearing; skull films (especially skull base views), evaluating neural foramina; complete computed tomographic (CT) scan or magnetic resonance imaging (MRI) with views delineating the upper and lower extent of the lesion; chest x-ray; hemogram; and chemistry panel⁵⁻⁷.

Major prognostic factors adversely influencing outcome of treatment include large size of the tumor,

higher T stage, and the presence of involved neck nodes⁸.

The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification to define nasopharyngeal cancer⁹.

Incorporation of chemotherapy with standard RT has improved the therapeutic outcome of patients with locoregionally advanced NPC. This is supported by a meta-analysis of six randomized trials suggesting that when compared with RT alone, the addition of chemotherapy in any sequence increases disease-free survival by 35% at 2 to 4 years and overall survival by 20% at 3 to 4 years¹⁰. A key question remains regarding the optimal sequencing of chemotherapy and RT. Many published randomized trials of concurrent chemoradiotherapy have demonstrated a progression-free (PFS) and/or overall survival (OS) benefit over RT

alone¹¹⁻¹³. In this regard, neoadjuvant chemotherapy may have better tolerability, and moreover impressive tumor response rates have been reported in phase II studies¹⁴.

MATERIAL AND METHODS

Twenty patients with locally advanced nasopharyngeal carcinoma (stage III-IVB) with no distant metastasis who presented to the Oncology Centre at King Fahd Specialist Hospital, Dammam in Saudi Arabia were enrolled in this study during the period between July 2007 and April 2012. All patients received two cycles of TPF induction chemotherapy: Docetaxel: 75 mg/m², Cisplatin: 75 mg /m² and continuous infusion of 5-Fluorouracil: 750 mg / m² CI over 96 hours followed 3-4 weeks later by concurrent weekly Cisplatin (40 mg /m²) and IMRT (GTV:70 Gy over 35 fractions). All patients had a non-metastatic disease as proved by doing chest and abdominal CT scan, bone scan and PET/CT scan. In this study, tumor staging was based on the American Joint Committee on Cancer (AJCC) criteria for NPC⁹.

Patient Monitoring and Follow up:

Before treatment, patients underwent a complete history and physical examination, including evaluation of performance status, assessment for the presence of concurrent co-morbid conditions with estimation of body weight, height, vital signs and measurement of palpable or visual lesions. Laboratory studies included a complete blood count (CBC) with white blood cell differential count, biochemistry profile, kidney function test, liver function tests, hepatitis markers, random blood sugar and Epstein-Barr virus (EBV) DNA assay. Radiological examinations, including CT head and neck, chest, abdomen and pelvis, were required before starting treatment, at the end of induction chemotherapy, post concurrent chemoradiation and then periodically. Isotopic bone scan was not done routinely. PET/CT was done at presentation and post induction chemotherapy. Patients should have dental clearance before initiation of radiation therapy.

During therapy, performance status, weight, vital signs and full blood counts were obtained before each chemotherapy cycle. In addition a complete medical history, including assessment of subjective and objective toxicity according to the WHO Common Toxicity Criteria (CTC) was obtained before the start of each new cycle¹⁵⁻¹⁶.

The primary end point of this study was response rate (RR). The treatment response was categorized according to Response Evaluation Criteria in Solid Tumors (RECIST)¹⁷ The secondary end point was to assess the toxicity and tolerability of chemotherapy.

Chemotherapy Protocol:

Neoadjuvant chemotherapy consisted of two cycles of TPF regimen: Docetaxel (75 mg/m² administered intravenously [IV] over 1 hour), Cisplatin (75 mg/m² administered intravenously [IV] over 1 hour) and continuous infusion of 5-Fluorouracil (750 mg / m² CI over 96 hours) given on days 1 and 21. Docetaxel infusion was preceded by IV Dexamethasone 20 mg, Chlorpheniramine 50 mg, Ranitidine 50 mg and Granisetron 1 mg. During RT, cisplatin at a dose of 40 mg/m² IV infusion was administered weekly for 7 weeks, given at approximately 60 minutes before receiving RT.

Radiation Therapy Technique:

Intensity Modulated Radiation Therapy (IMRT) using Simultaneous Integrated Boost (SIB) was used in treating patients, three planning target volumes (PTVs) were created: PTV 70 Gy to the primary and involved nodes, PTV 60 Gy to rest of nasopharynx, the oropharynx, posterior two thirds of the anterior maxillary sinuses and to non involved upper neck nodes and finally PTV 54 Gy to non involved lower neck nodes.

RESULTS

From July 2007 to April 2012, 20 patients referred to Oncology Centre at King Fahd Specialist Hospital, Dammam in Saudi Arabia were enrolled in this study. Patients and tumor characteristics are shown in Table 1. The mean age was 42 years with a range of 17-64 years and SD 13.2. Fourteen patients (70%) were males, while 6 patients (30%) were females. Performance status of ECOG (Eastern Cooperative Oncology Group) (0-1) and (2) was present in 14 patients (70%) and 6 patients (30%), respectively. Five patients (25%) in the study presented with tumor stage T2, 3 patients (15%) presented with T3 stage and 12 patients (60%) with T4 disease. One patient (5%) had no lymph node metastasis at presentation, 1 patient (5%) with N1 disease, 9 patients (45%) with N2 disease and 9 patients (45%) with N3 disease. The main symptom at presentation was neck swelling which was present in 14 patients (70%). Other symptoms were headache, ear symptoms and epistaxis.

Overall, toxicity related to neoadjuvant chemotherapy with Docetaxel, Cisplatin and Fluorouracil was manageable. Induction chemotherapy was generally well tolerated. Nineteen patients completed the planned treatment, and were assessable for response and toxicity. Three patients (15%) had a dose delay of ≥ 7 days, because of delayed neutrophil recovery. Grade 3-4 neutropenia occurred in eight patients (40%), while grade 3-4 thrombocytopenia

without bleeding occurred in two patients (10%). Three patients (15%) developed uncomplicated, culture-negative grade 2 febrile neutropenia during induction chemotherapy. Grade 3-4 anorexia and nausea occurred in 60% of patients while, grade 3-4 vomiting occurred in 15% of patients. Ninety percent of patients developed reversible grade 3 and 4 alopecia. Two patients (10%) developed hypersensitivity reaction to Docetaxel during the first cycle which was mild and manageable. One patient (5%) developed reversible renal impairment. Treatment-related death was encountered in one patient during induction chemotherapy.

Concurrent Cisplatin with radiation was tolerable and of accepted toxicity profile. The most commonly reported grade 3-4 toxicity were mucositis, dysphagia, skin reactions and weight loss which occurred in 60%, 25%, 20% and 30%, respectively, (Table 2).

The overall response rate to induction chemotherapy reached 90% with complete remission (CR) and partial remission (PR) rates of 30% and 60%, respectively. Six weeks post concurrent chemoradiation therapy, 85% and 10% of patients were in complete remission and partial remission, respectively, (Table 3).

Table 1: Patients and Characteristics.

Characteristic	No	%
Age, years		
Median	42	
Range	17-64	
Male: Female	14:6	70:30
ECOG performance status		
ECOG (0-1)	14	70
ECOG (2)	6	30
T stage		
T2	5	25
T3	3	15
T4	12	60
Nodal stage N		
N0	1	5
N1	1	5
N2	9	45
N3	9	45

Table 2: Toxicity of Induction Chemotherapy.

Type of Toxicity	No	%
Neutropenia	8	40
Thrombocytopenia	2	10
Febrile Neutropenia	2	10
Anorexia & Nausea	12	60
Vomiting	3	15
Alopecia	18	90
Renal Impairment	1	5

Table 3: Treatment response.

Mode of Assessment	6 Weeks Post Induction Chemotherapy		6 Weeks Post Concurrent CRT	
	No	%	No	%
CR	6	30	17	85
PR	12	60	2	10

CR: Complete Remission, PR: Partial Remission.

DISCUSSION

Patients with locoregionally advanced NPC have traditionally been treated solely with conventional RT; however, many develop local and/or distant failures and the long term survival rates were not satisfactory. In an attempt to improve treatment outcomes, several groups have incorporated chemotherapy adjuvantly, neoadjuvantly or concurrently with RT in randomized controlled trials^{11-13,18-20,22,23}. The results of a meta-analysis of 1528 patients from six randomized trials have shown that the addition of chemotherapy to radical RT for locoregionally advanced NPC increased both disease free/progression free and overall survival by between 20 and 40% at 2-4 years after treatment¹⁰.

The primary rationale for induction or adjuvant chemotherapy in nasopharyngeal cancer has been to decrease the risk of developing distant metastases. Promising 4-5 years OS rates exceeding 75% have been reported in studies from Australia and North America using sequential neoadjuvant chemotherapy and chemoradiotherapy. Al-Amro *et al.*²¹ used two cycles of Cisplatin and Epirubicin followed by concomitant RT at 66 Gy in 2 Gy fractions and concurrent Cisplatin for three cycles 25 mg/ m² for 4 days on Days 42, 63, and 84. In another study, Hong *et al.*²⁴ used three cycles of induction chemotherapy with Mitomycin, Epirubicin, Cisplatin, Fluorouracil, and Leucovorin (MEPFL) before RT.

Three large trials of induction without concurrent chemotherapy have not demonstrated improved overall survival compared with radiation alone²⁵⁻²⁷ Chan *et al.* used induction chemotherapy of 2 cycles of Taxol (Paclitaxel) and Carboplatin followed by concurrent Cisplatin RT²⁸. Another study used induction chemotherapy of 2 cycles of Docetaxel and Cisplatin followed by concurrent Cisplatin with radiotherapy²⁹.

In our study induction chemotherapy was generally well tolerated and of acceptable toxicity profile. Ten percent of patients developed grade 3-4 anaemia. Wee *et al.* in 2003 reported grade 3-4 anaemia of 3% in their study³⁰. Grade 3-4 neutropenia occurred in 40% of patients. Our results are lower than what reported in 2001 by Hong *et al.*²⁴ who reported an incidence of 59% of grade 3-4 neutropenia in his study. Al-Amro *et al.*²¹ and Chan *et al.*²⁸ reported an incidence of grade 3-4 neutropenia of 31% and 36% respectively. This could be explained by the low myelotoxic potential of the regimen they used. Our results are much less than that reported by Chan *et al.*²⁹ who reported an incidence of grade 3-4 neutropenia of 100% who used the same regimen of induction chemotherapy but without fluorouracil. One patient experienced grade 3-4 febrile neutropenia post first cycle of induction chemotherapy and died because of complications. Ninety percent of our patients developed grade 3-4 alopecia. Chan *et al.*²⁸ did not report any grade 3-4 alopecia in his study.

Chemotherapy related toxicity during concurrent Cisplatin with radiation was seen in 60% of our patients who developed grade 3-4 mucositis within the radiation field which concurs with the results of Chan *et al.*²⁸ and Lee *et al.*³¹ who reported an incidence of 55% and 62% of grade 3-4 mucositis, respectively. Al-Amro *et al.*²¹ reported an incidence of grade 3-4 mucositis of 49%.

The overall response rate (CR and PR) to neoadjuvant Taxotere, Cisplatin and Fluorouracil in the study was 90%. Chan *et al.*²⁸ reported an overall tumor response of 97%. Chan *et al.*²⁹ reported an overall response rate to neoadjuvant chemotherapy of 86%. Hong *et al.*²⁴ reported complete remission rate of 45.5%, while Paccagnella *et al.*³² reported very low incidence of complete remission rate post induction chemotherapy which was 6.5% compared to 30% in our study.

In our study, 6 weeks post concurrent chemoradiation 85% of patients were in complete remission. Chan *et al.*²⁸ reported complete remission rates of 100% in his study, while Paccagnella *et al.*³², Cho *et al.*³³ and Yamouni *et al.*³⁴ reported complete remission rates of 50% and 48% and 76.8%, respectively.

The current study confirms the feasibility of combining neoadjuvant TPF (Taxotere- Cisplatin-Fluorouracil) followed by concurrent chemoradiotherapy in patients with advanced NPC and resulted in a complete remission rate (CR) in 85% of patients. Patient tolerability and compliance to neoadjuvant TPF chemotherapy was acceptable.

CONCLUSION

Neoadjuvant chemotherapy using Docetaxel, Cisplatin and Fluorouracil (TPF) followed by concurrent Cisplatin-RT used for patients with locally advanced nasopharyngeal cancer results in excellent tumor control, manageable toxicity profile and achieving complete remission rate of 85%.

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