



Neo-adjuvant Docetaxel and Cisplatin followed by Concurrent Cisplatin with Radiation Therapy in Treatment of Locally Advanced Nasopharyngeal Carcinoma

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Abstract

Aim of the study

To assess the tolerability, toxicity and efficacy of neo-adjuvant Docetaxel and Cisplatin (TC) followed by concurrent Cisplatin and radiotherapy (RT) in patients with loco-regionally advanced nasopharyngeal carcinoma (NPC).

Patients and methods

Fourteen patients with locally advanced NPC received two cycles of Docetaxel (75 mg/m² on days 1, and 21) and Cisplatin (75 mg/m² on days 1, and 21) followed by 7 weeks of Cisplatin (40 mg/m² weekly) and RT at 70 Gy in 2-Gy per fraction.

Results

Response to neo-adjuvant TC was as follows: 5 patients (36%) and 11 patients (79%) achieved partial remission (PR) in regional nodes and nasopharynx, respectively. Nine patients (64%) and 1 patient (7%) achieved complete remission (CR) in regional nodes and

nasopharynx, respectively. At 6 weeks after RT, 12 patients (86%) achieved CR in regional nodes and nasopharynx, and 2 patients (14%) achieved partial response (PR) in regional nodes and nasopharynx. Neo-adjuvant TC was well tolerated. The most common acute toxicity of Cisplatin plus Docetaxel was grade 3-4 leucopenia (57%) and alopecia (43%). The most common acute toxicity of Cisplatin plus RT was grade 3-4 mucositis (64%). At median follow-up of 12 months, one distant and one loco-regional failure occurred.

Conclusions

Neo-adjuvant Docetaxel and Cisplatin (TC) followed by concurrent Cisplatin and radiotherapy (RT) in patients with loco-regionally advanced nasopharyngeal carcinoma (NPC) was feasible and resulted in excellent local tumour control with acceptable toxicity profile.

Key words

Nasopharyngeal carcinoma, neo-adjuvant chemotherapy, radiotherapy.

Introduction

Radiotherapy is the primary treatment modality for all locally and regionally confined stages of nasopharyngeal carcinoma. 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 metastases.⁽¹⁻⁴⁾

Diagnosis is made by biopsy of the nasopharyngeal mass. Workup includes careful visual examination (by mirror or endoscopic examination), documentation of the size and location of the tumour and neck nodes, evaluation of cranial nerve function and hearing, skull films (especially base of skull 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 panel. MRI is often more helpful than CT scans in detecting abnormalities and in defining their extent.⁽⁵⁻⁷⁾

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Major prognostic factors adversely influencing outcome of treatment include large size of the tumour, higher T stage, and the presence of involved neck nodes.⁽⁸⁾

The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification to define nasopharyngeal cancer.⁽⁹⁾

Incorporation of chemotherapy with standard RT has improved the therapeutic outcome of patients with loco-regionally 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 years.⁽¹⁰⁾ 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 alone.⁽¹¹⁻¹³⁾ In this regard, neo-adjuvant chemotherapy may have better tolerability, and moreover impressive tumour response rates have been reported in phase II studies.⁽¹⁴⁾ Despite the failure of randomized trials in demonstrating a survival advantage of this approach over RT alone⁽¹⁵⁾ two large trials have shown significant improvement in PFS in subgroups of patients with stage III and IV NPC.^(16,17)

Material and methods

Fourteen patients with locally advanced nasopharyngeal carcinoma with no distant metastasis were enrolled in this study. All patients received two cycles of induction chemotherapy with Docetaxel 75 mg/m² and Cisplatin 75 mg/m² on Days 1 and 21, followed by a radical course of radiotherapy (70Gy in 7 weeks, 200 cGy/fraction) starting on Day 42, with concurrent Cisplatin 40 mg/m² for 1 day on weekly basis till the end of radiation. All patients were free from metastatic disease as proved by chest and abdominal CT scan and bone scan. In this study, tumour staging was based on the 2002 American Joint Committee on Cancer (AJCC) criteria for NPC.⁽⁹⁾

Inclusion criteria

- Age > 16 years, < 75 years.
- ECOG scale performance status of 0–2.
- Stage II, III or IV disease.
- At least one site of bi-dimensionally measurable tumour as assessed by clinical examination, computed tomography (CT) or magnetic resonance imaging had to be identified.
- Life expectancy of > 3 months.
- No previous chemotherapy or radiotherapy prior to the study.
- Adequate hematopoietic reserve: absolute neutrophil count >1.5 x 10⁹/l, platelets >100 x 10⁹/l with adequate hepatic and renal function (serum creatinine <1.5 times the upper normal limit (UNL), creatinine clearance >60 ml/min, serum bilirubin, AST and ALT <1.5 times UNL).
- All patients were required to provide signed informed consent.

Exclusion criteria

Patients were excluded if they had received previous chemotherapy or radiotherapy. Patients who had active infections (including positive human immunodeficiency virus or unresolved hepatitis B patients), evidence of more than grade (1) peripheral neuropathy, or inadequate liver or renal functions. Also patients who were pregnant or with breast feeding, or had a second malignancy or other serious concomitant medical disorders, were excluded from the study.

Patient Monitoring and Follow up

Before treatment, patients had a complete history and physical examination, including evaluation of performance status, assessment for the presence of concurrent co-morbid conditions with estimation of weight, height, vital signs and measurement of palpable or visual tumour lesions. Laboratory studies included a complete blood count (CBC) with white blood cell differential

count, urine analysis, biochemistry profile, kidney function tests, liver function tests and glucose. Radiological examinations, including CT head and neck and CT scanning of chest, abdomen and pelvis, were required before starting treatment. Isotopic bone scan was not done routinely. Patients had dental care before initiation of radiation therapy.

During therapy, performance status, weight, blood pressure, pulse rate, and full blood counts were obtained before each chemotherapy cycle. In addition, a complete medical history, including assessment of subjective (non-laboratory assessments) and objective (laboratory assessments) toxicity according to the WHO Common Toxicity Criteria (CTC) were obtained before the start of each new cycle. ^(18, 19)

The primary end-point of this study was response rate (RR). All patients had disease re-assessment by physical examination, ENT examination and CT scan of the head & neck. The treatment response was categorized according to Response Evaluation Criteria in Solid Tumours (RECIST). ⁽²⁰⁾

Six weeks after the completion of concurrent chemoradiation therapy, patients were assessed by clinical examination, full ENT evaluation and radiologically by CT scans.

Chemotherapy protocol

Neoadjuvant chemotherapy comprised two cycles of Docetaxel, 75 mg/m² administered intravenously (IV) over 1 hour and given on days 1 and 21, followed by Cisplatin 75 mg/m² administered intravenously (IV) over 1 hour on day 1 and 21 and repeated every 3 weeks. Docetaxel infusion was preceded by IV Dexamethasone 20 mg, Chlorpheniramine 50 mg, Ranitidine 50 mg and Granistron 1 mg. All chemotherapy was given via a peripheral venous catheter in an outpatient setting. 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.

Normal saline (500 mL) were given before and (1 L) during cisplatin infusion, during which mannitol was also used to maintain a high urine output.

Radiation therapy technique

CT based planning was used. Phase I of radiation therapy to NPC was carried out through 2 lateral head and neck fields including the nasopharynx and all surrounding tissues at risk of involvement taking into account to included the primary tumour + 2 cm safety margin all around, the lateral neck nodes were included as well. The field set-up was 2 parallel-opposed beams with reference dose level at mid-line. The lower neck and supraclavicular nodes were treated via a single anterior neck field. Radiation dose to lateral neck was 40 Gy given in 20 fractions over 4 weeks (200 cGy per fraction), and the anterior neck field was given 50 Gy over 25 fractions in 5 weeks (200 cGy per fraction).

Phase II was given by reduced lateral neck fields to include the nasopharynx and the surrounding tissues till the area just in front of the spine (off cord field) and radiation was given at a dose of 10 Gy/ 5 fractions / 5days using 2 parallel opposed photon beam. Posterior neck nodes were boosted with an electron beam with variable energies dependent on depth of involved nodes, the dose given was 10 Gy/ 5 fractions / 1 week.

In Phase III the nasopharynx proper was treated to 20 Gy/, 10 fractions/ 2 weeks midline dose using 2 parallel-opposed beams and high photon energy.

Results

From September 2005 to October 2006, 14 patients were enrolled into this study. Patients and tumour characteristics are shown in Table 1. The mean age was 42 years with a range of 30-66 years. Twelve patients (86%) were males, while 2 patients (14%) were females. According to the Eastern Co-operative Oncology Group assessment of performance status, 10 patients (71%) and 4 patients (29%) had a performance of 0-1 and 2 respectively. Twelve patients (86%) had

WHO grade 2 histology. Eight patients (57%) in the study had stage T3, 5 patients (36%) T2 and, 1 patient (7%) had T4. Ten patients (71%) had N2 disease, 2 patients (14%) N1 and 2 patients (14%) had N3 disease. The main symptom at presentation was neck swelling which was present in 71% of cases followed by pain.

Characteristics	No	%
Age, (years)		
Median	42	
Range	30-66	
<i>Male: Female</i>	12:2	86:14
<i>ECOG performance status</i>		
ECOG (0-1)	10	71
ECOG (2)	4	29
<i>WHO Histology</i>		
2	2	14
3	12	86
<i>Tumor stage T</i>		
T1	-	-
T2	5	36
T3	8	57
T4	1	7
<i>Nodal stage N</i>		
N1	2	14
N2	10	71
N3	2	14
<i>Metastasis M</i>	-	-
<i>Symptom at presentation</i>		
Neck swelling	10	71
Odynophagia	9	64
Nasal symptoms and epistaxis	9	64

Table 1: Patients and Tumor Characteristics.

	WHO CTC Grade			
	1-2		3-4	
	No	%	No	%
Anemia	13	93	1	7
Leucopenia	6	43	8	57
Thrombocytopenia	9	64	1	7
Anorexia& Nausea	13	93	1	7
Vomiting	12	86	2	14
Sensory Neuropathy	7	50	-	-
Alopecia	8	57	6	43

Table 2: Chemotherapy-Related Toxicity during Neo-adjuvant Docetaxel/Cisplatin.

Overall, toxicity related to neo-adjuvant Docetaxel and Cisplatin was manageable. Induction chemotherapy was generally well tolerated. A total of 28 cycles were given. All patients received 2 cycles of neo-adjuvant chemotherapy. All 14 patients completed the planned treatment, and all were assessable for response and toxicity. During induction chemotherapy, most of the patients developed grade 1-2 WHO toxicity [Table 2]. Three patients (21%) had a dose reduction of Docetaxel and Cisplatin. Five patients (36%) had a dose delay of 5 days, most commonly because of delayed neutrophil recovery. Grade 1-2 anaemia occurred in 93% of patients and only 7% of patients developed grade 3-4 anaemia. Grade 3-4 leucopenia occurred in 57% of patients, while grade 3-4 thrombocytopenia without bleeding occurred in 7% of patients. Two patients (14%) developed uncomplicated, culture-negative grade 2 febrile neutropenia during induction chemotherapy. Grade 3-4 anorexia and nausea occurred in 7% of patients while, grade 3-4 vomiting occurred in 14% of patients. Grade 1-2 sensory neuropathy occurred in 50% of cases. Forty-three percent of patients developed grade 3 and 4 alopecia. Two patients (14%) developed hypersensitivity reaction to Taxotere during the first cycle which was mild and manageable.

Concurrent Cisplatin with radiation was tolerable and of accepted toxicity profile. Most of the patients developed only grade 1-2 WHO hematologic toxicity. Non-hematologic toxicities related to Cisplatin, such as nausea, vomiting, and sensory neuropathy, were mild, and renal impairment was not encountered.

The most commonly reported toxicity experienced during Cisplatin-RT was grade 3-4 mucositis within the RT field which occurred in 64% of cases. Grade 3-4 odynophagia occurred in 36% of patients. Grade 3-4 xerostomia and RT related skin toxicity were rare, while grade 1-2 was common, [Table 3]. Treatment-related deaths were not encountered in this study.

	WHO CTC grade			
	1-2		3-4	
	No	%	No	%
Dysphagia	14	100	-	-
Mucositis within the field	5	36	9	64
Xerostomia	13	93	1	7
Odynophagia	9	64	5	36
Radiation Dermatitis	13	93	1	7

Table 3: Toxicity Related to Cisplatin-RT.

Mode of Assessment	6 Weeks Post Induction Chemotherapy		6 Weeks Post Concurrent CRT	
	No	%	No	%
LN, Clinical Examination				
CR	9	64	12	86
PR	5	36	2	14
NPX, CT Scan				
CR	1	7	12	86
PR	11	79	2	14

Table 4: Treatment outcome and response.

Baseline TNM	Overall Response	Site of Relapse
T3N2	CR	Bone
T3N3	PR	Nasopharynx & neck nodes

Table 5: Characteristics of 2 Patients who had Treatment Failure.

All patients showed response (CR or PR) to treatment both clinically and radiologically. The overall response rate (CR and PR) to neo-adjuvant chemotherapy was 100% and 86% for lymph nodes and nasopharynx [Table 4]. After 6 weeks of neo-adjuvant chemotherapy using Docetaxel and Cisplatin, 5 patients (36%) achieved partial response (PR) and 9 patients (64%) achieved complete response (CR) in the regional nodes. Eleven patients (79%) achieved PR and one patient (7%) achieved CR in the nasopharynx. Six weeks post concurrent chemo-radiation therapy, 86% of patients were in complete remission in regional nodes and nasopharynx.

With a median follow-up of 12 months, one patient developed distant metastases to bone,

while the other developed loco-regional failure, [Table 5].

Discussion

Patients with loco-regionally 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 the treatment outcomes, several groups have incorporated chemotherapy adjuvantly, neo-adjuvantly or concurrently with RT in randomized controlled trials.^(11-13, 15, 16, 21-26) The results of a meta-analysis of 1528 patients from six randomized trials have shown that the addition of chemotherapy to radical RT for loco-regionally advanced NPC increased both disease free/progression free and overall survival by 19 to 40% at 2–4 years after treatment⁽¹⁰⁾.

The primary rationale for induction or adjuvant chemotherapy in nasopharyngeal cancer has been to decrease the risk of developing distant metastases. Promising 4-5 year OS rates exceeding 75% have been reported in studies from Australia and North America using sequential neo-adjuvant chemotherapy and chemoradiotherapy. Rischin et al⁽²⁴⁾ used three cycles of the Cisplatin, Epirubicin, and infusional Fluorouracil (ECF) followed by concomitant RT at 60 Gy in 2-Gy fractions and Cisplatin (administered daily for 5 days in week 1 and 6). In another study, Hong et al⁽²⁷⁾ used three cycles of induction chemotherapy with Mitomycin, Epirubicin, Cisplatin, Fluorouracil, and Leucovorin (MEPFL) before RT.

The three large trials of induction without concurrent chemotherapy have not demonstrated improved overall survival compared with radiation alone.⁽²⁸⁻³¹⁾ Chan et al⁽³¹⁾ used induction chemotherapy of 2 cycles of Taxol (Paclitaxel) and Carboplatin followed by concurrent Cisplatin RT. Chan et al⁽³²⁾ used induction chemotherapy of 2 cycles of Taxotere (Docetaxel) and Cisplatin followed by concurrent Cisplatin RT.

In our study induction chemotherapy was generally well tolerated and of acceptable toxicity profile. Seven percent of patients developed grade 3-4 anaemia. This figure concurs with what had been reported by Rischin et al and Wee et al ^(24,33) who reported grade 3-4 anaemia of 0% and 3% respectively. Grade 3-4 leucopenia occurred in 57% of patients. Our results are comparable to that of Hong et al ⁽²⁷⁾ who reported incidence of 59% of grade 3-4 leucopenia in his study. This finding is slightly higher than that reported by Rischin et al and Chan et al ^(24,31) who reported incidence of grade 3-4 leucopenia of 19% 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 ⁽³²⁾ who reported incidence of grade 3-4 leucopenia of 100% although they used the same regimen of induction chemotherapy. Grade 3-4 thrombocytopenia occurred in 7% of patients which coincide with Chan et al and Wee et al ^(32,33) who reported incidence of grade 3-4 thrombocytopenia of 1.4% and 3% respectively. None of the patients experienced grade 3-4 febrile neutropenia or sensory neuropathy which again concurs with the results of Chan et al. ⁽³¹⁾ Grade 3-4 vomiting occurred in 14% of our patients which was slightly higher than what is reported by Chan et al ⁽³²⁾ who reported a figure of 7%. Forty three percent of our patients developed grade 3-4 alopecia which is slightly higher than what is reported by Rischin et al ⁽²⁴⁾ who reported incidence of grade 3-4 alopecia of 31%. Furthermore Chan et al ⁽³¹⁾ did not report any grade 3-4 alopecia in his study.

Chemotherapy related toxicity during concurrent Cisplatin with radiation were comparable to that reported by Chan et al. ⁽³¹⁾ In our study 64% of our patients developed grade 3-4 mucositis within the radiation field which concurs with the results of Chan et al and Lee et al ^(31,34) who reported incidence of 55% and 62% of grade 3-4 mucositis, respectively. Our results are higher than what had been reported by Rischin et al ⁽²⁴⁾ who reported incidence of 31% of grade 3-4 mucositis.

The current study confirms the feasibility of combining neo-adjuvant TC (Taxotere-Cisplatin)

followed by concurrent chemoradiotherapy in patients with advanced NPC and resulted in (CR) complete remission rate in 86% of patients. Patient tolerability and compliance to neo-adjuvant TC was good, and there were no treatment-related deaths. The outpatient administration of TC also avoids the need for hospital admission or indwelling catheters.

Tumour response in the regional nodes and nasopharynx were studied separately. The overall response rate (CR and PR) to neo-adjuvant Taxotere and Cisplatin in the regional nodes and nasopharynx was 100% and 86%, respectively. Chan et al ⁽³¹⁾ reported an overall tumour response in the lymph nodes and nasopharynx of 97% and 16% respectively. This apparently differential response may be partially attributed to inadequacy of endoscopic and CT examination in evaluating the nasopharynx. Although CT scan is good in assessing bony structures of the head and neck and most nodal groups in the neck, it does not surpass MRI in assessing the retropharyngeal nodes or the soft tissue structures around the NP (especially parapharyngeal disease). ⁽³⁵⁾ Chan et al ⁽³²⁾ reported an overall response rate to neo-adjuvant chemotherapy of 80% and 86% in the regional nodes and nasopharynx, respectively. Hong et al ⁽²⁷⁾ reported complete remission rate of 45.5% and 6.4% in the regional lymph nodes and nasopharynx, respectively.

In our study, 6 weeks post concurrent chemoradiation 86% of patients were in complete remission in the regional lymph nodes and nasopharynx. Chan et al ⁽³¹⁾ reported complete remission rate of 97% and 100% in the regional lymph nodes and nasopharynx, respectively. Chan et al ⁽³²⁾ reported complete remission rate of 80% and 96% in the regional lymph nodes and nasopharynx, respectively. Hong et al ⁽²⁷⁾ reported complete remission rate of 67% in his trial.

Conclusion

Neo-adjuvant Docetaxel and Cisplatin (TC) followed by concurrent Cisplatin-RT used for patients with locally advanced nasopharyngeal cancer results in excellent tumour control and manageable toxicity profile.

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