INDUCTION CHEMOTHERAPY IN ADVANCED NASOPHARYNGEAL CANCER

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ABSTRACT

OBJECTIVES:
Aim of this study:
1- To evaluate clinical outcomes
2- To record toxicity of neoadjuvant chemotherapy (NACT) followed by concomitant chemoradiotherapy (CRT) in a non endemic population affected by advanced nasopharyngeal carcinoma (NPC).

METHODS:
From 2004 to 2008 forty consecutive patients with NPC were treated with three cycles of induction chemotherapy (CHT) with cysplatin (100 mg/m^2) plus epirubicin (90 mg/m^2), followed by cysplatin (100 mg/m^2 on days 1-22-43) and concomitant radiotherapy, consisted of 70 Gy in 35 fractions. All patients completed the protocol. Objective responses and toxicity were recorded. Statistical analysis was performed using SPSS 16.0 version.

RESULTS:
After induction CHT plus CRT we observed the following objective response rates: 90% (95%CI 76.1%-97.6%) and 100% (95%CI 85.1%-100%) respectively. No severe toxicity was recorded. The 3 and 5 year disease free survival was 75% (95%CI 52–81) and 65.4% (95%CI 55-78) respectively and the 3 and 5 year overall survival was 84% (95%CI 69-92) and 77.5% (95%CI 62-87) respectively (median follow-up 54.5 months).
Three and five years loco-regional control was 82.4% (95%CI 72-91) and 70.3% (95%CI 59-83) respectively and five years distant metastases free survival was 75% (95%CI 62-87).

CONCLUSION:
NACT with cysplatin and epirubicin followed by concomitant CRT represents a feasible and efficient treatment for patients affected by advanced NPC. This regimen ensures an excellent locoregional disease control and overall survival with a low incidence of distant metastases.

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INTRODUCTION

The results of the last meta-analysis confirm the role of concurrent chemoradiotherapy as a standard treatment for locoregionally advanced NPC.
In this paper, we report our experience with neoadjuvant chemotherapy followed by concomitant chemoradiotherapy (CRT) in locally advanced NPC, observed in a non-endemic population.

METHODS AND MATERIALS

In the present study were included patients having histological confirmed NPC, stages III–IVB according to 2002 AJCC stage classification (6th ed.), who had received no previous CHT and/or RT.
Neoadjuvant CHT comprised three cycles of cisplatin (CDDP) (100 mg/m2 administered intravenously (IV) over 2 h) plus epirubicin (EPI) (90 mg/m2 in bolus given on day 1). During RT, CDDP was administered at a dose of 100 mg/m2 iv infusion on days 1, 22 and 43, given approximately 60 min before radiation.
Dose modifications were allowed for neoadjuvant CHT based on the toxicity in the last cycle.
Radiation treatment was started 3 weeks after the three cycles of neoadjuvant chemotherapy (NACT). Three-dimensional conformal radiotherapy (3D-CRT) was performed on all patients.
Planned radiation therapy consisted of 70 Gy, in 35 fractions, over 7 weeks to all known sites of disease and 50 Gy to sites of potential spread, including the uninvolved neck. Residual cervical lymphoadenopathy was supplemented with electron beams.
Objective response rate (ORR) represented the primary endpoint, and it could be defined as the proportion of patients whose best response was either partial or complete (PR + CR).
Secondary endpoints included disease control rate (DCR), defined as the proportion of patients whose best response was either PR or CR or stable disease (SD), occurrence of grades 3–4 adverse events, as well as disease-free survival (DFS) and overall survival (OS).

Table 1 - Tumour stage versus Node stage (AJCC Staging 2002)

	T1	T2	T3	T4	Total
N0	--	--	3	10	13
N1	--	--	1	0	1
N2	4	2	12	5	23
N3	1	--	--	2	3
Total	5	2	16	17	40

RESULTS

From March 2004 to June 2008, 40 patients were enrolled. Twenty-nine (72%) patients were males and 11 (27%) patients were females with a median age of 53 years (range 20–66). ECOG performance status was 0 in 36 patients (90%) and 1 in 4 patients (10%).
22 patients had stage III (55%), 15 patients had stage IVa (37%) and 3 patients had stage IV b (7%) disease; T3–4 lesions were 33/40 (82.5%) while N2-3 lesions were 26/40 (65%)
All 40 patients completed the planned treatment without protocol violations.
After three cycles of neoadjuvant CHT, we registered the following results: 12 patients (30%) achieved clinical and imaging CR; 24 patients (60%) had a PR; 8 patients (20%) achieved PR on the tumour site (T) and NC in regional lymph nodes (N); 16 patients (40%) achieved a PR on T and N; and 4 patients (10%) had no change neither in T nor in N site. Objective response rate was 90% (95% CI 76–97%), while disease control rate was 100% (95% CI 90%–100%).
At the end of CRT, 30 patients (75%) achieved a clinical CR at both T and regional nodes, and 10 patients (25%) were in PR (8 patients on T and N and 2 patients on T only) for an overall response rate of 100% patients. Objective response rate was 100% (95% CI 85–100%).
Tables summaryze tumour characteristics and a list of acute toxicities with reference to WHO Criteria is reported in table 1 and 2.

DISCUSSION

In such report, the use of induction CHT resulted in a 5% improvement in disease specific survival rate (p = 0.029) at 5 years, while no significant difference was found in the overall survival rates.
Our neoadjuvant scheme has achieved a higher percentage of CR (30%), in comparison with the data reported by Rischin (6%) with a combination of CDDP + EPI + continuous infusion of 5-fluorouracil.
Our percentage of distant metastases is relatively low (15%).
In our experience the regimen was well tolerated with good patient's compliance; no toxic deaths were recorded. Acute toxicity was acceptable and reversible in most cases.
In conclusion, NACT with CDDP/EPI followed by concomitant CDDP + RT is a safe and effective treatment for a non-endemic population affected by locoregionally advanced NPC: this approach needs further phase 3 trials.

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Table 2 - Acute toxicity (WHO criteria), maximum toxicity per patient during induction CHT

WHO Grade	0	1-2	3-4
Neutropenia	0 (0%)	24 (60.0%)	16 (40.0%)*
Thrombocytopenia	25 (62.5%)	10 (25.0%)	5 (12.5%)
Anaemia	30 (75.0%)	10 (25.0%)	--
Nausea/Vomiting	12 (30.0%)	20 (50.0%)	8 (20.0%)
Anorexia	32 (80.0%)	8 (20.0%)	--
Oropharyngeal Mucositis	32 (80.0%)	7 (17.5%)	1 (2.5%)
Alopecia	0 (0%)	10 (25.0)	30 (75.0%)
Skin	0 (0%)	--	--
Cardiotoxicity	39 (97.5%)	1 (2.5%)	--
Renal toxicity	38 (95.0%)	2 (5.0%)	--
Neurotoxicity	0 (0%)	--	--
Weight loss	36 (90.0%)	4 (10.0%)	--

*Febrile neutropenia in 1 patient (2.5%).

Table 3 - Acute toxicity (WHO criteria), maximum toxicity per patient, during CRT

WHO Grade	0	1-2	3-4
Neutropenia	16 (40.0%)	16 (40.0%)	10 (20.0%)
Thrombocytopenia	30 (75.0%)	7 (17.5%)	3 (7.5%)
Anaemia	19 (47.5%)	20 (50.0%)	1 (2.5%)
Nausea/Vomiting	13 (32.5%)	22 (55.0%)	5 (12.5)
Anorexia	28 (70.0%)	10 (25.0%)	2 (5.0%)
Oropharyngeal Mucositis	7 (17.5%)	20 (50.0%)	13 (32.5%)
Alopecia	38 (95.0%)	2 (5.0%)	--
Skin	30 (75.0%)	10 (25%)	--
Cardiotoxicity	40 (100%)	--	--
Renal toxicity	38 (95.0%)	2 (5.0%)	--
Neurotoxicity	25 (62.5%)	13 (32.5)	2 (5.0%)
Weight loss	32 (80.0%)	8 (20.0%)	--
NGT	yes 3 pts (7.5%)	--	--

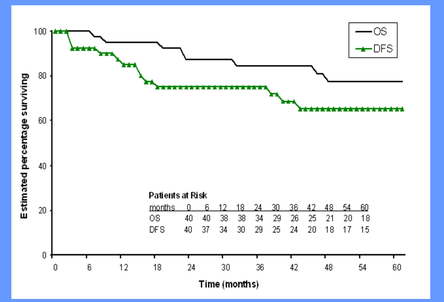

Fig. 1 Overall Survival (OS) and Disease Free Survival (DFS) in 40 patients.

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