

Concurrent Chemoradiotherapy with Daily Low Dose Intra-arterial Cisplatin Plus 5-Fluorouracil for Stage IV Nasopharyngeal Cancer

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ABSTRACT

This study aims to treat locally-advanced nasopharyngeal cancer by concurrent conventional irradiation at 2.0 Gy/day five days per week up to a total dose of 68 Gy, and daily intra-arterial infusion of cisplatin 3 mg/m² plus 24 hours intravenous drip infusion of 5-fluorouracil 150 mg/m² per day, five days per week. All of five enrolled patients completed the schedule, and treatment compliance was considered to be identical. Of the five patients evaluable for response, four with complete response (80%) and one with partial response (20%), with an overall response rate of 100% was achieved. The median survival time was 26 months. Two-year survival of the patients was 80%. This regimen showed marginal mucositis but well tolerated. We concluded that this treatment option is safe and effective for the locally-advanced nasopharyngeal cancer.

Keywords: chemoradiotherapy, low dose intra-arterial cisplatin, 5-fluorouracil, stage IV nasopharyngeal cancer

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INTRODUCTION

The prognosis for locally-advanced nasopharyngeal cancer (NPC) is extremely poor. According to Huang et al, the actuarial 5-year survival rate for Stage I was 95.5%, Stage II, 84.5%, Stage III, 60%, and Stage IV, 0%, with an overall survival of 70.6%⁽¹⁾. NPC is known to be highly radiosensitive tumour⁽²⁾. NPC also appears to be highly responsive to cisplatin (CDDP)-containing chemotherapy regimens^(3,4). Meta-analysis of randomised controlled trials of chemotherapy in head and neck cancer suggests that chemotherapy may improve survival for advanced head and neck cancer, and that improvement is found much more frequently in chemotherapy given synchronously with radiotherapy^(5,6).

CDDP and 5-fluorouracil (5FU) are drugs with significant activity in head and neck cancer⁽⁷⁾ and are known to act as radiosensitisers⁽⁸⁾. Our initial trial with low-dose and long-term exposure of CDDP plus

5FU demonstrated that our treatment schedule results in the same magnitude of activity with less toxicity than the conventional CDDP plus 5FU regimen⁽⁹⁾. Based on these findings, we designed this study of the synchronous use of conventional irradiation with low-dose CDDP plus 5FU for the treatment of locally advanced stage IV NPC.

MATERIAL AND METHODS

Patients with histologically-proven stage IV NPC were eligible. All patients gave informed consent before enrolment in the study. All patients required to have an Eastern Co-operative Oncology Group (ECOG) criterion's performance status of less than two, and an expected survival of greater than three months. Patients were excluded if there was third space fluid accumulation, or if they did not give written informed consent. Initial evaluation included complete physical examination, blood cell count, liver biochemical test, chest radiograph, and oropharyngolaryngeal fiberoptic endoscopic examination. Patients were required to have normal renal (creatinine clearance of >60 ml/min, blood urea nitrogen (BUN) of <20 mg/dl and serum creatinine level of <1.5 mg/dl) and hepatic (serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvate transaminase (SGPT) <40 units/dl, bilirubin <1.5 mg/dl) functions. Staging classification criteria was done according to the Union Against Cancer staging system.

Intra-arterial catheterisation was performed after local anaesthesia of the temporal region. The superficial temporal artery was exposed by a skin incision in the preauricular region. An Atom feeding tube (Atom Medical, Tokyo, Japan) was used for catheterisation upstream to the external carotid artery. Systemic heparinisation was not performed during catheterisation. The position of the catheter was confirmed with fiberoptic endoscopic nasopharyngeal examination by injection of indigo carmine. After the atom tube was fixed, the catheter was filled with 2000 U of heparin to prevent coagulation. No additional antiplatelet medication was given.

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Chemoradiotherapy consisted of conventional irradiation at 2 Gy/day, five days per week up to a total dose 68 Gy, and CDDP 3 mg/m² by intra-arterial infusion through the superficial temporal artery plus 5FU 150 mg/m² by intravenous infusion over 24 hours per day, five days per week. Anti-emetic premedication was not given and no hydration was provided prior to CDDP administration. All patients were examined weekly during the treatment period for assessment and management of treatment-related toxicity. Careful attention was paid to oral fluid and food intake, as well as mucosal skin care. Patients were advised to commence prophylactic mouthwash and tooth brushing. Two or three drops of Propolis (honey extract) were used for stomatitis.

Response to treatment was assessed as the decrease in the total tumour area measured directly with calipers (neck node) or through radiological features (neck node and primary site) using magnetic resonance (MR) imaging. Complete response (CR) was defined as disappearance of all measurable and assessable disease for a minimum duration of four weeks. Partial response (PR) was defined as a 50% or greater reduction in the sum of the products of the perpendicular diameters of all measured lesions without an increase in the size of any lesion or appearance of new lesions for at least four weeks. No change (NC) was defined as a change of the sum of the products of the perpendicular diameter of all measured lesions less than 25%. Progressive disease (PD) was defined as an increase of 25% in the sum of the products of the perpendicular diameters of all measured lesions from the point of maximal response or the appearance of new lesions. Those who did not meet criteria for partial or complete response were classified as non-responders. The survival was calculated from the first day of treatment on protocol until death or last patient contact.

RESULTS

Patients' characteristics are shown in Table I. Five patients were entered for the study, and all completed the treatment schedule. All patients had Stage IV and T4 disease with many having advanced N disease. The catheter was successfully inserted into target artery

Table I. Patient characteristics (five evaluable patients).

Male:Female	4:1
Age median (range)	41 (28-55)
Stage IV	5
T4	5
N1/N2/N3	1/2/2
Performance status 0/1	3/2

Table II. Analysis of enrolled patients.

No.	Age	Gender	PS	Maximal response	Recurrence local	Recurrence distant	Survival (month)
1	43	M	0	CR	-	-	41+
2	28	M	I	CR	-	-	37+
3	45	F	0	CR	-	-	26+
4	55	M	0	CR	+	-	24+
5	38	M	I	PR	+	+	15

Key: PS, performance status; CR, complete response; PR, partial response.

Table III. Adverse reactions to intra-arterial chemotherapy (five patients).

Grade	I (%)	II	III
Nausea or vomiting	2 (40)	1 (20)	
Anaemia	1	1	1
Leukopenia		2	1
Thrombocytopenia		1	1
Mucositis		2	2
Diarrhoea	1		
Alopecia	1		
Renal ^(a)	1		

^(a) Transient increase in serum creatinine.

in all five cases. Of the five patients evaluable for response, 4 CR (80%) and 1 PR (20%), with an overall response rate of 100%, was achieved. The median duration of follow-up at the time of analysis was 26 months. Among the five patients, loco-regional recurrence occurred in two patients, and distant metastasis in one. All four CR patients are still alive, and the remaining PR patient died with distant metastasis (Table II). The median survival time was 24 months. Actuarial two-year survival of the patients was 80%.

There was no intra-arterial catheterisation-related complication. Adverse reactions with this regimen are listed in Table III. Myelosuppression was the major adverse reaction of chemotherapy (20% greater than WHO grade III). One patient developed grade III pancytopenia at the end of the scheduled treatment period and recovered within 10 days. As expected, the mucositis was most frequently observed as dose-limiting toxicity (40% greater than WHO grade III), but no supportive care, including enteral nutrition administered through a feeding tube, was required. Other toxicities, including nausea and vomiting, hyponatremia, and facial oedema, were all mild and transient. Clinically significant ototoxicity was not seen, and no neurotoxicity or cardiac toxicity was documented.

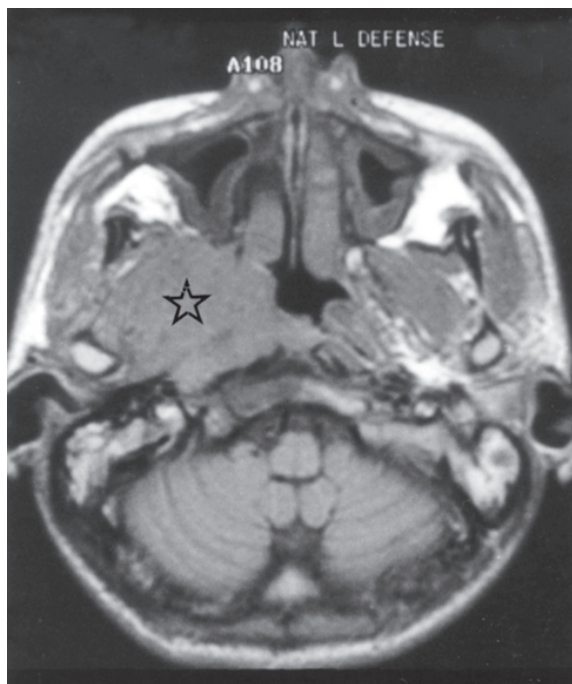


Fig. 1 Axial T1-weighted MR image shows a nasopharyngeal mass deeply invading into pterygoid fossa.

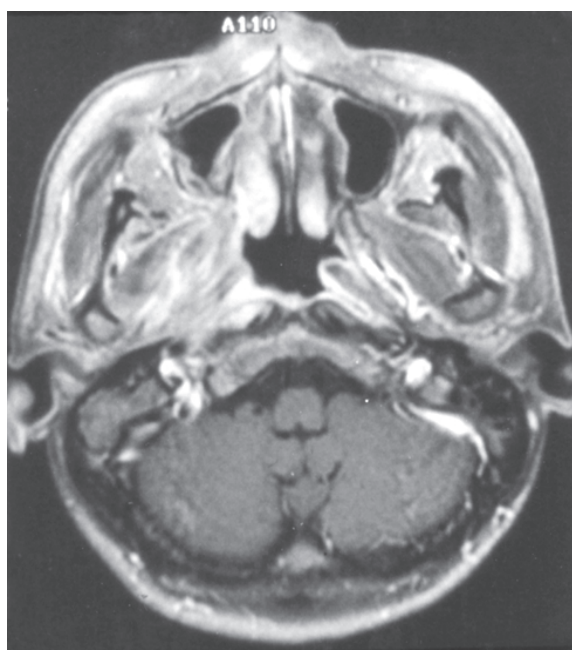


Fig. 2 Enhanced axial T1-weighted MR image at the three years after chemoradiotherapy. The tumour mass in a nasopharynx and pterygoid fossa responded with treatment and resulted in complete response.

CASE REPORT

A 24-year-old Japanese man visited our hospital in December 1998 complaining of a neck lump, diplopia, headache, and severe nausea, which gradually worsened. Cranial MR imaging clearly demonstrated a prominent mass lesion, 4 cm in diameter, in the right nasopharynx and pterygoid fossa (Fig. 1), as well as a swollen bilateral upper jugular neck node. A fine needle aspiration biopsy from the neck mass and a

punched biopsy from the granular mass of the nasopharynx revealed undifferentiated carcinoma. The diplopia, headache, and severe nausea were suggestive of intracranial invasion. On the basis of these findings, the patient was diagnosed as having NPC with T4N3M0.

Starting in January 1999, the patient was given concurrent chemoradiotherapy. Chemoradiotherapy consisted of conventional irradiation at 2 Gy/day five days per week, and cisplatin 3 mg/m² by intra-arterial infusion over five minutes plus 5-fluorouracil 150 mg/m² by intravenous infusion 24 hours per day, five days per week. The tumour responded rapidly to this treatment. After two and six weeks, PR and CR were achieved, respectively. Seven weeks later, the scheduled therapy was completed with 68 Gy. The total CDDP and 5FU doses were 175 mg and 7000 mg, respectively. His complete blood cell count and blood chemistry findings were within normal range throughout the therapy. Although the patient had developed grade III mucositis, no supportive care, including enteral nutrition through a feeding tube, was required. The histopathological examination carried out two months after the chemoradiotherapy revealed no evidence of viable cancer cells. In January 2002 (37 months after the chemoradiotherapy) the patient is still alive without local recurrence or distant metastasis (Fig. 2).

DISCUSSION

The present study demonstrates that patients with advanced nasopharyngeal cancer show an excellent response to concurrent chemoradiotherapy with low-dose and long-term exposure of CDDP plus 5FU. In addition, this treatment schedule was found to be less toxic and better tolerated than other concurrent chemoradiotherapies studied⁽¹⁰⁾. We employed concurrent chemoradiotherapy for locally advanced NPC. The reported patient had a lesion of the deep pterygoid fossa with intracranial and parapharyngeal space invasion. Both intracranial invasion and parapharyngeal involvement are recognised to be important factors with regard to local relapse and metastatic risk⁽¹¹⁾. Thus, we have attempted to combine the theoretical advantages of concurrent chemoradiotherapy to improve the local control rate and to achieve disease-free survival over conventional radiotherapy in patients with locoregionally advanced NPC who are at high risk of both locoregional and distant failure after conventional radiotherapy alone. Moreover, considering the toxicity and synergistic reactions of CDDP plus 5FU, concomitant use of a small dose of drugs was incorporated into this study.

Wibault et al reported simultaneous chemoradiotherapy with the same drug combination used in our study, which consisted of CDDP 80 mg/m² given over one hour with adequate hydration on days 5, 26, and 47, and 5FU 300 mg/m² continuous intravenous infusion on days 1 through 47 and daily fractions of 2 Gy radiotherapy, five consecutive days per week for seven consecutive weeks, up to a total dose of 70 Gy. The overall response rate was 70% with 42% CR. Survival results were excellent, though there were four treatment-related deaths (7%)⁽¹²⁾. Taylor et al has also reported a simultaneous chemoradiotherapy regimen with CDDP 60 mg/m² on day 1, 5FU infusion 800 mg/m² on days 1 to 5, and radiation, 2 Gy on days 1 to 5, every other week, for a total of seven cycles. The CR rate was 55%, and the survival of all patients was substantially improved. The toxicities, however, were increased. Weight loss of 10% or more and severe mucositis were the most common side effects (53% and 48%, respectively)⁽¹³⁾. Compared with these studies, our schedule resulted in more tolerable and acceptable side effects. All the enrolled patients were given full doses of scheduled drugs and irradiation, so treatment compliance was considered to be identical.

For advanced nasopharyngeal cancer, Al-Sarraf et al has reported excellent results with simultaneous chemoradiotherapy followed by adjuvant chemotherapy with three cycles of CDDP plus 5FU. This phase III randomised intergroup study demonstrated three year survival rates of 76% and 46% for patients receiving randomised chemotherapy, and radiotherapy alone (P<0.001)⁽¹⁴⁾, respectively. We assumed that the key to success of Al-Sarraf's study was not only the simultaneous use of chemoradiotherapy, but also the additional adjuvant chemotherapy. Because our regimen is primarily aimed at increasing local control, adjuvant chemotherapy should be added to decrease distant metastasis in a future study.

The primary weakness of our study was the limited number of enrolled patients. Since the background of the study was locally-advanced nasopharyngeal cancer, a small sample size was unavoidable. In non-endemic countries, other than the southern part of China, where NPC is prevalent, it has been difficult to carry out a prospective randomised trial of concomitant chemoradiotherapy because of the relatively low incidence of NPC. We do, however, consider it to be notably significant that the side

effects of our low-dose CDDP plus 5FU regimen were tolerable for all enrolled patients, and our regimen resulted in an excellent response. We therefore conclude that this treatment schedule is useful for advanced nasopharyngeal cancer, and that further randomised trials appear warranted.

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REFERENCES

- Huang SC, Lui LT, Lynn TC. Nasopharyngeal cancer: Study III. A review of 1206 patients treated with combined modalities. *Int J Radiat Oncol Biol Phys* 1985; 11:1789-93.
- Qin DX, Hu YH, Yan JH, Xu GZ, Cai WM, Wu XL, et al. Analysis of 1379 patients with nasopharyngeal carcinoma treated by radiation. *Cancer* 1988; 61:1117-24.
- Al-Kourainy K, Crissman J, Ensley J, Kish J, Kelly J, Al-Sarraf M. Excellent response to cisplatin-based chemotherapy in patients with recurrent or previously untreated advanced nasopharyngeal carcinoma. *Am J Clin Oncol* 1988; 11:427-430.
- Choo R, Tannock I. Chemotherapy for recurrent or metastatic carcinoma of the nasopharynx; a review of the Princess Margaret Hospital experience. *Cancer* 1991; 68:2120-4.
- Munro A. An overview of randomized controlled trials of adjuvant chemotherapy in head and neck cancer. *Br J Cancer* 1995; 71: 83-91.
- Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous cell carcinoma: three meta-analysis of updated individual data. *Lancet* 2000; 355:949-55.
- Kish JA, Weaver A, Jacobs J, Cummings G, Al-Sarraf M. Cisplatin and 5-fluorouracil infusion in patients with recurrent and disseminated epidermoid cancer of the head and neck. *Cancer* 1984; 53: 1819-24.
- Aisner J, Jacobs M, Sinibaldi V, Gray W, Eisenberge M. Chemoradiotherapy for the treatment of regionally advanced head and neck cancers. *Semin Oncology* 1994; 21: 35-44.
- Kohno N, Kitahara S, Kawaida M, Ichikawa G, Shirasaka T. Outpatient setting chemotherapy for recurrent and/or advanced squamous cell carcinoma of the head and neck. *Int J Clin Oncol* 1999; 4:285-8.
- Adelstein DJ, Kalish LA, Adams GL, Wagner H, Oken MM, Remik SC, et al. Concurrent radiation therapy and chemotherapy for locally unresectable squamous cell head and neck cancer: an Eastern Cooperative Oncology Group pilot study. *J Clin Oncol* 1993; 11:2136-42.
- Teo PML, Tsao SY, Ho JHC, Yu P. A proposed modification of the Ho stage-classification for nasopharyngeal carcinoma. *Radiation Oncol* 1991; 21:11-23.
- Wibault P, Bensmaine MA, de Forni M, Armand JP, Tellez Bernal E, et al. Intensive concomitant chemoradiotherapy in locally advanced unresectable squamous cell carcinoma of the head and neck: a phase II study of radiotherapy with cisplatin and 7-week continuous infusional fluorouracil. *J Clin Oncol* 1996; 14:1192-200.
- Taylor SG, Murthy AK, Caldarelli DD, Showel JL, Kiel K, Griem K L, et al. Combined simultaneous cisplatin/fluorouracil chemotherapy and split course radiation in head and neck cancer. *J Clin Oncol* 1989; 7:846-56.
- Al-Sarraf M, LeBlanc M, Giri PGS, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099. *J Clin Oncol* 1998; 16:1310-7.