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Neoadjuvant Chemotherapy and Radiation Therapy in Advanced Stage Nasopharyngeal Carcinoma

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Purpose : To assess the feasibility and the toxicity of the neoadjuvant chemotherapy on the treatment of patients with locoregionally advanced nasopharyngeal carcinoma.

Methods and Materials : We analyzed 77 previouly untreated and histologically confirmed advanced stage nasopharyngeal carcinoma patients treated with neoadjuvant chemotherapy followed by radiation therapy at the Seoul National University Hospital between 1984 and 1996. The stage distribution was therapy at the Seoul National University Hospital between 1984 and 1996. The stage distribution was as follows : AJCC stage III-2, stage IV-75, Sixty-six patients received infusion of 5-FU (1000 mg/m^2, on Day 1~5) and cisplatin (100 mg/m^2, on Day 1), eleven patients received infusion of 5-FU (1000 mg/m^2, on Day 1~5) and carboplatin (300 mg/m^2 on Day 1), as neoadjuvant chemotherapy prior to radiation therapy. The median follow-up for surviving patients was 44 months.

Results : The overall chemotherapy response rates were 87%. The toxicities of chemotherapy were mild. Only 3 patients experienced Grade 3 toxicities (1 for cytopenia, 2 for nausea/vomiting). The degree of radiation induced mucositis was not severe, and then patients developed Grade 2 mucositis. The 5-year overall survival rates were 68% and the 5-year disease free survival rates were 65%. The 5-year overall survival rates were 68% and the 5-year disease free survival rates were 65%. The 5-year freedom from distant metastasis rates were 82% and 5-year locoregional control rates were 75%.

Conclusion : This single institution experience suggests that neoadjuvant chemotherapy improves overall survival and disease free survival for patients with advanced stage nasopharyngeal carcinoma without increase of toxicity.

INTRODUCTION

Nasopharyngeal carcinoma has a natural history distinct from that of other head and neck cance. Because of the anatomic location of nasopharyngeal tumors, they are traditionally treated by radiation therapy. Whereas the control of early stage disease with radiation therapy alone is successful, the response of locally and regionally advanced nasopharyngeal carcinomas to radiation therapy is poor. Most studies report 5-year survival rates of 40~50%, because of both local relape and distant metastasis. 1~3)

Up to 80% of patients with nasopharyngeal carcinoma have evidence of cervical lymph node metastasis at presentation. Moreover, metastatic spread is a major concern in patients with massive nodal involvement, because it occurs in 50% to 70% of cases.[3),4)] In one large series of nasopharyngeal carcinoma, the distant failure rate was 29%; in 17%, distant metastaseswere the only sites of failure, 3,5,6) For nasopharyngeal carcinoma, studies of sequentially delivered neoadjuvant chemotherapy followed by radiotherapy have routinely shown this tumor to be highly sensitive to neoadjuvant chemotherapy in primary or recurrent disease.[7)] Active chemotherapeutic agents are cisplatin (CDDP), bleomycin, doxorubicin, epirubicin, mitoxantrone, methtrexate and 5-FU.[8~11)] Several primary chemotherapy phase II studies of CDDP-based combination chemotherapy have shown an overall response rate as high as 80~90%,[12~15)] with a strong suggestion of added therapeutic benefit in most series.

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This study retrospectively analyzed outcomes of patients with advanced nasopharyngeal carcinoma, focused on the response rates of the treatment, the patterns of failure and the toxicity through the use of neoadjuvant chemotherapy.

MATERIALS AND METHODS

Between September 1984 and June 1996, seventy-seven patients with histologically proven nasopharyngeal carchinoma were treated with radiation therapy after completion of neoadjuvant chemotherapy at the Department of Therapeutic Radiology Seoul National University Hospital. The median age was 46 years (range 14~68 years), with 57 males and 20 females. Methods of tumor evaluation and staging workup included general physical examination, laboratory studies including complete blood cell count, blood chemistry, chest radiography, abdominal ultrasonography or bone scintigraphy if liver enzyme were elevated, head and neck examination with nasopharyngoscopy, and computed tomography (CT) and/or magnetic resonance imaging (MRI). All patients were staged retrospectively according to the 1992 AJCC staging system.[16] The majority of patients had stage IV disease (T4N0-1, 19; T1-4N2-3, 56) ; only 2 patients had stage III disease. The histology was squamous cell carcinoma in 28 patients (36%) and undifferentiated carcinoma in 49 patients (64%). The patient characteristics are shown in ' Table 1. Sixty-six patients received continuous infusion of 5-FU (1000 mg/m^2, on Day 1~5) and IV push of cisplatin (1000 mg/m^2, on Day 1), and eleven patients received continuous infusion of 5-FU (1000 mg/m^2, on Day 1~5) and IV push of carboplatin (300 mg/m^2, on Day 1) as neoadjuvant chemotherapy. Sixty-eight patients (88%) received all 3prescribed cycles delivered 3 weeks apart. Seven patients (9%) received two cycles: three with poor or no response after two cycles of chemotherapy, four with toxicity or refusal. Two patients(3%) received only one cycle: one with of severe neutropenia, one with refusal.

Chemotherapy was not administered until the abolute neutrophil count was 2,000/μL and the platelet count was 100,000/μL. If the absolute neutrophil count was 1,500/μL and the platelet count was 75,000/μL, no dose modification was made. If the absolute neurtophil count nadir was between 1,000 and 1499 and/or the platelet count nadir between 50,000 and 74,999, cisplatin (carboplatin) was decresed to 80 (240) mg/m^2. If the absolute neutrophil count was less than 1,000 and/or the platelet nadir less than 50,000, chemotherapy was withheld until the white blood cell count and platelet count were greater than 2,000μL and 100,000 μL, respectively, and then cisplatin (carboplatin) was decreased to 60(240) mg/m^2. The dose of cisplatin (carboplatin) was adjusted according to the value of creatinine after the last cource. Forty-seven patients (38 for FP, 9 for FC) received their neoadjuvant chemotherapy with full dose, twenty-one patients (19 for FP, 2 for FC) received with dose modification. In nine patients, chemotherapy were performed outside hospitals, no information about chemotherapy dose modification was available.

The response to neoadjuvant chemotherapy was assessed 2 to 4 weeks after completion of the last cycle of chemotherapy, clinically by nasopharyngoscopy and radiographically by CT and/or MRI studies. Complete response (CR) was defined as no clinical and radiographic evidence of residual disease, partial response (PR) was defined as tumor regression more than 50%, and no response (NR) was defined as no evidence of tumor regression or tumor progression. Definitive radiation therapy began 3~5 weeks after the last cycle of chemotherapy.

Table 1. Patients Characteristics

Characteristics	No. of Patients
Age (median)	14~68 (46)
Sex	
Male	57
Female	20
Performance	
ECOG 1	72
ECOG 2	5
Stage (AJCC 1992)	
III	2
IV	75
T Stage	
T1	0
T2	7
T3	25
T4	45
N stage	
N0	12
N1	7
N2a	6
N2b	12
N2c	20
N3	20
Histology	
Squamous cell carcinoma	28
Undifferentiated carcinoma	49

At the same period, one hundred seventeen patients were treated for their nasopharyngeal carcinoma with radiation therapy alone at our institution. Among those patients who treated radiation therapy alone, eighty-two patients had stage III or IV disease and histologically squamous cell carcinoma or undifferentiated carcinoma. The median age was 46 years (range 14~74 years), with 64 males and 18 females. Twenty-one patients had stage III disease (T3NO, 7; T1-3NI,14) and 61 patients had stage IV disease (T4NO-1, 14;T1-4N2-3, 47). The histology was squamous cell carcinoma in 32 patients (39%), undifferentiated carcinoma in 50 patients (61%)

All patients were treated with a Co-60 teletherapy unit or 4MV photon beam produced by Clinac 4/100 linear

accelerator (Varian). The nasopharynx, the base of skull and the upper part of the neck were irradiated by two lateral, shaped, parallel opposing portals. The lower neck was irradiated by anterior one portal with midline shielding. The dose to the primary site was 59.4~75.2 Gy (median 70.2 Gy), delivered in daily fractions of 1.75 to 2 Gy, treating 5 days per week. The posterior and inferior limits of the lateral ports were reduced when dose of 45 Gy was lower neck was 45 Gy. The palpable nodes were given boost treatment with 9~12 MeV electron beam.

All patients continued to be examined by nasopharyngoscopy and physical examination every 2 months during the first 2 years and at 4~6 months interval thereafter. Survival was calculated from the start of treatment to the death or to the most recent follow-up date if the patient is alive. The median follow-up time was 44 months (range 3~177 months) and the minimum follow-up time of surviving patients was 24 months. The survival curves were plotted using Kaplan-Meier method.17) Survival differences for treatement were analyzed using the Cox regression model.18)

RESULTS

1. Response to treatment

After competion of chemotherapy, 5 patients (6%, all with FP) achieved clinically and radiographic CR; 62 patients (81%, 53 with FP, 9 with FC) achieved PR; 10 patients (13%, 8 with FP, 2 with FC) had NR.

After radiation therapy, five patients with CR and forty six patients with PR (forty-one patients with FP, one with FC) after chemotherapy achieved clinical and radiographic CR(58 patients, 75%). Fifteen patients with PR(twelve with FP, three with FC), two patients with NR (one with FP, one with FC) after chemotherapy achieved PR (17 patients, 22%). One patient with PR(with FC) and one patient with NR (with FP) after chemotherapy had NR (two patients, 3%) There were no significant differences in response rates between full dose chemotherapy group and dose modification group.

2.Toxicity

The toxicity of chemotherapy is summarized in Table 2. the main nonhematologic toxicities were nausea/vomiting, with 2 patients experiencing WHO Grade 3 nausea/vomiting.,and 10 patients experiencing Grade 2 nausea/vomiting. There was one case of cisplatin-related neuropathy. Hematologic toxicity was mild; only 1 patients developed Grade 3 leukocytopenia and 5 patients developed Grade 2 leukocytopenia. There was one case of pneumonia due to cytopenia requiring short hospital admissions for antibiotic therapy. There was no death related to treatment.

The princial toxicity of radiation therapy was mucositis. RTOG Grade 2 mucositis occurred in 10 patients (13%) There were few severe chronic complications in these patients. One patient developed radiation-induced osteosarcoma, and one patient developed temporal lobe necrosis. There was no spinal cord myelopathy or optic pathway neuropathy.

Table 2. Chemotherapy Toxicity

	Total			FP*			FC†		
	Gr. 1	Gr. 2	Gr. 3	Gr. 1	Gr. 2	Gr. 3	Gr. 1	Gr. 2	Gr. 3
Leukocytopenia	15	5	1	13	5	0	2	0	1
Nausea/Vomiting	17	10	2	12	9	1	5	1	1
Infection	0	1	0	0	1	0	0	0	0
Peripheral neuropathy	1	0	0	1	0	0	0	0	0
Phlebitis	0	1	0	0	1	0	0	0	0
Diarrhea	1	1	0	1	1	0	0	0	0

*5-FU and cisplatin, †5-FU and carboplatin

3. Patterns of failure

Twentry-one patients (27%) had locoregional disease recurrence. The actuarial 5-year locoregional control rates were 74%

Tweleve patients (16%) developed distant metastasis. The 5-year freedom from distant metastasis rates were 82%. The lung metastasis was found in seven patients 99%), bone metastasis in four patients (5%) and liver metastasis in one patient (1%). The incidence and sites of progression or recurrence disease are shown in Table 3.

4. Survival

The actuarial 5-yearl overall survival rates were 68% and 5-year diease free survival rates were 65% (Fig. 1.)There was no significant difference of survival rates according to chemotherapy response, but favoring CR and PR group. For the patients with CR or PR to chemotherapy (n=67), 5-year overall survival rates and disease free survival were 70% and 66% compared with 58% and 62% for NR patients (n=120, respectively. The lack of statistical significance may due to the small number of events needed for analysis.

The dose modification of chemotherapeutic agent had no significance on survival. Between both groups, 5-year overall survival and disease free survival were similar.

In radiation therapy alone group, the 5-year overall survival rate was 63% and the 5-year disease free survival rates were 53%. There were significant differences between neoadjuvant chemotherapy and radiation therapy group and radiation therapy alone group, favoring combined treatment group (p=0.04, 0.09, respectively).

Table 3. Incidence and Site of Progression or Recurrent Disease

Site	No. of Patients (%)
Local only	7
Regional only	7
Local and Regional	2
Local and Distant	1
Regional and Distant	1
Local, Regional and Distant	3
Distant only	7
Total	28 (36)
Lung	7
Bone	4
Liver	1

After locoregional or distant metastasis occurred, five patients received palliative chemotherapy, and one patient with lung metastasis had been performed wedge resection.

There were two patients who achieved NR after radiation therapy. These patients died of progressive disease.

DISCUSSION

The initial use of chemotherapy as an adjunct to surgery and radiation therapy is being widely studied to optimize the overall management of advanced disease. Not only are patients apt to better tolerate chemotherapy, but also response rates achieved with chemotherapy are substantially higher, creating an opportunity for cure. The theoretical basis of neoadjuvant chemotherapy was to enhance locoregional control by tumor debulking and provide early treatment for occult micrometestases. [19]

Cisplatin, of which the major toxicity was not mucositis, with single-agent activity of 25~30%, was nevertheless established as one of the most active agents in the treatment of head and neck cancer and has become the backbone of multidrug therapy. [7] And cisplatin was reported to enhance the response when combined with ionizing irradiation. [20,21]

The role of neoadjuvant chemotherapy in advanced nasopharyngeal carcinoma has been explored for many years.

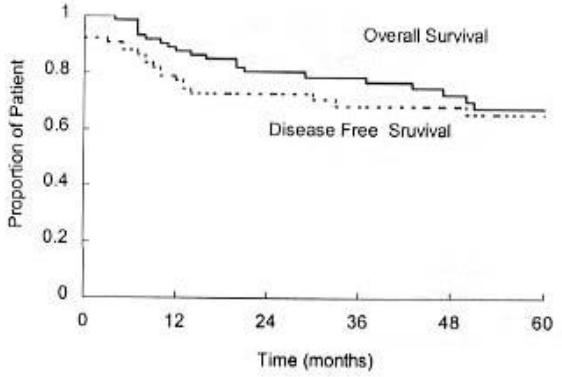

Fig. 1. The 5-year overall survival rates and the 5-year disease free survival rates using Kaplan-Meier method.

Although many retrospective and pilot studies have reported excellent and promising results, 14,22,23) others have reported opposing findings. 24,25)

The chemotherapy regimen used in the current study was effective. The 87% response rate to chemotherapy was consistent with the best results obtained in other studies using cisplatin-based regiments, although 6% complete

response rate was lower than other studies. In the literature, complete response rate was quite variable (0~70%).7) These findings were probably dependent on the extent of assessment for definition of compete response. Although clinical examination alone is often accurate enough to detect response in lymph node disease, the same dose not apply to the primary tumor, thus, if CT assessment of response to chemotherapy was performed, the complete response rate could be lower than that with clinical examination alone. Our findings also revealed that the toxicity of neoadjuvant chemotherapy was not so significant as concurrent chemoradiation. An American intergroup study that was reported by Al-Sarraf et al., with cisplatin 100 mg/m^2 on days 1,22, and 43 during radiotherapy; postradiotherapy, chemotherapy with cisplatin 80mg/m^2 on day 1 and 5-FU 1000mg/m^2/d on days 1 to 4 was administered every 4 weeks for three courses. The 3-year progression free survival rate was 24% in radiation therapy only group, 69% in concurrent chemoradiation group. Grade 3 or 4 complication occurred in 36% of patients in concurrent chemoradiation group.[26)]

In current study, we achieved 68% of 5-year overall survival rates and 65% of 5-year disease free survival rates. Compare to these results, the 5-year overall survival rates of patients who were treated with radiation therapy alone at our institute (n=82) was 63% and the 5-year disease free survival rates were 53%. There were significant differences between two groups (p=0.04, 0.039, respectively). These differences were mainly due to lower incidence of distant metastasis. The 5-year freedom from distant metastasis rates were 68% for historical radiation therapy alone group (p=0.01)

Neoadjuvant chemotherapy used in current study was effective and the patients well tolerated it. And there has been an improvement of outcome in our patients with advanced nasopharyngeal carcinoma treated with neoadjuvant chemotherapy followed by radiation therapy.

CONCLUSION

While recognizing that the value of chemotherapy has not been conclusively established, we consider the results presented here along with other studies sufficiently compelling to recommend combined treatment for patients presenting advanced nasopharyngeal carcinoma.

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국문초록

진행된 병기의 비인강암에서의 선행보조 항암화학요법과 방사선치료

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목 적 : 국소적으로 진행된 비인두암환자에서 선행보조 항암화학요법의 실행 용이성과 부작용의 정도를 평가한다.

대상 및 방법 : 77명의 조직학적으로 비인두암으로 확진 되고 이전에 치료를 받은 적이 없는 진행된 병기의 비인두암 환자들이 1984년부터 1996년까지 서울대학교병원에서 선행보조 항암화학요법과 방사선치료를 시행받았다. 환자군의 병기분포는 다음과 같다. 1992년 AJCC 분류법에 따라 제 3 병기에 속하는 환자가 2명이었고 제 4병기에 속하는 환자가 75명이었다. 방사선치료 시행 전에 선행보조 항암화학요법으로 66명의 환자가 5-FU와 Cisplatin의 정맥내 투여를 시행 받았고, 11명의 환자가 5-FU와 Carboplatin의 정맥 내 투여를 시행 받았다. 생존환자의 중앙추적기간은 44개월이었다.

결 과 : 항암화학요법에의 반응율은 87%였다. 항암화학요법의 부작용은 심하지 않았다. 3명의 환자만이 3도의 부작용을 경험하였다. 1명은 백혈구 감소증을 보였고 2명은 오심과 구토의 부작용을 보였다. 방사선에 의한 점막염도 심하지 않았는데, 10명의 환자에서 2도의 점막염이 발생하였다. 5년 생존율과 5년 무병생존율은 각각 68%와 65%였다. 5년 무원격전이율은 82%였으며 5년 국소 치유율은 75%였다.

결 론 : 선행보조 항암화학요법이 진행된 병기의 비인두암 환자에 있어서 부작용을 크게 증가시키지 않으면서 효과적인 치료방법임을 알 수 있었다.

핵심용어 : 비인두암, 선행보조 항암화학요법, 방사선치료