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Concurrent Chemoradiotherapy Using Weekly Cisplatin with or without Daily Oral UFT in Nasopharyngeal Cancer

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비인강암에서 저용량 시스플라틴±경구용 UFT를 이용한 동시항암방사선치료의 효과

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연구방법 :

근치적 목적의 동시항암방사선치료를 시행받은 비인강암 환자들을 대상으로하여 치료 효과와 독성에 대한 후향적 분석을 시행하였다.

환자 및 방법 :

1993년 8월부터 1999년 3월까지 원격전이가 없는 50명의 비인강암 환자들이 방사선 치료기간 중 주 1회의 시스플라틴 20mg/m^{2}을 투여받았고, 1999년 4월부터 2000년 4월까지 20명의 환자가 상기 용량의 시스플라틴에 더하여 경구용 UFT 300mg을 추가적으로 투여받았다. 총 70명 환자들의 임상기록과 병리 기록지를 검토하였다.

결 과 :

연령의 중앙값은 47세(범위 18~76)였고, 남자와 여자가 각각 53명과 17명 이었으며, 병기 II, III, IVA, IVB가 각각 23명, 14명, 15명, 18명이었다. 치료에 대한 반응율은 92.8%(95% C.I. 42~143%)였고(완전반응 57명, 부분반응 8명), 총 34개월의 추적 관찰 기간 동안에 완전반응을 보인 57명 중 21명에서 재발(국소재발 5, 원격전이 11, 복합전이 5)을 하였다. 3년 무진행 생존율은 51.5%였으며 5년 생존율은 60.3%였다. 경구용 UFT의 추가적 사용은 주 1회 시스플라틴 항암치료에 비하여 반응율과 생존율 및 독성에 유의한 영향을 미치지 않았다.

결 론 :

주 1회 저용량 시스플라틴±경구용 UFT를 이용한 동시항암방사선요법은 비인강암 환자의 치료에 있어서 비교적 적은 독성으로 높은 반응율을 나타내었으나, 향후 재발율을 감소시키기 위한 연구가 지속되어야 할 것으로 사료된다.

중심 단어 : 비인감암 · 항암치료 · 방사선치료 · 시스플라틴 · UFT.

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Introduction

Nasopharyngeal cancer (NPC) has unique characteristics different from other head and neck cancers that have endemic distributions in Southeast Asia. Radiotherapy (RT) has been the primary treatment modality for almost all NPC because of anatomic constraints and a high degree of radiosensitivity.[1-3] However, the results of treatment with conventional RT are unsatisfactory in patients with locoregionally advanced NPC with significant rates of both distant metastases and local recurrences. Different strategies of combined chemotherapy (CHT) and RT have been tested in some randomized trials, and the use of adjuvant and neoadjuvant chemotherapy failed to show a survival benefit over RT alone.[4-6] On the other hand, based on recent meta-analysis, concurrent CRT is known to be the best strategy, demonstrating favorable results to local control and/or overall survival.[7-9]

A recent intergroup trial conducted by Al-Sarraf, et al compared RT and RT plus 3 cycles of cisplatin 100mg/m^2, followed by 3 additional cycles of adjuvant CHT with cisplatin and 5-fluorouracil (5-FU), in patients with locally advanced NPC.[10] Although this study showed that CRT was superior to RT alone (3-year survival rate, 78% vs 47%) and changed the standard of care for NPC, these improvements were accompanied by an increase in acute toxicity and a high-rate of late systemic recurrence. Thus, no regimen has been adopted as standard CHT during RT, and there has been a continuing effort to develop different doses or a schedule of concurrent CHT regimen with low toxicity profiles, including continuous low-dose cisplatin or oral UFT.[11-15]

Since 1993, we have treated nonmetastatic NPC patients, primarily with concurrent CRT, using weekly administered cisplatin 20mg/m^2. Starting in the middle of 1999, we have added daily oral UFT 300mg to this CHT to enhance response rate on the premise so that oral UFT could substitute continuous infusion of 5-FU with minimal toxicity.[16] We reviewed our experiences of concurrent CRT using weekly cisplatin with or without oral UFT to evaluate the treatment efficacy and toxicities of this regimen, and failure pattern of nonmetastatic NPC, retrospectively.

Materials and Methods

1. Patients

The eligibility criteria were no distant metastasis ; no previous chemotherapy ; age $\leq$80 years ; performance status $\leq$2 according to the Eastern Cooperative Oncology Group (ECOG) criteria ; white blood cell count $\geq$4,000/mm^3 and platelet count $\geq$100,000/mm^3 ; adequate renal function demonstrated by serum creatinine concentrations <2mg/dL ; adequate hepatic function with transaminase levels < 3.0 times the upper normal value. Patients who were medically unstable, or who had uncontrolled infections or cerebral metastasis were excluded from the study. Patients who had a stage I disease or a rapidly progressive disease at the time of diagnosis were also excluded in this study.

2. Radiation therapy

RT was delivered using a linear accelerator of 4−6MV photons, and was given at the rate of 1.8Gy/fraction daily, 5 times per week. CT scans were used to assess the extent of the primary tumor, as well as the neck nodes. The primary tumor and the upper neck were treated by means of a bilateral upper neck field and a single anterior field to the lower neck. The suggested minimum total dose to the primary tumor was 64.8Gy/36 fractions/7−8 weeks, and the patients with a suspicion of residual tumor at the nasopharynx were boosted by intracavitary RT (ICR) at the rate of 5.0Gy/fraction 3 times a week. The whole neck was irradiated, and the total dose to the neck nodes was 50 Gy for a node negative neck area and more than 70Gy for a node positive region. RT was delayed only if when a physician determined that a patient could not tolerate severe toxicity.

3. Chemotherapy

Fifty patients received weekly CHT using cisplatin 20 mg/m^2, which was diluted with 500ml of 0.9% normal saline by intravenous infusion over 1 hour, during RT. Prehydration of 1 liter of isotonic saline was infused before the administration of cisplatin. From March 1999, 20 patients were treated with weekly cisplatin of the same dose and schedule as above and daily oral UFT during RT. Oral UFT was given at a dose of 300mg daily. CHT was administered from the start date to the end date of RT.

4. Treatment evaluation

The initial examination prior to the treatment included a medical history, a physical examination, a complete blood count, a biochemical analysis, and an electrocardiogram. All patients underwent biopsy of the nasopharynx with direct nasopharyngoscopy, and a computed tomography (CT) scan or MRI of the head and neck for staging of the primary disease. Metastatic workup included a chest x-ray, a liver ultrasound, and a bone scan in all patients. Within 2 months of the end of concurrent CRT, treatment response

was assessed radiographically by a CT scan or MRI of the head and neck and clinically by palpation of neck nodes and flexible nasopharyngoscopy. A biopsy was performed if a residual disease was suspected. Treatment response was evaluated according to the WHO response criteria.[17] Acute and late toxicities were evaluated according to the Radiation Therapy Oncology Group (RTOG) criteria. Hematologic assessment with a complete blood count was performed once a week during the course of CRT. We underwent direct nasopharyngoscopy and imaging study once in every 3 months during the first 2 years, once in every 6 months after 2 years, and followed them yearly after the fifth years.

5. Statistical analysis

The duration of objective responses was calculated from the start date of treatment to the date of the documented disease progression among responding patients. Overall survival (OS) and progression-free survival (PFS) were determined from the first date of starting RT by the Kaplan-Meier method. Locoregional PFS (LRPFS) and distant metastasis-free survival (DMFS) rates in patients who developed either type of failure were calculated. Seven patients were considered lost to follow-up and they were censored from the analysis at that point.

RESULTS

1. Patient characteristics

Between August 1993 and May 2000, a total of 70 patients with histologically confirmed NPC were included in this study ; 50 patients received weekly cisplatin and 20 patients received weekly cisplatin plus daily oral UFT during RT. The patient characteristics are listed in Table 1. Fifty-three patients were male and 17 were female. The median age was 47 years old, with a range of 18 to 76 years. According to AJCC/UICC TNM Classification and Stage grouping,[18] the numbers in patients of stage II, III, IVA, and IVB were 23, 14, 15, and 18, respectively. Sixty-four patients had a palpable neck lymph node, the most common sign at the time of the diagnosis. Cranial nerve palsy was observed from 10 patients. All patients completed the planned dose of RT during a median period of 9 weeks. The median number of administered CHT cycles was 6 per patient (range 2~9), and there was no difference in the median number of cisplatin cycles according to the administered concurrent CHT regimen. Most patients kept to the schedule of daily oral UFT administration.

Table 1. Patient characteristics

Characteristics		No. of patients	Percent (%)
Sex	Male	53	75.5%
	Female	17	24.5%
Median age	Years, (range)	47 (18–76)	
Histology	Class I-keratinizing	21	30.0%
(WHO)	Class II-nonkeratinizing	4	5.7%
	Class III-undifferentiated	34	48.6%
	Unknown	11	15.7%
Primary tumor	Nasopharynx only	30	42.9%
extension	Oropharynx or nasal fossa	22	31.4%
	Skull base destruction	4	5.7%
	Intracranial extension	14	20.0%
N classification	N0	6	8.6%
	N1	27	38.6%
	N2	17	24.3%
	N3	20	28.6%
TNM stage	IIA	1	1.4%
	IIB	22	31.4%
	III	14	20.0%
	IVA	15	21.4%
	IVB	18	25.7%
Dose of RT, Gy	Nasopharynx / neck (median)	7440 / 7540	
Chemotherapy	Weekly cisplatin alone	50	71.4%
	Weekly cisplatin and oral UFT	20	28.6%

2. Treatment response

Primary nasopharyngeal disease had a higher complete response (CR) rate (88.6%), compared with neck lymph node disease (81.4%). No patients experienced locoregional failure during concurrent CRT. Among the 70 patients, 57 (81.4%) patients obtained CR (95% C.I. 72~91%) after the completion of treatment, including 5 patients showing a suspicious residual neck mass with negative pathologic finding by neck node biopsy. The median response duration of patients who achieved CR has not been reached yet. Eight patients (11.4%) showed partial response (PR). Thus, there was an overall response rate of 92.8% (65/70) (95% C.I. 42~143%). Three of 8 partial responders received additional therapy of more than 4 cycles of combination CHT with 5-FU plus cisplatin and obtained CR. In 1 patient who had PR in a neck node and underwent ipsilateral radical neck dissection, locoregional relapse was detected 20 months after surgery. The other 5 patients did not receive further therapy and ultimately, they showed distant metastasis. Five patients (7.2%) had a distant metastasis at the time of evaluation of treatment response, even though locoregionally CR or PR were obtained. Of these 5 patients, 4 patients received salvage CHT and showed progressive disease. As shown in Table 2, there was no significant difference in CR rate between patients treated with weekly cisplatin and those treated with weekly cisplatin plus oral UFT.

3. Patterns of relapse and survival

With a median follow-up duration of 34 months, relapse was detected in 21 (36.8%) of 57 patients showing CR ; 5 with locoregional relapse alone, 11 with distant metastasis, and 5 with combined relapse. Common sites of distant metastasis were as follows : lung 9, bone 7, liver 1, and brain 1. Among the 21 relapsed patients, 81% of the relapses occurred within 18 months from the date of CR. As shown in Fig. 1, the 3-year PFS of all 70 patients was 51.5%. The 3-year LRPFS rate was 70.4% ; 10 patients failed at the nasopharynx, and 5 at the neck (Table 3). The 3-year LRPFS of 10 patients with cranial nerve palsy (48.2%) was worse than those without it (p=0.0390). Twenty-two of the total 70 patients had distant metastasis, and the 5-year DMFS rate was 64.5%. The 5-year DMFS rate in stages II, III, IVA and IVB were 82.0%, 76.6%, 60.6%, and 36.5%, respectively (Fig. 2). Salvage CHT with or without reirradiation was performed in 16 of 21 patients with recurrence of disease. Nine patients who received salvage CHT alone for distant metastasis showed progressive disease. Among 7 patients who received salvage therapy containing reirradiation for a locoregional relapse, 5 patients obtained CR.

The 5-year OS rate of all 70 patients was 60.3%. Nineteen patients died of the disease and 2 patients died of unrelated diseases : gastrointestinal bleeding and aggravation

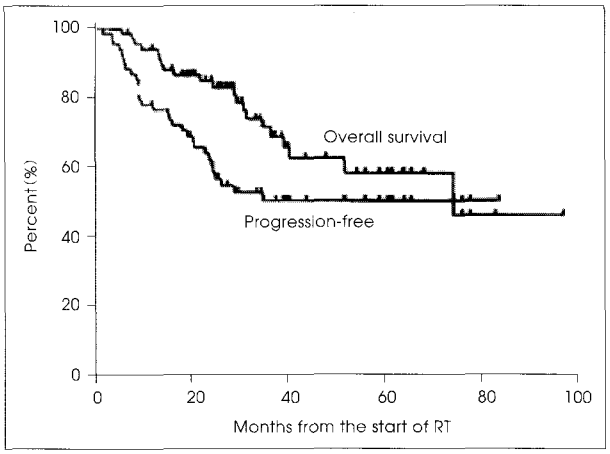

Fig. 1. Progression-free survival and overall survival of all patients.

Table 2. Response rates

	Total patients (N=70)	weekly cisplatin (N=50)	weekly cisplatin and daily UFT (N=20)
CR*	57 (81.4%)	41 (82.0%)	16 (80.0%)
PR**	8 (11.4%)	6 (12.0%)	2 (10.0%)
PD†	5 (7.2%)	3 (6.0%)	2 (10.0%)
Overall response	65 (92.8%)	47 (94.0%)	18 (90.0%)

* : complete response, ** : partial response, † : progressive disease

Table 3. Pattern of Failure in all 70 patients

Stage	No. of patients	Locoregional failure			Distant metastasis	Total failure
		Nasopharynx	Neck	Total		
II	23	1	2	3	3	6
III	14	1	1	2	3	5
IVA	15	6	0	6	5	8
IVB	18	2	2	4	11	12
Total	70	10	5	15	22	31

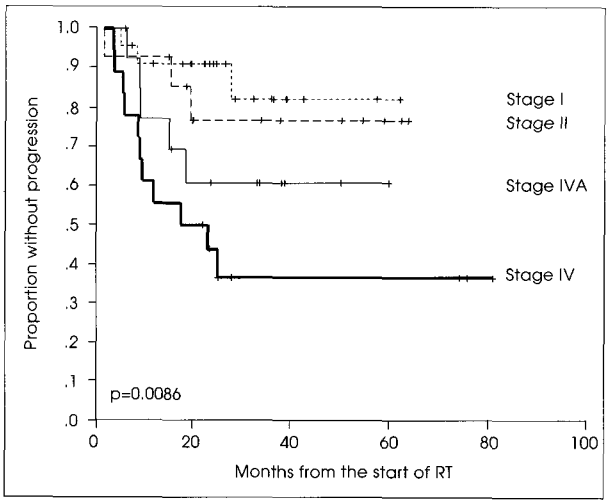

Fig. 2. Distant metastasis-free survival according to the stage.

of idiopathic pulmonary fibrosis. There were no significant factors affecting overall survival (Table 4).

4. Toxicity

No serious adverse effects or death related to planned treatment occurred in any patients. Treatment toxicities are summarized in Table 5. The major acute toxicity was oral mucositis with 27.1% grade II, 10% grade III, and 1.4% grade IV. Twenty-three patients (32.9%) encountered grade II neutropenia, and grade III neutropenia occurred in 3 patients. There was no febrile neutropenia or other infection during the concurrent CRT. RT was interrupted in 3 patients for 1-5 weeks because of oral mucositis and neutropenia. Four patients stopped weekly cisplatin due to poor oral intake related to mucositis and/or nausea and vomiting,

Table 4. Univariate analysis of prognositc factors

Variables		3-PFS* (%)	p-value	3-OS** (%)	p-value
Sex	Male	46.5%	0.1820	64.9%	0.1872
	Female	68.0%		85.6%	
Age	≤ 50	45.8%	0.2734	72.7%	0.7096
	> 50	59.6%		67.0%	
T classification					
	T1/2	56.8%	0.2364	69.5%	0.7642
	T3/4	38.8%		69.1%	
Cranial nerve palsy					
	No	56.2%	0.0346	71.3%	0.5939
	Yes	30.0%		65.6%	
N classification					
	N0	66.7%	0.2165	100%	0.2093
	N1	64.2%		70.9%	
	N2	42.8%		79.5%	
	N3	39.8%		50.4%	
Stage					
	II	67.1%	0.0973	69.8%	0.3396
	III	61.9%		92.8%	
	IVA	43.2%		74.9%	
	IVB	32.4%		43.9%	
Chemotherapy regimen					
	Cisplatin	53.0%	0.6217	73.9%	0.3811
	Cisplatin/UFT	45.7%		79.7%	

* : 3-year progression-free survival, ** : 3-year overall survival

Table 5. Acute toxicities during concurrent chemoradiotherapy

	Toxicity Grade (n=70)				
	Grade O	Grade I	Grade II	Grade III	Grade IV
Neutropenia	13	31	23	3	0
Thrombocytopenia	0	0	1	0	0
Oral mucositis	12	31	19	7	1
Nausea/vomiting	42	15	8	5	0
Skin reaction	6	45	16	3	0

and 1 patient stopped weekly cisplatin due to azotemia. The late complications were usually mild. All patients suffered from varying degree of xerostomia. Five patients complained of hearing impairment. Three patients suffered from transient Lhermitte's sign and 3 patients had trismus.

Discussion

This study has a unique aspect in that the efficacies and toxicities of concurrent CRT using weekly cisplatin with or without UFT were observed in a homogenous population of NPC. The overall 5-year survival rate has been around 50% for patients treated by RT alone and has improved very little in the last 20 years.[1-3] In our study, with concurrent CHT using daily oral UFT300 mg and/or weekly cisplatin 20mg/m^2 during RT, a CR of 81.4% and an overall response rate of 92.8% were obtained without increase of toxicity. The 3-year PFS rate was 51.5% and the 5-year OS rate was 60.3%. However, distant metastasis was a frequent cause of failure as evaluated in previously reported studies. The 5-year DMFS rate was 64.5%, and there was a significant difference in DMFS between stages (stage II, 82.0% ; stage III, 76.6% ; stage IVA, 60.6% ; stage IVB, 36.5%). Also, the 5 patients who did not respond until the end of RT showed distant metastasis, irrespective of locoregional response. Previous studies on NPC using combined CRT reported that a response rate was 80~100% and the overall 5- and 10-year survival rates were 40~70% and 30~45%, respectively[10][19][20]. Our results showed similar treatment efficacy with previous reports, but a relatively high incidence of systemic failure is a continuing issue to be solved, especially in more advanced disease.

Until now, it was unclear which chemotherapeutic agent and schedule would be best in combination with RT. Theoretically, chemotherapeutic agents could work as radiosensitizer and cytotoxic agents. Cisplatin and 5-FU have been frequently selected because they are active against head and neck cancer, and both are known to be a potent radiosensitizer.[21][22] Kyriazis, et al suggested that the antitumor effects were greater when cisplatin was administered by continuous infusion because it may be a cell-cycle-phase-specific drug with preferential action on the G1 phase of the cell cycle.[23] In addition, laboratory data show that the effect of a chemotherapeutic agent such as a radiosensitizer is most profound, when the drug is present in target cells at the moment of irradiation, that is, continuous infusion as opposed to bolus administration.[24] A recent randomized study showed that concurrent low-dose daily cisplatin 6mg/m^2 during hyperfractionated RT offered a survival advantage.[11] There was a randomized trial that did not show the addition of weekly low doses (20mg/m^2) of cisplatin to the RT is superior to RT alone,[12] even though in an adjuvant setting, postoperative RT concurrently with 50mg of cisplatin every week showed better locoregional control and survival with marginal toxicity.[13] Also, concurrent CRT using weekly cisplatin 50mg was effective for oropharyngeal cancer.[14] Furthermore, the cisplatin dose used in the intergroup study, which demonstrated that concurrent CRT could improve the survival of NPC, was 100mg/m^2 every 3 week.[10] As above, there seemed to be correlation between the dose of cisplatin and treatment outcome. However, whether these trials are applicable to all the ethnic and histologic groups in which the disease is endemic, such as Asia, is unclear.[25] In recently reported Chinese data, a CRT regimen of weekly cisplatin 40 mg/m^2 was well tolerated and resulted in a benefit over RT alone in 321 patients with locoregionally advanced NPC.[26] So our regimen of weekly cisplatin 20 mg/m^2 as a concurrent CHT might be inadequate to produce cytotoxicity for eradication of micrometastasis, especially in more advanced diseases.

The rationale for addition of UFT, a combination of uracil and tegafur, is that continuous infusion of 5-FU has proved superior to bolus administration, and that UFT has similar pharmakokinetic activity as protracted infusion of 5-FU.[16] Recently, oral UFT has been investigated for head and neck cancer. Cisplatin plus oral UFT was as effective as the classic cisplatin plus continuous 5-FU, and had the advantages of outpatient oral administration and a low incidence of toxicity in a neoadjuvant trial.[27] However, to our knowledge, concurrent CRT using weekly cisplatin and oral UFT has never been conducted in NPC. Our results showed no difference in response rate, 3-year PFS, and OS between weekly cisplatin and weekly cisplatin plus oral UFT. However, these findings might be ascribed to the limitation of the small number of patients, and an inadequate dose of UFT.

In our study, CHT was administered in an outpatient setting. The most frequently encountered grade III/IV toxicity was oral mucositis (11.4%). Five patients required discontinuance of further chemotherapy and in only 3 patients was RT interrupted during 1-5weeks. The addition of UFT to weekly cisplatin during RT did not increase toxicity and did not decrease compliance to weekly cisplatin. Concurrent intensive CRT using a high- or intermediate-dose of cisplatin or continuous intravenous infusion of 5-FU enhanced treatment efficacy in many randomized studies, but

it also added significant toxicity, including mucositis, neutropenia, or infections, and often required treatment interruptions.[28)29)] The intergroup study by Al-Sarraf, et al revealed that only 55% of patients completed the combined modality treatment as planned.[10)] Our patients, however, experienced a tolerable acute toxicity profile and this did not compromise delivery of a full course of RT.

Conclusion

Our concurrent CRT regimen using weekly cisplatin 20 mg/m^2, with or without UFT, demonstrated acceptable toxicity and response comparable to the results of previous reports. We plan to do further study using a moderately intensified dose of weekly cisplatin and oral UFT with RT, especially in patients with more advanced NPC due to its high incidence of distant metastasis.

KEY WORDS : Nasopharyngeal neoplasms · Chemotherapy · Radiotherapy · Cisplatin · UFT.

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