Radiosensitization of Cis-Platimum in the Treatment of Advanced Head and Neck Squamous Cell Carcinoma

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Cis-Platinum (DDP) was utilized as a radiosensitizer in a pilot study for stage III and IV squamous cell carcinoma between 1984-1987, and DDP 20 mg/M^2/day was administered for 4 days at 3 week interval with concurrent radiotherapy. This study consisted of three phases: cytoreduction phase, eradicative treatment phase and adjuvant phase. Total 59 patients were subjected to evaluate a tumor response and its toxicity. During the eradicative phase, 27 patients underwent surgery (group I), 29 patients were treated with radiotherapy only (group II) and 3 patients did not complete the second phase of therapy. At the cytoreduction phase, 95% response rate with complete response (CR) 47.5% and partial response (PR) 47.5% was observed. Complete tumor clearance (CTC) rate following 2nd phase of therapy was 84% (47/56) with 26/27(96%) in group I achieved CTC with surgery and 21/29 (72%) patients in group II achieved CTC following 2nd phase. 67% of primary lesions and 70% of nodal diseases in group I showed no tumor in the surgical specimen. 34% of patiets who achieved CTC at 2nd phase developed recurrence and median time to recur was 8 months. Actuarial disease free survival at 4 years was 59% and 51% (24/27) of patients who achieved CTC at 2nd phase were alive without any evidence of disease at median follow-up 31 months (range, 10-48 months). There was no significant difference in overall and disease free survival between group I and II, between CR and PR group following 1st phase. Only significant prognostic factor in this study was the complete tumor clearance following 2nd phase theapy. In general, toxicity was not excessive. Author concludes that this study confirmed the significant radiosensitizing effect of DDP with the acceptable toxicity and warrant the prospective study to determine optimum scheduling for DDP and radiotherapy which maximizes the therapeutic gain.

Key Words: Head and Neck Cancer, DDP, Radiosensitization

INTRODUCTION

For several decades, surgery and radiotherapy have been the main treatments for advanced squamous cell carcinoma of the head and neck. Loco-regional tumor control and the ultimate survival rate at 5 years is 10% to 30%[1]. The high rate of loco-regional recurrence has been the primary cause of failure and poor prognosis in patients with advanced head and neck cancer. In the past 10 years chemotherapy has added a new dimension to the multimodality approach for head and neck cancer. The primary role of chemotherapy has been to improve loco-regional control with its cytotoxic activity. It has been utilized as an adjuvant therapy to radiation and/or surgery and as an adjunctive therapy to palliate the patients. But its role as a radiosensitizer has not been extensively explored. A number of recent studies have shown the potential of DDP not only as an antitumor agent in squamous cell carcinoma of the head and neck but also as a radiation sensitizer[2~4]. Given the functional, cosmetic and psychological consequences of radical surgery for patients with advanced head neck cancer, DDP-sensitized radiotherapy would be welcomed if this regimen produces a loco-regional control rate similar to or greater than that of radical surgery plus radiation therapy. Many induction chemotherapy trials have been reported in recent years. One of the most effective chemotherapy regimens, DDP plus 5-fluorouracil (5-FU), produced a complete response rate of 54% with an overall response rate of 93%[5]. Although initial response retes with chemotherapy in addition to surgery and/or radiation therapy

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have been encouraging, it is not clear if there is any advantage in long-term loco-regional control and ultimate survival[6~10]. There is a distinct advantage for concomitant use of DDP with radiotherapy in the management of head and neck cancer, because DDP does not produce clinically significant mucosal toxicity. Based on this background, pilot study utilizing DDP as a radiosensitizer in stage III and IV squamous cell carcinoma of the head and neck was conducted at Rhode Island Hospital since 1984. Preliminary results from this study were reported[11] and this report includes total 59 patients to evaluate the tumor response and its toxicity from DDP-sensitized radiotherapy.

METHODS AND MATERIALS

The study included three phases; cytoreduction phase, eradicative treatment phase and adjuvant phase (Fig. 1): a) cytoreduction phase--DDP administered intravenously 20 mg/M² for 4 days beginning on day 1 of radiation therapy and again at 3 weeks, concomitant with radiation therapy (45Gy/5weeks); b) eradicative treatment phase--radical surgery (group I) or a boost of radiation consisting of 20Gy in 3 weeks with DDP administered intravenously 20 mg/M²/day for 4 days (group II); and c) adjuvant phase--combined 5-FU infusion, 1 gm/M² infused over 24 hours daily for 4 days plus DDP 80 mg/M² administered intravenously on day 1 of the 5-FU infusion, given at 4 week intervals for a total of 6 cycles following initial therapy to the primary site. Between 1984 and 1987, 59 patients were treated. The characteristics of these patients were presented in table 1. During the eradicative treatment phase, 27 patients underwent surgery after 45Gy/5 weeks of radiotherapy with 2 cycles of DDP (Group I), 29 patients were treated with 65Gy/8 weeks with 3 cycles of DDP (Group II) and 3 did not complete the thrapy after the 1st phase. At the time of original staging, all patients were determined to have technically operable disease. However, some patients refused to consider surgery and/or some surgeons were either discouraged by the medical condition of the patients, or--at the time of evaluation for surgery--by the primary site of disease, in which cosmetic or fuctional impairment would result from radical surgery. These patients were treated in Group II. Table 2 shows the sites of primary cancer of 59 patients and table 3 shows the primary and nodal tumor clissifications of patients' cancer according to the American Joint Committee on Cancer (AJCC) classification. Clinical tumor response at the 1st phase was defined as CR for complete tumor regression of measurable disease, as PR for 50% or more volume reduction of measurable disease and as stable or no response for less than 50% volume reduction of measurable disease. Survival curves were esti-

Table 1. Patient Characteristics

Total entered	59
Male/Female	46/13
Median Age in Years (range)	61 (36-80)
Median Performance Status (range)	70 (60-90)
Stage	
III	20
IV	38
Treatment	
Group I	27+
Group II	29
Off study after cytoreduction phase	3

+Four patients underwent radical neck dissection only following negative biopsy from primary site and their primary diseases were treated with radical radiation therapy.

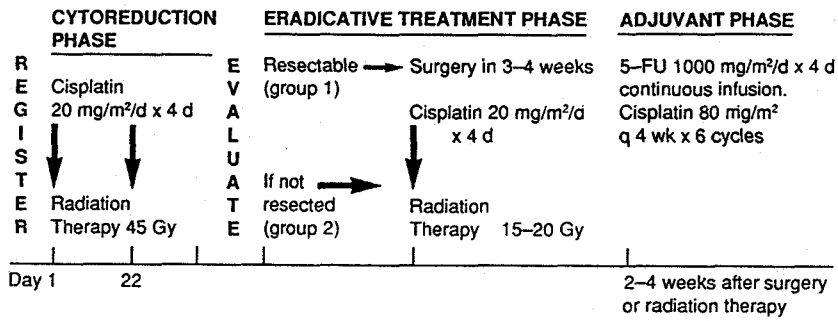

Fig. 1. The schema of the treatment protocol.

mated by the Kaplan-Meier technique, and survival was measured from the day of diagnosis. Disease-free survival was measured from the day of completion of the eradicative treatment phase. For the patients who did not achieve complete tumor clearance following the 2nd phase therapy the length of disease-free survival was defined as zero. To eliminate any potential bias in the interpretation of data resulting from selection, separate disease-free survival analyses were done both including and excluding these patients. Comparisons of survival among the different subgroups were made using the parametric exponential multivariate regression model[14].

RESULTS

1. Tumor Response Following Cytoreduction Phase

95% (56 of 59 patients) clinical tumor response rate was observed; 47.5% (28 of 59) showed complete response, 47.5% (28 of 59) showed partial response and 5% (3patients) showed stable disease or no response (Table 4). The degree of tumor response following 1st phase therapy had no bearing on their survival if patients achieved complete tumor clearance at the 2nd phase therapy (Fig. 5).

2. Tumor Clearance Following Eradicative Treatment Phase

Total 56 patients completed the eradicative treatment phase; 2 patients in partial responder and one from no responder following 1st phase did not advance to the 2nd phase therapy. 84% of patients achieved complete tumor clearance following 2nd phase (Table 4). In group I (27 patients), all but one achieved complete tumor clearance with surgery and one who had tumor at the resection margin developed extensive recurrence in 5 months. Thus, 96% of patients in group I had CTC at the end of the eradicative treatment phase. Four patients in group I underwent radical surgery for neck disease following negative biopsy in the primary site; their primary diseases were treated with radical doses of radiation. 7 of 29 patients in group II (28%) did not achieve complete tumor clearnce and died with disease within one year. 72% of patients (21/29) achieved CTC. Table 5 showed histologic evaluation of the primary and nodal disease according to their classification in group I following the 1st phase. 67% of primary disease and 70% of nodal disease showed no histologic evidence of tumor on the surgical specimen following DDP and concurrent radiation therapy, 45Gy/5 weeks. 76% primary and nodal tumor

Table 2. Site of Primary Cancer

Site	
Oral cavity	17
Oropharynx	13
Larynx	8
Hypopharynx	13
Nasopharynx	4
Paranasal Sinus and Nose	3
Unknown	1
Total	59

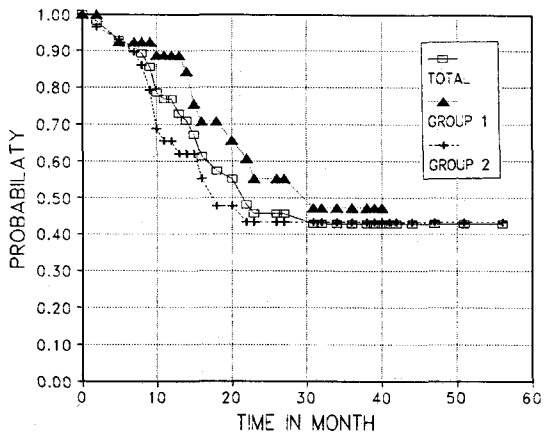

Fig. 2. Actuarial Overall Survival in Group I and Group II.

Table 3. Primary and Nodal Tumor Classification

	Tx	T1	T2	T3	T4	Total
No	1(0:1)			10(2:8)	8(4:4)	19(6:13)
N1			2(2:0)	8(5:3)	4(2:2)	14(9:5)
N2			3(2:1)	8(4:4)	4(1:3)	15(7:8)
N3	1(0:1)	1(1:0)	2(1:1)	4(1:3)	3(2:1)	11(5:6)
Total	2(0:2)	1(1:0)	7(5:2)	30(12:18)	19(9:10)	59(27:32)

Numbers in parenthesis indicate number of patients in Group I and Group II respectively.

in group II following 3 cycles of DDP and concurrent radiation therapy, 65Gy/8 weeks, regressed completely at 2 months after completion of radiotherapy. Only 11 patients among 21 patients who were assessed as complete tumor clearance following 2nd phase in group II, underwent the histologic examination and all of them had negative histologic examination on biopsy specimens.

3. Recurrence and Survival

Among the patients who achieved complete tumor clearance at 2nd phase, 77% of the primary tumor and 79% of nodal disease have sustained complete response upon their latest followup (median followup time 35 months, minimum followup time 10 months). 34% of whom achieved complete tumor clearance developed locoregional recurrence (31%, 38% in group I and group II respectively) and the median time to recur was 8 months (range, 2-17 months). 24 patients were alive without any evidence of disease and their median followup time was 31 months with a range, 10-51 months (Table 6). Actuarial overall survival for 56 was 44% at 4 years (Fig. 2) and disease free survival at 4 years was 59% (Fig. 3). Between group I and group II, there was no significant difference in disease free survival (Fig. 3). Gender, cancer stage and adjuvant chemotherapy did not significantly influence the overall survival and disease free survival. The only significant prognostic factor in our study was complete tumor clearance following the 2nd phase therapy (Fig. 4).

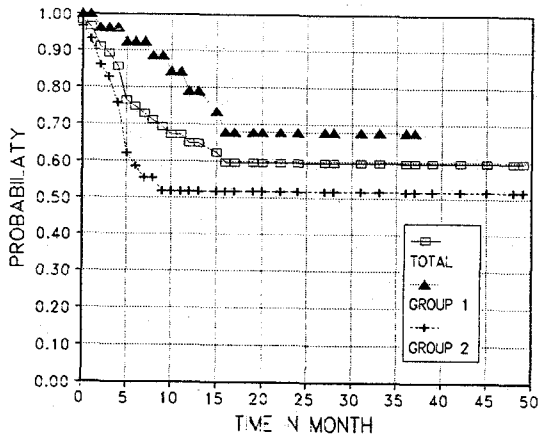

Fig. 3. Actuarial Disease-free Survival in Group I and Group II (p= . 25).

4. Toxicity

1) Toxicity related to cytoreduction phase

All patients experienced some degree of mucositis and weight loss. Severe mucositis requiring more than 7 days interruption of treatment occured in 19% (11 of 59) and more than 10% weight loss occured in 29% (19/59). In general, toxicity related to DDP and concurrent radiotherapy was not excessive and transient hematologic toxicity (platelets<50,000, WBC<2, 000) and transient peripheral neuropathy were observed in less thatn 5%.

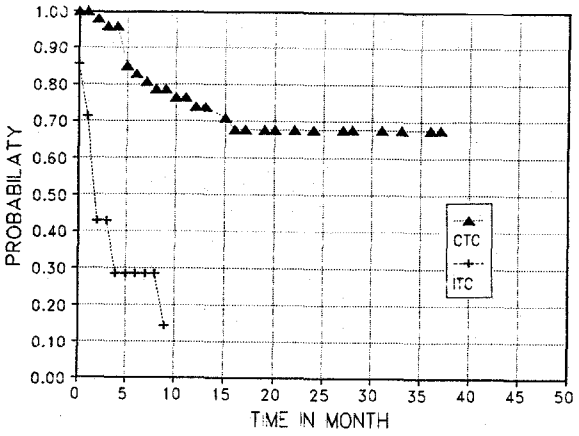

Fig. 4. Actuarial disease-free survival (p< .001)
CTC; complete tumor clearance following the eradicative phase,
ITC; incomplete tumor clearnce following the 2nd phase therapy.

Table 4. Tumor Response to Treatment

	Group I	Group II	Off-study	Total
Number of patients	27	29	3	59
Clinical response following 1st phase				
Complete response	17	11		28(47.5%)
Partial response	10	16	2	28(47.5%)
Stable or no response		2	1	3(5%)
Complete tumor clearance following 2nd phase	26(96%)	21(72%)		47(84%)

Table 5. Primary and Nodal Tumor Status From Examination of Surgical Specimen in Group I (After 45 GY/5 Weeks with 2 Cycles of DDP

Satage	Evaluable no of patients	Positive	Negative
T1	1	0	1(100%)
T2	5	2	3(60%)
T3	12	2	10(83%)
T4	9	5	4(44%)
Total	27	9	18(67%)
N0	6	0	6(100%)
N1	9	3	6(67%)
N2	7	2	5(71%)
N3	5	3	2(40%)
Total	27	8	19(70%)

Table 6. Follow-UP DATA

	Group I	Group II	Total
Evaluable No. of patients	27	29	56
No evidence of disease, alive (disease free survival, 10-51M, median 31M)	12*	12+	24
Treatment failure			
Persistent disease	1	8	9
Locoregional recurrence	8*	8+	16
Distnt metastasis only	3		3
Dead, other causes	5	2	7

* One patient was salvaged with surgery and one salvaged with irradiation.

+ One patient was salvaged with surgery.

2) Toxicity related to eradicative treatment phase

In group I. our surgeons did not observe any excessive difficulty during surgery and post-surgery in terms of wound healing when compared it to the patients who were treated with preoperative radiotheapy without DDP. We did not observe any additional cumulative toxicity in patients from group II except one patient with nasopharyngeal primary who lost left vision during 2nd phase.

3) Toxicity related to adjuvant chemotherapy phase

The compliance rate in the maintenance adjuvant chemotherapy phase was very low; 22 of 56 patients received two or more cycles of chemotherapy. All patients experienced some nausea and vomiting, and intense stomatitis was observed in most patients. 20% of patients showed weight loss during adjuvant phase. One patient developed myocarditis which was attributed to 5-FU.

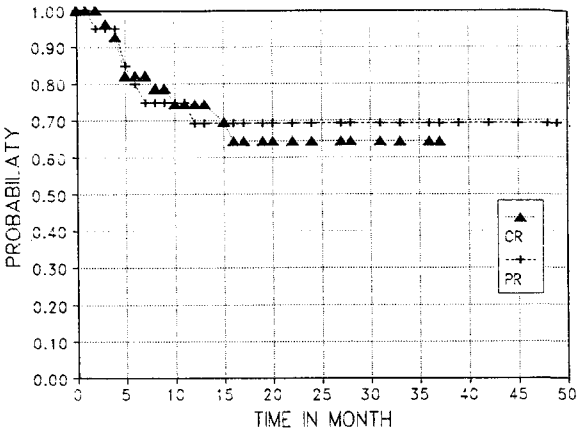

Fig. 5. Actuarial Disease-free Survival
CR; complete response following cytoreduction phase.
PR; partial response or stable disease following 1st phase.

DISCUSSION

Induction chemotherapy trials for advanced head and neck cancer have produced a response rate of 70%~90% with complete response ranging from 20% to 50% before definitive local treatment[5,10,15~17]. The final report from the Head and Neck Contract Program (HNCP)--a prospective randomized trial by the National Cancer Institute for resectable stages III and IV head and neck cancers--has shown a response rate of 37% with complete response of 3% with a 4-week course of induction chemotherapy[10]. The HNCP study did not demonstrate a significant effect of one cycle of induction chemotherapy on overall and disease free survival. The concomitant use of chemotherapy with radiation therapy has received continuous attention[18~20]. For patients with advanced head and neck cancers, a recent randomized trial conducted by the Northern California Oncology Group (NCOG) has shown improved states of complete regression, loco-regional control, and relapse-free survival (but not crude survival) in ptients who received chemothrapy (without DDP) and concurrent radiation therapy, compared with radiation therapy alone[20]. The radiation sensitizing effect of chemotherapy, particularly with DDP and 5-FU, has recently been explored. Clinical trials employing DDP plus 5-FU with radiation produced complete response rates of 60%~100%[21,22]. Various combination of DDP sensitized radiation therapy have

been conducted and complete responses of 40% ~78% have been reported[23~28]. The results of this study demonstrated that the schedule for DDP and radiation therapy-DDP administered I.V. 20 mg/M² for 4 day, beginning on 1 day of radiation therapy and repeated at 3 weeks-was well tolerated. The cytoreduction phase resulted in 95% clinical tumor response rate (CR 47.5% and PR 47.5%). In group I, 67% of primary lesions and 70% of nodal disease achieved pathologic CR--no tumor in their surgical specimen. These observations are comparable to those reported by others[5,29,30]. The eradicative treatment phase resulted in 84% CTC (96% in group I, 72% in group II). In group II, 76% of primary and nodal disease regressed completely at 2 months after the completion of radiotherapy. In contrast to the findings of others, freedom from the tumor as determined from histologic study following the 1st phase did not benifit overall or disease free survival[29]. Among the patients who achieved complete tumor clearance at 2nd phase, 77% of primary tumor and 79% of nodal disease sustained complete response upon their latest follow-up (median follow-up 35 months, minimum follow-up 10 months). 34% of patients (31%, 38% in group I and II respectively) developed loco-regional recurrence and the median time to recur was 8 months (range, 2-17 months). 51% (24/47) of patients who acheived CTC at 2nd phase were alive without any evidence of disease at median follow-up 31 months (range 10-51 months). Although the loco-regional recurrence rate was higher in group II, disease free survival of patients who achieved complete tumor clearance following the 2nd phase showed no statistically significant difference in group I and II (Fig. 3). This observation supports the NCOG report that suggested the possibility of omitting radical surgery without compromising survival for advanced head and neck cancer[30]. A current Veterans Administration Cooperative Study is exploring this question. Disease free survival for all 56 patients at 4 years was 59%. Only significant prognostic factor in this study was CTC with 2nd phase therapy (Fig. 4). In general, toxicity from 1st phase therapy was not excessive and well tolerated. As expected, mucositis and weight loss were common. In group I, the surgeons did not observe any excessive difficulty during surgery and post-op in terms of wound healing when compared it to the patients who were treated with pre-op irradiation without DDP. Low compliance in the adjuvant phase may have contributed to the absence of benefit from adjuvant chemotherapy. 39% (22/56) accepted two to six cycles of therapy. The Dana-Farber trials of adjuvant chemotherapy suggested a significant survival advantage in the subgroup with partial response to induction chemotherapy[31] and others observed no survival benefit but did observe significant toxicity[32,33]. Our study showed encouraging results with improved tumor response and disease free survial. The results of our study demonstrated the radiosensitizing effect of DDP and warrant a prospective randomized study to determine optimum scheduling for DDP and raidation therapy. Human pharmacokinetic studies suggest that daily administration of DDP may maximize interaction with the resistant cell fraction during radiation therapy because of a stepwise increase in ionized, unbound DDP[33]. Author hopes that future trials might suggest the possibility of omitting radical surgery, without compromising survival for an advanced head and neck cancer.

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= 국문초록 =

국소 진행된 두경부편평 상피암에 대한 CIS-PLATINUM과 방사선치료의 동시 병행요법

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치료방사선과

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CIS-PLATINUM(DDP)을 제3기, 제4기 두경부종양환자에게 방사선 민감제로 사용한 임상연구 결과를 보고한다. 1984년부터 1987년까지 DDP 20 mg/M²/day를 4일간 방사선 치료와 동시에 투여하였으며 DDP는 3주 간격으로 반복투여 되었다. 치료는 종양세포 감소시기, 근치시기및 보조 치료 시기로 나누어 시행되었다. 본 논문에서 59명 환자의 치료결과및 합병증에 대하여 보고한다. 근치시기동안 27명이 방사선치료 45Gy 후 근치적 수술을 시행한 제 I 치료군으로, 29명이 근치적 방사선치료 65Gy를 시행한 제II치료군으로 분류되고 3명의 환자는 근치시기의 치료를 끝내지 못하였다. 종양세포 감소시기의 치료로 완전관해 47.5%, 부분관해 47.5%로 전체 반응률 95%를 보였다. 근치시기 치료후 전체적으로는 84%(47/56)의 완전 관해를 보였고, 제 I 치료군에서는 96%(26/27), 제II치료군에서는 72%(21/29)가 완전 관해를 보였다. 제 I 치료군에서 원발병소의 67%에서, 임파절 병변의 70%에서 병리소견상 종양이 관찰되지 않았다. 근치시기치료후 완전관해 환자중 34%에서 재발하였으며 재발까지의 평균시간은 8개월이었다. 전체 56명 환자의 4년 무병생존율은 59%였고 근치시기에 완전관해를 보인 환자중 51%(24/47)가 31개월의 평균 추적관찰기간(범위 : 10~51개월)동안 무병생존하였다. 제 I 치료군과 제II치료군 사이에 전체생존율, 무병생존율에 있어서 유의한 차이는 보이지 않았다. 종양세포감소시기에 완전관해및 부분관해를 보인 환자들 사이에 생존율에서는 차이가 없었으며 가장 중요한 예후인자는 근치시기 치료로 완전관해 되었는지 여부이었다. 전체대상 환자의 합병증은 일반적인 치료시에 비하여 심하지 않았으며 치료에 잘 적응하였다. 본 연구에서 DDP가 비교적 적은 합병증을 동반한 의미있는 방사선 민감제임을 확인하였으며 치료효과를 증대시키기 위하여 DDP와 방사선치료의 적절한 투여 계획을 결정하는 전향적연구가 필요하다고 생각한다.