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RADIATION THERAPY AND CONCURRENT CISPLATIN ADMINISTRATION IN LOCALLY ADVANCED HEAD AND NECK CANCER

A Hellenic co-operative oncology group study

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In an attempt to improve local control of locally advanced head and neck cancer, radiation therapy was combined with cisplatin. Forty-eight patients entered into this study. All patients were irradiated with a ^{60}Co unit and according to the protocol they should receive 70 Gy in the tumor area and 45 Gy in the rest of neck. Cisplatin was administered at a dose of 100 mg/m^2 on days 2, 22 and 42. Thirty-seven (80%) patients received the total radiation dose as initially planned. Thirty-four (72%) patients achieved complete and 5 (10%) partial response. Grade 3–4 toxicities included vomiting (14%), stomatitis (4%), diarrhea (2%), myelotoxicity (14%), hoarseness (4%), dysphagia (30%), weight loss (32%), nephrotoxicity (4%) and dermatitis (2%). After a median follow-up of 26 (range, 18–33) months, 16 patients have died. Among the 35 complete responders 6 later on relapsed. Median relapse-free survival has not yet been reached. Combined radiation therapy and cisplatin appears to be a highly active treatment in patients with advanced head and neck cancer as far as primary locoregional response is concerned.

The prognosis of patients with locally advanced head and neck cancer (HNC) is generally poor. Despite mutilating surgery and/or radical irradiation, 50–60% of the patients relapse within 2 years and an additional 20–30% develop distant metastases (1).

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Induction chemotherapy followed by irradiation has been extensively investigated during the last decade. Unfortunately, there seems to be no survival benefit from such combined modality and most patients develop locoregional recurrence (2). One disadvantage of induction chemotherapy is that a considerable number of patients refuse local therapies after completion of induction chemotherapy, and for this reason their survival may be compromised. To improve local control of the tumor, several investigators have administered, concurrently with irradiation, different drugs, such as cisplatin (DDP), 5-fluorouracil, mitomycin, hydroxyurea, etc, which may give an additive therapeutic effect or act as potentiators of the radiation therapy (3–7).

In a phase II study, the Radiation Therapy Oncology Group (RTOG) administered, concurrently with irradiation, DDP at a dose of 100 mg/m^2 on days 1, 22 and 42. The complete response (CR) rate in this study was 69% (3). The group then decided to repeat a similar study to see whether this high CR rate could be confirmed.

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Material and Methods

Only patients with locally advanced HNC were included in the present study. Eligibility criteria included measurability of evaluable disease, performance status (PS) >40% in Karnofsky's scale, normal renal and hepatic functions, WBC count $\geq 4 \cdot 10^9/l$, and platelet count $\geq 100 \cdot 10^9/l$, age ≤ 75 years, no active ischemic heart disease and no prior anticancer treatment. Informed consent was obtained from all patients and the protocol was approved by the ethics committee responsible for each center. Initial examination included history, clinical examination, laryngoscopy, esophagography, complete blood count, sequential multiple chemical analysis (SMA-12), electrocardiogram, chest x-ray, bone scan and computed tomography (CT scan) of the head and neck region. Audiogram was not routinely required. All patients were initially evaluated by an ENT surgeon, a medical oncologist and a radiotherapist and staged by AJC/UICC criteria (8). From April 1991 until October 1992, 48 patients entered this study, which was conducted by the Hellenic Co-operative Oncology Group for Head and Neck Cancer. There were 44 men and 4 women with a median age of 62 (range, 18–75) years and a median performance status of 90 (range, 60–90). Patients characteristics are shown in Table 1.

All patients were irradiated with a ^{60}Co unit. The target volume to be irradiated was the primary site, the lymph nodes of the neck and supraclavicular fossa. According to the protocol they should receive 70 Gy to the tumor area and prophylactically 45 Gy to the uninvolved cervical and supraclavicular lymph nodes. Five fractions per week of 1.8 Gy each were delivered. For the irradiation the patient was placed in a supine position and the primary site as well as the upper neck lymph nodes were treated with two lateral opposed fields up to 45 Gy in 4.5 weeks. After reaching this radiation dose, reduced lateral fields were used for the primary and the involved nodes, sparing the spinal cord (lateral and contralateral oblique fields were used in case of ipsilateral node involvement) up to 70 Gy in seven weeks. Wedges were used when necessary. The uninvolved lower neck and the supraclavicular nodes were treated with an anterior field, starting 0.5 cm below the lateral fields and with a total dose of 45 Gy at 3–3.5 cm depth in 4.5 weeks with shielding of the lung apices. All fields were irradiated every day. DDP was infused in a 3-h period at a dose of 100 mg/m^2 on days 2, 22 and 42. Ondansetron (with or without dexamethasone) was used as antiemetic in all cases. Dose modifications or discontinuation of DDP were performed according to hematologic or renal toxicity. DDP was reduced to 50% if creatinine clearance was less than 50 ml/min despite hydration or if the patient had a transient increase in serum creatinine over the upper normal limits. DDP was discontinued if the patient had a permanent abnormal increase in serum creatinine. In case of hematologic toxicity, leukocyte count should return to $4 \cdot 10^9/l$ and platelets to $90 \cdot 10^9/l$ before treatment was continued.

Patients were evaluated for response 10–12 weeks after completion of the irradiation, and subsequent treatment depended on the primary site of the tumor and the status of the cervical lymph nodes. Patients with laryngeal tumors who did not respond completely underwent total laryngectomy. Patients with residual disease in other sites received adjuvant chemotherapy which consisted of 4 monthly cycles with carboplatin (300 mg/m^2), methotrexate (40 mg/m^2) and bleomycin (15 IE). Neck dissection was generally performed in patients who achieved histologically confirmed complete response of the primary tumor but had residual lymph node metastases or relapsed in the neck. Complete response (CR) was defined as a complete disappearance of all clinically evident disease. Partial response (PR) was defined as a decrease of more than 50% of the sum of the products of the largest perpendicular diameters of the measurable lesions. Stable disease (SD) was defined as an objective response without satisfying the criteria of PR or an increase of less than 25% in the absence of new lesions. Progressive disease (PD) was a more than 25% increase of the above measurements or the appearance of a new lesion. CT scans of the head and neck region from all complete responders were reviewed by one of the authors (A. K.-F.). The RTOG/EORTC acute radiation morbidity scoring criteria were used to assess toxicity from irradiation and the WHO criteria to assess toxicity from chemotherapy.

Survival was estimated from the initiation of combined treatment to the date of last follow-up or until patient's death. Time to progression was defined as the time between initiation of treatment and progression documented clinically and/or radiologically. Product limit survival and time to progression were calculated using the Kaplan-Meier method (9). Log-rank test (10) was used to compare survivals.

Results

Response and survival. All 48 patients are considered evaluable for toxicity and survival but only 47 for response since one patient presented with early disease (T2 N0). After completion of irradiation 34 (72%, 95% C.I. 60–85%) patients achieved CR, 5 (10%, 95% C.I. 2–19%) PR whereas 3 (6%) demonstrated SD, and 2 (4%) PD. Complete responses were seen at all locations of the primary tumors (Table 1). One patient with laryngeal tumor who responded partially to combined treatment became disease-free after total laryngectomy. Up to March 1, 1994 after a median follow-up of 26 (range, 18–33) months for the surviving patients, 17 had died. Causes of death were disease progression (n = 13), myocardial infarction (n = 1), sudden death (n = 1) and treatment (n = 2). Among the 34 complete responders, 9 later on relapsed

Table 1

Various characteristics, treatment and survival data of all patients

No.	Age	Sex	Primary site	Histology Grade	Stage		No. of cycles	Delays of RT (days)	Total dose of RT (Gy)	Response	Site of relapse	RFS (mo)	S (mo)
					T	N							
1	66	F	HP	3	T4	N2c	2		67	CR		27+	27+
2	65	M	HP	1	T3	N0	3		68.4	CR	DIS	7	11
3	62	M	HP	2	T3	N0	2		70	CR		8+	8
4	72	M	HP	2	T2	N2a	3		70	SD			11
5	65	M	HP	2	T3	N0	3	6	68	NE			2
6	62	M	LA	1	T4	N0	3		70	CR		33+	33+
7	32	M	LA	1	T4	N2c	3		70	CR	LR	12	28+
8	48	M	LA	2	T4	N3	3		70	CR		23+	23+
9	60	M	LA	2	T2	N2c	3		70	SD			9
10	67	M	LA	2	T3	N2c	3		70	CR		22+	22+
11	48	M	LA	2	T4	N0	3		70	CR		20+	20+
12	63	M	LA	1	T4	N2b	2		70	SD			8
13	50	M	LA	2	T3	N2a	3	7	70	CR	LR	17	18
14	67	M	LA	2	T4	N2b	2		70	PR			8
15	63	M	LA	2	T2	N0	3		65	CR		19+	19+
16	60	M	LA	1	T1	N1	3		65	CR		28+	28+
17	67	M	LA	UNK	T2	N1	3	2	70	PR			21+
18	57	M	LA	2	T4	N0	3	21	70	CR		22+	22+
19	61	M	LA	2	T3	N3	3		68	PR			15
20	55	M	LA	3	T2	N1	3	5	66	CR		25+	25+
21	68	M	LA	2	T3	N0	3		70	CR		27+	27+
22	56	M	LA	1	T3	N3	3		70	CR		12	24+
23	77	M	LA	3	T2	N3	3	7	70	CR		33+	33+
24	69	M	LA	3	T4	N0	3	7	70	CR		11+	11+
25	53	M	NP	4	T4	N0	3	7	70	CR	LR	17	27
26	49	F	NP	3	T2	N2b	3		70	CR	LR	27	36+
27	64	M	NP	2	T3	N0	3		70	CR	LR	21	28+
28	60	M	NP	4	T2	N2b	3		70	PR			27+
29	41	F	NP	4	T3	N2c	3		70	CR		22+	22+
30	60	M	NP	1	T4	N2b	3	15	70	CR		24+	24+
31	70	M	NP	4	T2	N3	3	6	70	CR		29+	29+
32	17	F	NP	4	T4	N3	3		70	CR		18+	18+
33	70	M	OC	UNK	T4	N0	3		70	CR		30+	30+
34	56	M	OC	1	T4	N0	3		70	CR		20+	20+
35	70	M	OC	2	T4	N2b	3		70	PD			12
36	55	F	OC	1	T2	N2c	3	25	70	CR		29+	29+
37	66	M	OC	1	T2	N1	3	7	66	PD			5
38	58	M	OP	UNK	T4	N1	3		63	CR		29+	29+
39	52	M	OP	UNK	T4	N2a	2		70	CR		14+	14
40	37	M	OP	1	T1	N1	3		70	CR		26+	26+
41	62	M	OP	2	T4	N0	3		70	CR		26+	26+
42	66	M	OP	3	T3	N1	3		70	CR	LR	13	20+
43	53	M	OP	2	T3	N2b	3		66	CR		5+	5+
44	63	M	OP	2	T3	N0	3	10	70	NE			2
45	75	M	OP	3	T3	N1	3	5	68	CR	LR	20	21+
46	58	F	SG	2	T4	N1	3		70	CR		32+	32+
47	70	M	UNK	2	TX	N3	2		60	PR			9
48	60	M	UNK	3	TX	N3	3	12	70	CR	LR	6	15

NE: non-evaluable, RFS: relapse-free survival, S: survival, LR: loco-regional, DIS: distant, HP: hypopharynx, LA: larynx, NP: nasopharynx, OC: oral cavity, SG: salivary glands, OP: oropharynx, UNK: unknown
One patient with laryngeal cancer and PR after RT became disease-free after total laryngectomy

(Table 1). Another 2 complete responders developed second primaries, the first one in the esophagus and the second in the lung 8 and 15 months after the initial diagnosis respectively. Median time to progression was 27 months while median relapse-free survival has not yet been reached (Figure). Complete responders had significantly better survival than the others ($p < 0.001$), as expected.

Compliance and toxicity. Thirty-seven (80%) patients received the total radiation dose as initially planned. Dose reductions of DDP had to be performed in one patient

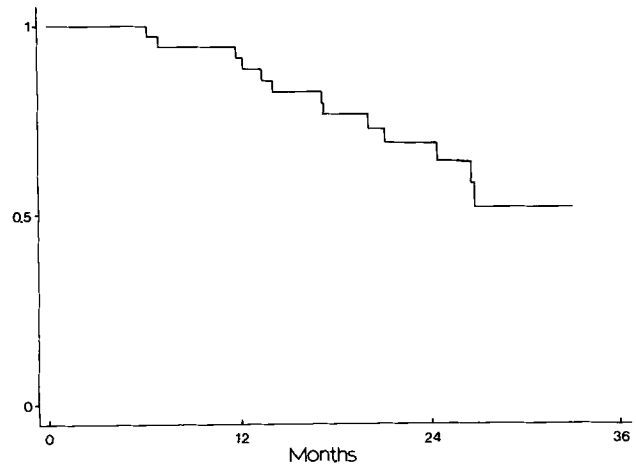

Figure. Relapse-free survival.

during the first and second course because of poor nutritional status and in another 3 during the third course because of serious toxicities. Finally, irradiation was interrupted temporarily in 15 (31%) patients due to toxicity, which resulted in prolongation of treatment for a median of 7 (range 2–25) days. DDP was discontinued during the third course in 2 patients because of nephrotoxicity. Two patients died at home approximately two weeks after the completion of treatment. Both were dehydrated, malnourished and refused to be hospitalized, despite their physicians' recommendation. Thus, both deaths are considered as treatment-related. The different forms of toxicity from combined chemo-radiotherapy are shown in Table 2. One-third of the patients suffered from dehydration and profound anorexia which resulted in weight loss > 15% from pretreatment baseline. As a result of this unpleasant situation 3 patients were hospitalized during the last two weeks of treatment for parenteral support.

Table 2

Acute treatment toxicities (%)

	Grade*				
	0	1	2	3	4
Nausea/vomiting	44	10	32	12	2
Stomatitis	10	54	32	2	2
Diarrhea	96	2		2	
Anemia	74	22	4		
Leukopenia	54	16	18	12	
Thrombocytopenia	96	2		2	
Infection	98	2			
Alopecia	80	12	8		
Otitis	66	24	8	2	
Mouth dryness	15	48	35		2
Hoarseness	38	48	12	4	
Dysphagia	22	52	22	2	28
Neurotoxicity	92	8			
Nephrotoxicity	76	8	12	4	
Weight loss	20	24	26	30	
Dermatitis	0	42	56		2

* RTOG/EORTC or WHO criteria
There were 2 treatment-related deaths

Discussion

It has been shown in tissue cultures and in experimental animals that platinum analogs act as radiation potentiators. The mechanism of potentiation has been proposed to be the inhibition of the repair of potentially lethal damages induced by radiation (11–15). Based on the in vitro data several investigators have explored the potential therapeutic benefit from concurrent DDP administration and irradiation in patients with HNC. After a computer search we identified 9 phase II studies in which radiotherapy was combined concurrently with DDP chemotherapy. In these studies, DDP was delivered in different fashions and the total radiation dose varied from 45 to 73.8 Gy. Despite disparity of patient populations and treatments, chemo-radiotherapy resulted in impressive CR rates, ranging from 31%–72% (Table 3). Possible explanations of the different CR rates reported may include small numbers of patients and different DDP dosages and schedules. The 72% CR rate observed in our study confirms the high CR rate that can be achieved with this combined modality. As the RTOG has shown, the long-term results with this treatment are superior when compared with historical controls treated with radiation alone. At 4 years after treatment, the estimated loco-regional tumor control rate was 43% and the survival 34% (24). Site of the primary tumor (nasopharynx versus others) and the absence of keratin were two factors that significantly influenced the response rate in that study. In our study, the small sample of patients obviously does not permit an analysis of prognostic factors. However, as previously mentioned clinical CR was observed at all locations of the primary tumors. The impressive efficacy of this combined treatment in patients with cancer of oropharynx (8/8 CR) and larynx (13/18 CR) is noteworthy. After a median follow-up of 26 months, 25 of these patients remained disease-free. Organ preservation is a fascinating area of clinical cancer research. As has been shown by the Veterans Administration Laryngeal Cancer Study Group as well as by other groups including ours, mutilating operations can be avoided in some or postponed in many patients with HNC, even in cases with advanced disease. Most importantly this can be achieved without compromising survival. Toxicity from chemo-radiotherapy as applied in our study appears to be manageable. The incidence of excessive vomiting as a consequence of high-dose DDP was reduced with the use of ondansetron. Myelotoxicity mainly consisted of mild anemia and leukopenia. The duration of the latter was minimized with the use of G-CSF. Only one case of serious infection was noticed in the present study. However, it should be noted that more than 50% of our patients

Table 3

Selected published phase II studies with concurrent DDP administration and radiation in patients with HNC

Investigator	No. of patients	Treatment	CR(%)
Higi et al. (16)	34	RT 60–70 Gy DDP 20 on days 1–5 and 28–33	69
Coughlin et al. (17)	21	RT 48 Gy DDP 100 on days 1, and 28 and then 20 on days 35, 42, 49	48
Leipzig et al. (18)	33	RT 60–65 Gy DDP 15 on days 1–5 and 28–33	61
Sonderman et al. (19)	36	RT 60–65 Gy DDP on days 1–5 and 28–33	31
McDonald et al. (20)	38	RT 20 Gy DDP 10–20 on days 1–5 After a 4-week split PRs received additionally RT 38.4 Gy DDP 10 3 times a week × 4	40
Slotman et al. (21)	18	RT 45 Gy DDP 20 mg/m^2 on days 1–4 and 21–24	72
Tobias et al. (22)	16	RT 60 Gy DDP 10* daily	56
Gasparini et al. (23)	43	RT 60–70 Gy DDP 80 on days 1, 21, 42	63
Al-Saraf et al. (3)	124	RT 66–73.8 Gy DDP 100 on days 1, 22, 43	69
Present study	47	RT 70 Gy DDP 100 on days 1, 22, 42	72

RT: Total radiation dose, DDP: cisplatin (mg/m^2)
* absolute dose

suffered from considerable weight loss. Also, as previously mentioned, two patients with profound dehydration and weight loss died at home a few days after the completion of treatment, from causes that were most probably related to the treatment. In our opinion, these serious side-effects can be partially prevented by hospitalizing the patients, especially during the last two weeks of treatment, and proper parenteral support. Nevertheless, despite these unpleasant situations the compliance of patients with the protocol remained satisfactory, since 90% of them received the total radiation dose, prescribed by the protocol and at the same time received three courses of DDP without dose reductions. In the RTOG study 81-17, which is similar to the present study, 1/3 of patients did not finish the combined treatment program because of refusal or prohibitive toxicity. This discrepancy between the two studies may be due to patient selection or other factors or simply to a chance phenomenon and it should be interpreted cautiously, given the small number of patients in both studies.

In conclusion, concurrent DDP administration and irradiation appears to be a highly active treatment in locally advanced HNC. However, its possible superiority over irradiation alone should be compared in phase III studies. Our Group has recently initiated a prospective randomized

study in which patients with locally advanced HNC are treated either with radiation alone or combined radiation and concurrent DDP or carboplatin administration.

The following centers contributed patients to the study: AHEPA Hospital (26 patients), 'Agii Anargyri' Cancer Hospital and 'Evangelismos' Hospital (16 patients) and 'METAXA' Cancer Hospital (6 patients).

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