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Combination of daily 4-h infusion of 5-fluorouracil and cisplatin in the treatment of advanced head and neck squamous-cell carcinoma: A South-East European Oncology Group study

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Summary. Between April 1986 and May 1989 a multicentre study was conducted to evaluate the efficacy of a 4-h intravenous infusion of 1000 mg/m^2 5-fluorouracil (5-FU) followed by a 1-h infusion of 25 mg/m^2 cisplatin (CDDP) given for 4 consecutive days every 4 weeks to patients with advanced squamous-cell carcinoma of the head and neck. A total of 189 consecutive patients entered the study, including 106 who had previously undergone chemotherapy and 83 who were chemotherapy-naive. Of the 165 evaluable patients, 96 (58%) responded to treatment, including 22 (13%) who achieved a complete remission (CR). In the group of previously untreated patients an objective response (CR+PR) was seen in 78% (CR, 14%) whereas in pretreated patients the response rate (CR+PR) was 40% (CR, 13%). The median survival period was 10 months. No significant difference in the duration of survival or of remission was found between the two groups in relation to previous therapy, tumour localisation, disease stage or performance status. Almost half of the patients (49%) experienced leucopenia but it was severe in only 11% of cases. Anemia (mainly WHO grades 1–2) occurred in 38% of the patients. Nausea and vomiting were common (84%). Nephrotoxicity (23%) was mild and of short duration. Moderate hair loss was seen in 42% of the patients, and phlebitis occurred in 8%. A few cases of cardiotoxicity and neurotoxicity were observed. This regimen is well tolerated and can be given even on an outpatient basis. The resultant response rate and side effects appear to be similar to those previously reported for combination chemotherapy with CDDP and continuous 5-FU infusion.

Introduction

Advanced squamous-cell carcinoma of the head and neck (HNSCC) continues to be a therapeutic challenge. The standard therapy for HNSCC is surgery and/or radiotherapy. These treatment modalities, however, have not provided adequate tumour control in the majority of patients with locally advanced disease. Unfortunately, at the time of diagnosis the majority of these tumours is large and not easily cured by local modalities [18]. Local recurrence and/or distant metastases develop in almost 60% of patients with stage III and IV head and neck cancer [7].

In an attempt to improve the therapeutic results, systemic chemotherapy has been added to these treatment modalities. Cisplatin (CDDP) alone has produced an objective response in 30%–40% of patients [28], whereas 5-fluorouracil (5-FU) has produced response rates ranging between 15% and 30% [1, 7, 18]. Experimental data support a synergistic effect of the combination of these two drugs [24]. Several studies have shown superior results for continuous infusion of 5-FU as compared with bolus administration in terms of response and toxicity [12, 15, 25]. Previous studies have demonstrated a high (80%–90%) rate of response to 100 mg/m^2 CDDP and 1000 mg/m^2 5-FU given as a 96-h infusion to previously untreated patients with HNSCC [4, 10, 21, 26]. A response rate of over 50% has been observed in patients with recurrent disease [2, 3, 11, 16, 22]. The administration of 5-FU by continuous infusion was purported to be essential in these studies [2–4, 10–12, 15, 16, 21, 22], since bolus injection of 5-FU combined with CDDP could safely be given only when lower doses of 5-FU (200–600 mg/m^2) were used [12, 15, 16].

Since continuous infusion might not easily be applicable in all cases and under all circumstances (particularly on an outpatient basis), a phase I trial was initiated in which 5-FU was given as a daily 4-h infusion followed by daily low-dose (25 mg/m^2) CDDP over 4 consecutive days [6, 9]. Since the tolerance of this treatment was acceptable and the results were very promising a large-scale multicen-

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Table 1. Characteristics of the 189 patients entered in the present study

	Patients	
	Number	(%)
Sex (M/F):		
M	164	(89)
F	25	(13)
Age (years):		
Median	55	
Range	31–75	
WHO performance status:		
0	40	(21)
1	101	(53)
2	43	(23)
3	5	(3)
Stage:		
I	9	(5)
II	8	(4)
III	41	(22)
IV	131	(69)
Previous therapy:		
None	83	(43)
Surgery (S)	9	(5)
Radiotherapy (R)	49	(25)
Chemotherapy (C)[a]	3	(2)
S + R	20	(11)
R + C[a]	16	(9)
S + R + C[a]	9	(5)
Tumour localisation:		
Lip	4	(2)
Oral cavity	48	(25)
Oropharynx	67	(35)
Nasopharynx	12	(6)
Hypopharynx	20	(11)
Larynx	25	(13)
Nasal cavities + sinuses	13	(7)

[a] Methotrexate or bleomycin

tric phase II study was initiated for final evaluation of the regimen.

Patients and methods

Patients. Patients with histologically confirmed HNSCC were enrolled in the study. Eligibility criteria for the trial included the presence of measurable or evaluable disease, an age under 75 years, a WHO performance status (PS) of 0–3, a serum creatinine level of ≤ 130 µmol/l, a serum bilirubin value of ≤ 25 µmol/l, a normal leucocyte count of $\geq 4 \times 10^9$/l, a platelet count of $\geq 100 \times 10^9$/l and the absence of severe pulmonary or cardiac disease. Informed consent was required for study entry. Both previously untreated and recurrent patients were accepted. Patients who had previously received CDDP or 5-FU were excluded.

Treatment. The therapeutic regimen consisted of 1000 mg/m^2 5-FU diluted in 1000 ml 5% dextrose and given as an intravenous drip infusion over 4 h into a peripheral vein followed by 25 mg/m^2 CDDP in 500 ml Rindex 5 solution given as a 1-h infusion together with 15 g mannitol in 100 ml solution for 15–30 min and 500 ml 5% dextrose. The regimen was given for 4 consecutive days every 4 weeks.

If the leucocyte count remained below 4×10^9/l or the platelet count remained below 100×10^9/l at the start of the next cycle the treatment interval was extended for no longer than 6 weeks. To be evaluable for response, patients had to receive at least two cycles of chemotherapy. Thereafter, the treatment was stopped if disease progression occurred. If a favourable response was obtained further courses were given up to a maximum of 12 cycles. Whenever possible, after the second course but no later than after the fourth cycle, surgery and/or radiotherapy was initiated. Local treatment was started within 4 weeks of the completion of chemotherapy.

Table 2. Response rates according to tumour characteristics

Tumour localisation	Total	CR	CR (%)	PR	CR+PR (%)
Lip + oral cavity	42	4	(10)	18	(52)
Oropharynx	61	13	(21)	26	(64)
Nasopharynx	11	2	(18)	4	(55) NS
Hypopharynx	15	2	(13)	9	(73)
Larynx	28	–	(0)	14	(50)
Nasal cav. + sinuses	8	1	(13)	3	(50)
Totals	165	22	(13)	74	(58)
Tumour sites:					
Primary	145	24	(17)	54	(54)
Lymph node(s)	118	30	(25)	33	(53) NS
Pulmonary metastases	8	2	(25)	5	(88)
Totals	271	56	(21)	92	(55)
Stage:					
I	8	3	–	–	
II	7	–	–	3	
III	34	7	(21)	18	(74) NS
IV	116	12	(10)	53	(56)
Histological grading:					
1	29	3	(10)	17	(69)
2	27	3	(11)	13	(59) NS
3–4	15	4	(27)	5	(60)
Unknown	94				

NS, Not significant, cav., cavities

Response and survival. Routine (WHO) response criteria were applied [17]. The Kaplan-Meier method was applied for the estimation of survival curves. Survival curves were compared using the generalised Wilcoxon (Breslow) test, and multivariate analysis was performed on the basis of the Cox proportional-hazards model [14]. BMDP 1L and 2L computer programs were used for statistical analysis.

Results

Between May 1986 and April 1989, 189 patients entered the study (Table 1). A total of 601 chemotherapy cycles was given, the median number of cycles per patient being 3 (range 1–12). All of the patients were considered to be evaluable for toxicity and 165 were found to be evaluable for response.

Response to chemotherapy

The overall response rate (CR+PR) was 58% and the complete remission rate (CR) was 13% (Table 2). A high CR rate was obtained in the oropharyngeal (21%) and nasopharyngeal (18%) localisations whereas no CR was

Table 3. Response rates according to patients' characteristics

Pretreatment	Total	CR	CR (%)	PR	CR+PR (%)
None	79	11	(14)	51	(78)
Pretreated	86	11	(13)	23	(40) p <0.01
Surgery (S)	5	1		2	
Radiotherapy (R)	46	7	(15)	12	(41)
Chemotherapy (C)[a]	3	–		–	
S + R	14	1	(7)	4	(36)
R + C[a]	10	1	(10)	3	(40)
S + R + C[a]	8	1		2	
Performance status:					
0	39	9	(23)	17	(67)
1	88	10	(11)	39	(56) NS
2	36	3	(8)	17	(56)
3	2	–		1	

NS, Not significant
[a] Methotrexate or bleomycin

Table 4. Termination of the study and further treatment

Causes of termination	Number of patients (%)
Progression	56 (30)
According to protocol	62 (33)
Death	34 (18)
Drug toxicity	11 (9)
Refused further treatment	2 (1)
Others	8 (4)
Further treatment:	
None	87 (53)
Radiotherapy (R)	60 (37)
Chemotherapy (C)	7 (4)
Surgery (S)	3 (2)
S + R	3 (2)
R + C	5 (3)

observed among the 23 laryngeal tumours (CR+PR, 50%). A PR was seen in 73% of the hypopharyngeal tumours and in 52% of the lesions in the oral cavity and lip, but only a few patients achieved a CR. Differences in overall response and CR rates observed between the different tumour localisations did not reach statistical significance.

Among the target lesions, there were 145 primary tumours (or recurrences at the primary site), 118 cases of nodal involvement and only 8 patients with pulmonary metastases. No statistically significant difference in response rate (CR+PR) was found between the primary tumours (54%) and the lymph node metastases (53%). Histological grading was recorded in 71 cases, and no correlation was found between tumour grade and response. A response was seen in 78% of the patients who had not received previous treatment and in 40% of those who had been pretreated (p <0.05; Table 3). The proportion of CRs was the same (11%) in pretreated and previously untreated patients. No significant correlation was found between the performance status and the response. In most of the patients who achieved a remission the maximal effect was seen during the first two cycles. In more than half of the cases, the total disappearance of all lesions in complete responders was achieved only during successive cycles (courses 3–4).

Termination of the study and further treatment

Treatment had to be discontinued in one-third of the patients due to disease progression and in 18% because of death due to advanced disease (except for one case of myocardial infarction; Table 4). In all, 33% of the patients was in remission or had stable disease at the time of the termination of chemotherapy. In only 6% of the patients (all of whom had received heavy pretreatment) was the therapy stopped due to grade 4 toxicity (myelotoxicity,

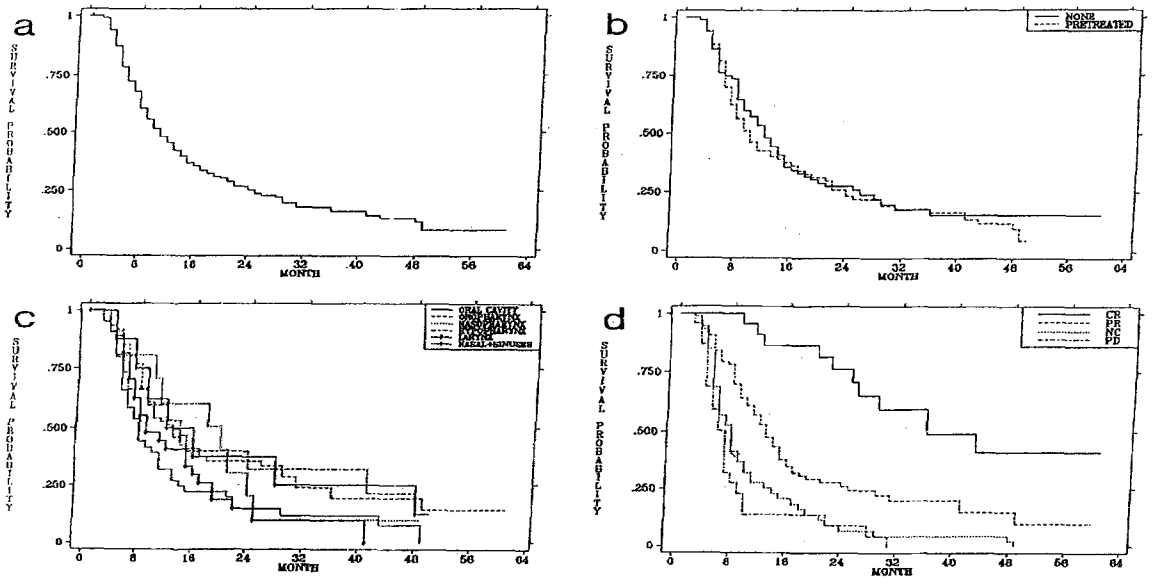

Fig. 1a–d. Survival of patients treated with the present regimen. **a** Overall survival. **b** Survival according to pretreatment. **c** Survival according to tumour localisation. **d** Survival according to response

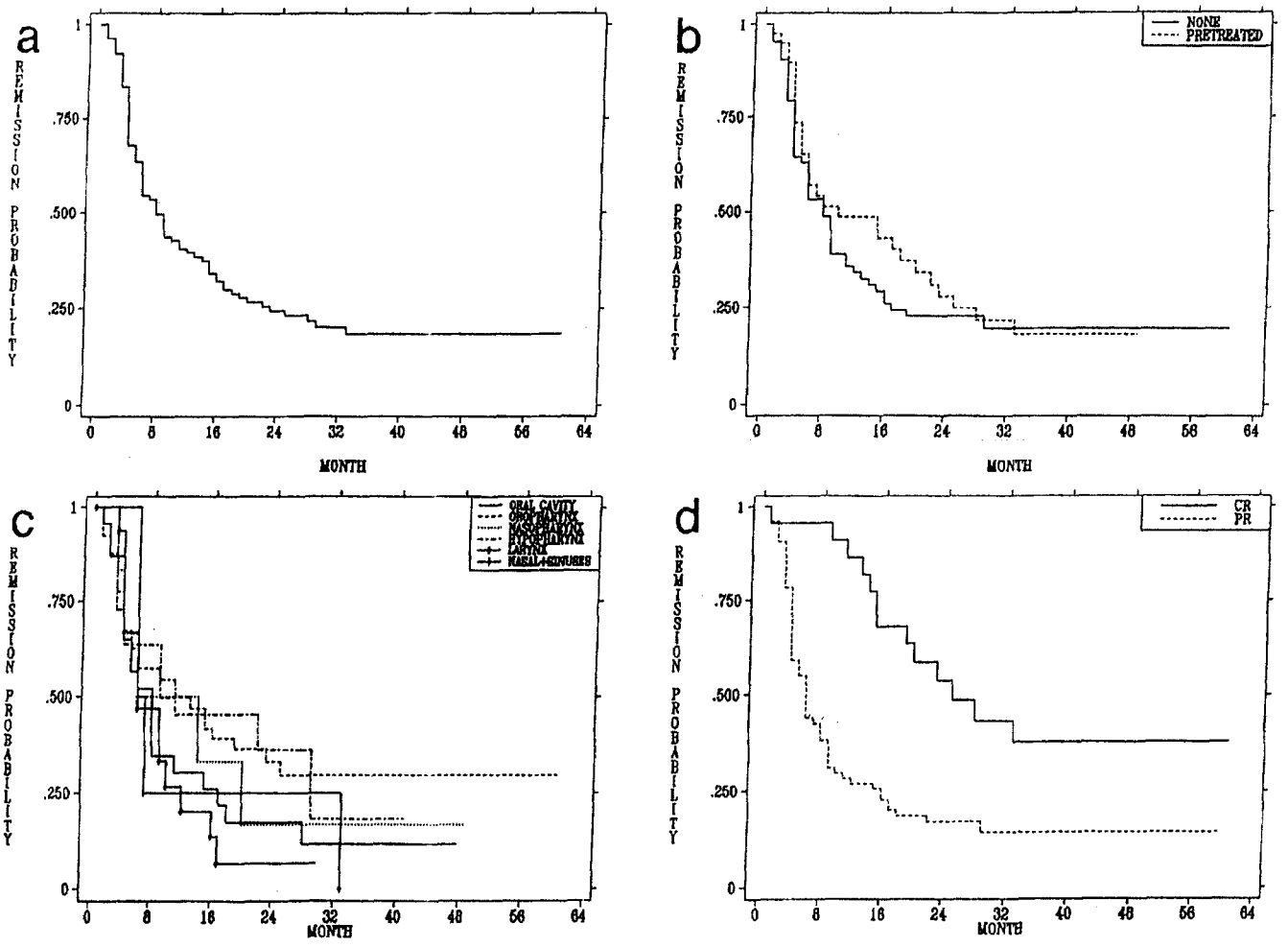

Fig. 2a–d. Duration of remission in patients responding to treatment with the present regimen. **a** Overall remission duration. **b** Remission duration according to pretreatment. **c** Remission duration according to tumour localisation. **d** Remission duration according to response

Table 5. Median survival and remission duration

Response to chemotherapy	Pretreatment	Median survival (months)[a]	Median remission duration (months)[a]
CR	None	26 (12–64)	15 (9–61)
	Pretreated	36 (9–50)	25 (1–46)
PR	None	13 (3–60)	6 (1–46)
	Pretreated	13 (4–9)	6 (2–43)

[a] Ranges are given in parentheses

infection, mucositis and cardiac toxicity, respectively). Following initial chemotherapy, 60 patients received radiotherapy as definitive local treatment.

Survival

The median duration of survival for all patients was 10 months (range, 1–64 months; Fig. 1). The median survival period for complete responders was 28 months (range, 9–64 months), but no tumour or patient characteristic (tumour site, pretreatment, disease stage or performance status) was predictive of a favourable prognosis. Multivariate analysis (Cox model) revealed that neither pretreatment nor tumour localisation had a significant influence on survival or remission duration. When the data were grouped according to the therapeutic result and the type of response to chemotherapy (CR versus PR), a statistically significant correlation with survival period and remission duration was obtained ($p < 0.001$), independent of any other characteristic (Table 5). The median duration of remission was 21 months for all patients, 25 months (range, 1–46 months) for complete responders and 6 months (range, 1–48 months) for partial responders (Fig. 2).

Toxicity

Leucopenia was experienced by almost half of the patients, but in most cases it occurred as WHO grades 1 and 2 toxicity (grades 3 and 4, 11%; Table 6). A few cases of thrombocytopenia were seen in patients who simultaneously experienced severe leucopenia. Nausea and vomiting were common (84%), mainly during the 1st day of therapy,

Table 6. Toxicity[a]

Toxicity	WHO grade				
	1	2	3	4	(%)
Anemia	37	30	3	1	(38)
Leucopenia	41	30	14	7	(49)
Thrombocytopenia	12	12	5	4	(17)
Nausea/vomiting	44	66	47	2	(84)
Diarrhoea	9	7	4	–	(11)
Stomatitis	2	4	3	1	(5)
Nephrotoxicity	38	5	–	–	(23)
Phlebitis	10	5	–	–	(8)
Hair loss	37	21	20	1	(42)
Cardiac rhythm	8	1	–	3	(5)
Cardiac function	1	3	1	3	(4)
Infection	14	6	1	3	(12)
Cutaneous toxicity	3	5	–	3	(6)
State of consciousness	1	1	1	–	(2)
Periph. neurotoxicity	4	3			(4)

[a] Number of evaluable patients, 189; total number of cycles given, 601; median number of cycles per patient, 3 (range, 1–12)
Periph., Peripheral

and their severity decreased during successive days of treatment. Oral mucositis (5%) and diarrhoea (11%) were rarely encountered. Renal toxicity was mild and always reversible. Phlebitis was seen in 8% of the patients, and hair loss occurred in 42%. A few cases of ischemic cardiac episodes were reported, for which three patients required hospitalisation. One patient died of a myocardial infarction during the 2nd week after the first cycle; this event might have been related to 5-FU cardiotoxicity [5]. All of these patients entered the study in poor general condition, showing a weight loss of more than 10%, and they were heavy alcohol and tobacco consumers. Seven cases of reversible neurotoxicity were reported.

Discussion

One of the most effective chemotherapeutic regimens used in the management of HNSCC seems to be the combination of CDDP followed by 96- to 120-h continuous infusion of 5-FU [2–4, 10–12, 21, 22]. This therapeutic regimen is not easily applicable under all circumstances and requires hospitalisation in most cases.

Preclinical in vitro and in vivo studies exploring this combination have proven that the importance of the sequence of administration of 5-FU and CDDP varies among tumours [20, 23, 24]. In vitro studies on human ovarian-carcinoma cell lines (A2780) have demonstrated superiority for the sequence of CDDP immediately followed by 5-FU [23]. In other studies on murine tumour models colon 26, Methylazoxymethanol acetate (MAM)-induced primary colon tumour and L1210 leukemia, 5-FU followed 24 h later by CDDP proved to be the schedule with the highest therapeutic index (lowest toxicity and highest therapeutic activity), whereas in murine P388 lymphoma the sequence of administration had no influence on the therapeutic activity [20, 24]. The combination of CDDP followed by repeated injections of 5-FU was tested on HNSCC xenografts and was found to have synergistic activity as compared with the single-agent treatment [27]. In a recent study using a human squamous-cell carcinoma xenograft model the administration of 5-FU followed by CDDP was found to be more effective and less toxic than the reverse sequence [13].

On the basis of our previous phase I study [6, 9] investigating the feasibility of shortening the 5-FU infusion, we selected the following schedule for further evaluation: a 4-h infusion of 1000 mg/m^2 5-FU followed by a 1-h infusion of 25 mg/m^2 CDDP given on 4 consecutive days every 4 weeks.

The present multicentric clinical study demonstrated the high efficacy of this regimen. The overall response rate achieved was 58%, including 78% for previously untreated patients and 40% for pretreated patients. In our study, the higher response rate seen in the group of previously untreated patients did not translate into longer survival (the median survival period was 12 months for patients who had not received previous treatment and 9 months for pretreated patients). Pretreatment, tumour localisation, disease stage, performance status and histological grading did not have a significant influence on survival.

As previously reported by other authors [8, 12], the survival of our patients appeared to be related to the type of response to chemotherapy, independent of the previous or subsequent therapy applied [8, 12]. The achievement of a CR appeared to improve survival significantly (median, 28 months; range, 9–64 months), but this was not the case for PRs (median, 12 months; range, 2–60 months).

Side effects were acceptable and were comparable with those obtained using the original continuous-infusion schedule, whereas the incidence of phlebitis appeared to be lower [10, 12, 16, 25]. As the present regimen is easily applicable, even on an outpatient basis, it might replace the continuous-infusion schedule. Further studies are necessary to enhance the CR rate, which seemed to have the most important impact on survival in the present investigation.

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