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A Randomized Study of Methotrexate, Bleomycin, Hydroxyurea With Versus Without Cisplatin in Patients with Previously Untreated and Recurrent Squamous Cell Carcinoma of the Head and Neck

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Abstract—*The value of a combination of methotrexate, bleomycin and hydroxyurea with vs. without cisplatin was randomly examined in* 62 *evaluable patients with previously untreated* (44 *patients*) *and recurrent* (18 *patients*) *squamous cell carcinoma of the head and neck. Methotrexate* (30 mg/m^2) *and bleomycin* (15 mg) *were given intravenously weekly, hydroxyurea* (1000 mg/m^2) per os 3 *times per week for* 4 weeks. *Cisplatin* (60 mg/m^2) *was added on* Day 1 *every month. A higher overall response rate was observed with the cisplatin-containing regimen* (66%, *included* 17% *complete*) *as compared with* 27% (3% *complete*) *with the* 3-*drug combination* (P *value* 0.0025). *The cisplatin-containing regimen was more active in both previously untreated patient group and in the group of recurrent patients. Toxicity was more pronounced in the cisplatin regimen and necessitated frequently reduced drug dosages. No survival difference was observed between the treatment groups. Median survival in previously untreated patients was* 16.2 months *and* 7.2 months *in patients who failed conventional local treatment. It is concluded that a cisplatin-containing regimen is more effective in advanced head and neck carcinoma than the same combination without cisplatin.*

INTRODUCTION

THE VALUE of a combination of bleomycin and methotrexate in recurrent squamous cell carcinoma of the head and neck had been established in Swiss pilot studies [1, 2]. The addition of hydroxyurea to these 2-drug combinations induced higher response rates in subsequent studies [3]. Using a combination of methotrexate, bleomycin, cisplatin and low dose hydroxyurea, Vogl *et al.* reported in 1983 results similar to those obtained in our group [4].

In randomized studies, methotrexate and cisplatin given alone appear to be equally active in recurrent head and neck cancer [5]. We designed this study in 1982 in order to test the value of cisplatin combined to methotrexate, bleomycin and hydroxyurea, with the aim of comparing two chemotherapy regimens differing only by the addition of cisplatin.

Preliminary data of our group have shown that a monthly dose of cisplatin (60 mg/m^2) can be safely and effectively combined to methotrexate, bleomycin and hydroxyurea [6].

MATERIALS AND METHODS

Patients with histologically proven advanced squamous cell carcinoma of the head and neck were eligible for this study. Nasal, paranasal and nasopharyngeal tumors were ineligible because of their frequent association to non-squamous histologies and possibly a different biological behavior.

Initial investigations were conducted by the head and neck surgeon and included a panendoscopy under general anesthesia. General examination, and complete hemogram, liver and renal function tests, as well as chest X-rays were also required. Other radiological investigations such as

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xeroradiography, barium swallowing or computerized tomography were performed as needed.

Patients with advanced and previously untreated disease were classified according to the T.N.M. method of the International Union against Cancer (U.I.C.C.) [7]. Previously untreated patients were selected for this study after complete evaluation by a team of head and neck surgeon, radiation therapist and medical oncologist. Only U.I.C.C. stages III–IV were eligible, or stage II lesions if local treatment was considered as too aggressive. Unidimensional lesions (defined as evaluable) or bidimensional lesions (measurable) were required.

Eligible patients were required to have a performance index of 0–3 (SAKK–ECOG scale), a normal hemogram (leukocytes ≥ 4.0, platelets $\geq 100 \times 10^9$/l), a bilirubin of less than 30 μmol/l and a serum creatinine below 120 μmol/l. Prior chemotherapy with any drug that was part of the present study regimens was not allowed.

Patients were stratified according to their primary tumor location in two groups: oral cavity and oropharyngeal tumors were analyzed together in the first group, whereas hypopharynx and larynx primaries were considered in the second group. Further, patients with tumor recurrences after any previous treatment (surgery, radiation therapy) were separately analyzed from previously untreated patients. This study was designed as a randomized phase II trial. Patients were randomized by telephone to the Central Office of the SAKK, after appropriate stratification.

Treatment regimens differed only by the presence or absence of cisplatin. Regimen A consisted of a weekly × 4 intravenous injection of methotrexate (MTX, 30 mg/m^2) and bleomycin (BLM, 15 mg). Hydroxyurea (HU) was given orally 3 times per week at the dose of 1000 mg/m^2 [3]. Regimen B was equal to A but cisplatin (60 mg/m^2) was given on Day 1 every 4 weeks, prior to other drugs. A short hydration program inspired from Vogl [8] was used.

In case of grade I drug-related toxicities, MTX and cisplatin were reduced by 33% and omitted for W.H.O. grade II–IV toxicities. Hydroxyurea was not given in case of grade II–IV toxicity. BLM was to be fully given, regardless of hematologic toxicities. Patients who received less than 4 weekly doses were considered as non-evaluable for response to treatment.

Complete remission was defined as a complete clinical disappearance of all known lesions. A reduction of $\geq 50\%$ of the sum of products of the perpendicular diameters of measurable and evaluable lesions was considered as a partial remission. Any reduction of less than 50% or an increase of less than 25% was qualified as no change. Progression was defined as a $\geq 25\%$ increase of the lesions.

For previously untreated patients, the duration of chemotherapy was left to the investigator's decision, but should not exceed 3 monthly cycles. Local therapy—if any—was not defined in this study, but left to the individual investigator's usual practice. Duration of the response was calculated from Day 1 only in patients with recurrent disease. Survival was determined from Day 1 to death or lost to follow-up, and plotted with the Kaplan–Meier method [9]. Comparison of survival curves was made with the log rank test [10].

RESULTS

The study was initiated in June 1982 and closed to patient entry in December 1983. During this 18-month period, a total of 90 patients were randomized. Ten patients were considered as ineligible because of simultaneous or previous tumors not originating from the head and neck (4 patients), squamous cell carcinoma with unknown head and neck primary (1), nasal fossae primary (1), serum creatinine elevation (2), and thrombocytopenia (2). Further, 18 patients were considered as inevaluable because of treatment cancellation (2), refusal without toxicity (3) or less than 4 week treatment and major protocol violation (4), and absence of measurable disease (9).

Table 1 shows the demographic data of the 62 evaluable patients. Forty-four were previously untreated for head and neck cancer. There were more patients with U.I.C.C. stage IV disease randomized to regimen A than stage IV patients in regimen B. Further, three patients who received regimen B had only stage II disease.

Median number of 4-week chemotherapy cycles was 2 (range 1–16+). Seven patients received only 4-week treatment, 26 received 8-week treatment, whereas 19 and 10 had, respectively, 12 and 16 weeks of treatment.

Response rate

Table 2 shows the response rates in both regimens. Regimen B (overall response rate 66%) was statistically superior to regimen A (27%), with a P value of 0.0025. The 95% confidence interval for the overall response rate was 13–46% in regimen A and 46–82% in regimen B. In oral cavity and oropharyngeal primaries, the response rate to regimen B was 68% (4 CR + 11 PR/22), statistically superior (P 0.002) to regimen A, with 22% (1 CR + 4 PR/23). For hypopharyngeal and laryngeal tumors, 1 CR + 3 PR/7 were observed in regimen B, and 4 PR/10 in regimen A.

The response rate increased according to the duration of chemotherapy: in patients receiving only 4 weeks of treatment, overall response rate was 29%. Response rate increased to 46, 47 and

Table 1. Evaluable patient demographic data

	Regimen A	Regimen B	Total (%)
Number	33	29	62
Mean age in years	57.1	60.7	58.8
(range)	(40.9–73.5)	(46.7–74.3)	(40.9–74.3)
P.S. 0–1	28	25	53 (85%)
2–3	5	4	9 (15%)
Male : female	30 : 3	26 : 3	56 : 6
T stage:			
T2	2 (8%)	4 (21%)	6
T3	7 (28%)	9 (47%)	16
T4	16 (64%)	6 (32%)	22
N stage:			
N0	2 (8%)	6 (32%)	8
N1	7 (28%)	3 (16%)	10
N2	3 (12%)	2 (11%)	5
N3	13 (52%)	8 (42%)	21
U.I.C.C. stage:			
II	0 (0%)	3 (16%)	3
III	2 (8%)	3 (16%)	5
IV	23 (92%)	13 (68%)	36
Total nb untreated pts	25	19	44
Nb pretreated pts	8	10	18

Table 2. Response categories

	Regimen A		Regimen B	
	Nb of patients	(%)	Nb of patients	(%)
Complete	1	(3%)	5	(17%)
Partial	8	(24%)	14	(48%)
No change	17	(52%)	8	(28%)
Progression	7	(21%)	2	(7%)
	33		29	

50% in patients receiving respectively 8, 12, 16 weeks of chemotherapy. Thus, the majority of the responses were seen after 8 weeks of treatment.

In previously untreated patients. Responses were observed in all primary tumor locations (see Table 3). Here again, regimen B (74% overall response rate) was statistically superior to regimen A (28%, *P* value 0.003). In T3 lesions, 3 PR/7 were seen in regimen A and 1 CR + 4 PR/9 in B. Four PR/16 in regimen A and 2 CR + 3 PR/6 were observed for T4 lesions in B. In NO-1 patients, regimen A gave 2 PR/9 and regimen B 4 CR + 3 PR/9, whereas in N2-3 patients, A yielded 5 PR/16 and B 7 PR/10.

Local therapy was subsequently conducted in 35 patients after induction chemotherapy. Eight patients, out of 15 who were operated, were considered as remitters to chemotherapy. Microscopical residual disease was found in all patients, except in one partial remitter in whom no tumor was found in the resected specimen. Radiation therapy alone or after resection was conducted in 24 patients.

In recurrent disease. There were 1 complete and 1 partial remission in 8 patients in regimen A, and 1 complete and 4 partial in 10 patients in regimen B. The duration of the complete remissions was 7 and 9 months respectively, and 2, 3, 3, 6, 17 months for partial responses.

Survival

The overall median survival was not different: 10.2 months in regimen A and 10.9 months in regimen B (Fig. 1). Responders to treatment had a median survival of 13.9 months, while the median survival of non-responders was only 8.7 months. There was a trend in favor of an increased survival for responders in B (14.7 months) vs. 10.1 months in regimen A. Previously treated patients lived only 7.2 months in median, whereas untreated patients had a median survival of 16.2 months (*P* value 0.0001). All 18 patients with recurrent disease had died, all because of cancer progression. Among the previously untreated patients, 20 were still alive and 1 lost to follow up, as of August 1984.

Toxicities

Table 4 describes the hematological toxicity and

Table 3. Evaluation of the response according to primary tumor location (untreated patients)

	Regimen A					Regimen B				
	CR	PR	NC	P	Total	CR	PR	NC	P	Total
Oral cavity										
buccal mucosa		1			1		2*			2
lower alveolus					0	1		1		2
tongue			1	1	2			1	1	2
floor of mouth		1	6		7		4			4
Oropharynx										
anterior wall			2		2	1**	1	1		3
lateral wall		2	4		6	1	1			2
superior wall					0	1				1
Hypopharynx										
junction		1	2	1	4					0
piriform sinus		2		1	3		1	1		2
Larynx										
supraglottic					0		1			1
	0	7	15	3	25	4	10	4	1	19

*2 patients with stage II (T2NO) disease.
**stage II (T2NO) disease.

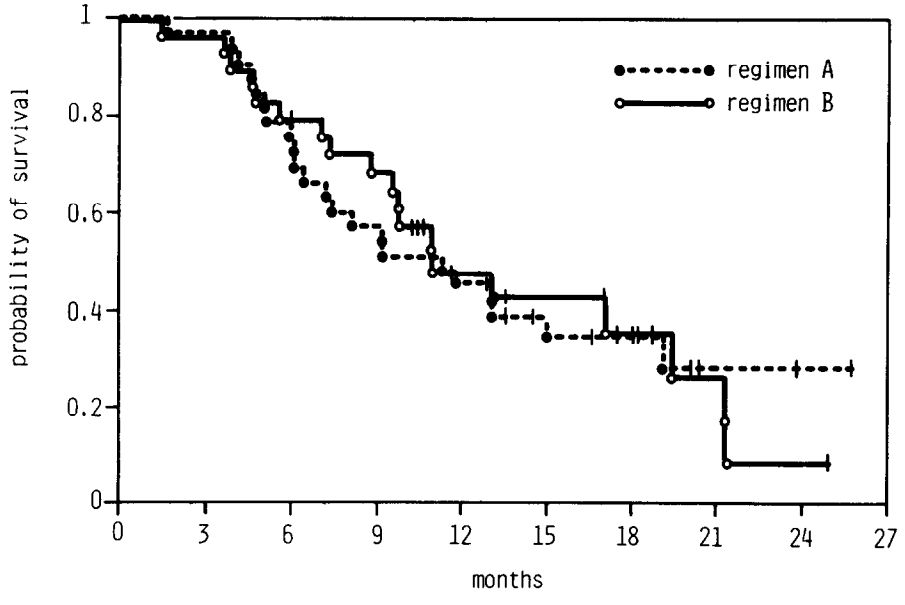

Fig. 1. Survival of evaluable patients according to treatment regimens.

Table 4. Hematological toxicities in the first cycle

	Hb in g/l (range)	Mean lowest values WBC × 10^9/l (range)	Platelets × 10^9/l (range)
Regimen A (37 patients)	12.6 (9.0–16.0)	4.4 (2.2–7.4)	195 (70–420)
Regimen B (35 patients)	11.6 (6.7–14.1)	3.1 (0.7–5.3)	151 (22–395)
P value	0.014	0.0002	0.02

indicates mean lowest values for hemoglobin leukocytes (WBC) and platelets after the first cycle in all evaluable cases. Regimen B was significantly more myelosuppressive than regimen A. W.H.O. grade III–IV toxicities were observed in 2 (5%) cases for hemoglobin, 6 (16%) for WBC and 4 (11%) for platelets with the cisplatin-containing regimen. No grade III–IV toxicity was encountered in regimen A. Mean lowest values in subsequent treatment cycles were not lower than in the first cycle.

Nausea and vomiting were the most frequently observed non-hematological side-effects. Grade I toxicity was seen in 14/38 (37%) patients in regimen A and in 19/36 (53%) in B. Grade I–II stomatitis was reported in 6/38 (16%) patients in A and in 14/36 (39%) in regimen B.

One patient in each regimen developed a transient grade I serum creatinine elevation after the first cycle. In the second cycle of regimen B, one patient developed a grade II creatinine elevation after a first non-toxic cycle. He died of a Gram-negative sepsis with grade IV leukothrombocytopenia. Other toxicities consisted of grade I alopecia (8% in A, 6% in B), and grade I skin toxicity (5% in A, 11% in B). No other toxicities were observed, in particular no clinically detectable lung toxicity.

Dose reduction

Figure 2 shows the proportion of patients receiving various drug dosages. The main fact was that only MTX and HU were significantly reduced in the first 4 weeks of regimen B, as compared to regimen A. The proportion of patients receiving BLM was not statistically different in regimen A and B during the first 4 weeks of treatment. In subsequent monthly courses of treatment, the statistical analysis did not show a difference in the drug dosages effectively administered.

CONCLUSIONS

The results of the present study show that cisplatin given with a combination of methotrexate, bleomycin and hydroxyurea induces a higher overall response rate than the same combination without cisplatin in advanced previously untreated as well as in recurrent squamous cell carcinoma of the head and neck. The statistical comparison of regimens is highly significant (P value 0.0025). An overall response rate of 66%, including 17% complete response, has been achieved with the four-drug combination. As expected, the overall response rate is higher in previously untreated patients than in patients with recurrent disease. Our results are comparable to other recently published studies with similar cisplatin-containing regimens in untreated [11–13] and in previously treated patients [14, 15].

Patient characteristics were well balanced in both treatment arms, as far as stratification for primary tumor location and previous treatment were concerned, but not for U.I.C.C. stages. If one excludes from the analysis the 3 patients with stage

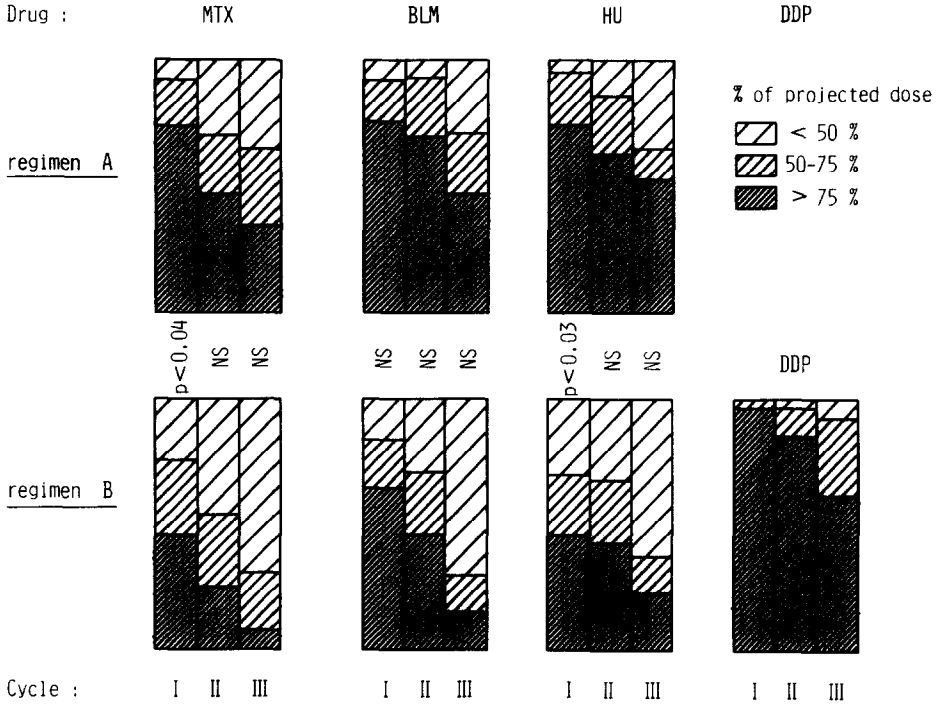

Fig. 2. Percentage of patients receiving various drug dosages in the first 3 monthly cycles.

II disease, the overall response rate to regimen B would be 68% with 19% complete response. This response rate is yet not very different from the results achieved in the randomized cohort of patients. Since the 95% confidence interval of both overall response rates does not overlap, we think that the difference is related to the addition of cisplatin, and not to patient characteristics.

The overall response rate seems to be related to the duration of chemotherapy, since it increases along with the length of induction chemotherapy. This observation may be of critical significance for scheduling induction chemotherapy and optimization of present results in locally advanced head and neck cancers [16].

Despite a higher overall response rate in the cisplatin-containing regimen, survival of both patient groups remains identical. In our opinion, this observation is related to the fact that the total number of patients included in this study is not sufficient to determine a possible difference in the survival curves.

The combination of methotrexate, bleomycin and hydroxyurea with cisplatin proved to be clearly more toxic than the three drugs alone, as far as myelosuppression and gastrointestinal toxicities were concerned. However, the mean lowest values achieved in this study were acceptable, and the frequency of grade III–IV hematological toxicities remained low. On the other hand, the addition of cisplatin to methotrexate, bleomycin and hydroxyurea required frequently a dose reduction of methotrexate and hydroxyurea because of the development of myelosuppression and stomatitis.

In conclusion, the results of our study demonstrates the superiority of a cisplatin-containing regimen as compared to a "standard" combination of methotrexate, bleomycin and hydroxyurea in squamous cell carcinoma of the head and neck. The superiority of the cisplatin-containing regimen has been proven in previously untreated patients and in patients with recurrent disease, with acceptable drug-related toxicities. Survival of patients remains, however, identical in both treatment arms.

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