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Phase II Study of Doxifluridine in Advanced Squamous Cell Carcinoma of the Head and Neck

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Abstract—*We conducted a phase II trial with 5'-deoxy-5-fluoridine (doxifluridine) in advanced squamous cell carcinoma of the head and neck. The drug was given at the dose of* 4 g/m² *daily* × 5 *every* 3 weeks. *Twenty eligible patients entered this trial,* 12 *being evaluable for response to doxifluridine. The majority of these patients received previous treatment for cancer. One complete and two partial remissions were observed* (25%). *Drug-induced toxicity consisted mainly of myelosuppression, mild nausea and vomiting, stomatitis and central nervous system side-effects. Other dosages or schedules for doxifluridine administration might be explored in poor-risk patients.*

INTRODUCTION

SQUAMOUS cell carcinoma of the head and neck is a tumor in which single-agent activity has been limited to a few drugs, such as methotrexate, cisplatin and bleomycin. The search of new active compounds is of utmost importance and phase II trials are needed in this disease. We decided to study a new fluoropyrimidine derivative, 5'-deoxy-5-fluorouridine, or doxifluridine (Fig. 1), since this substance had antitumor activity and, compared to 5-fluorouracil, a better therapeutic index in animals [1]. It is thought that doxifluridine acts as a 5-fluorouracil prodrug, releasing the latter under the action of a nucleoside phosphorylase. Using a daily × 5 schedule of administration, we were recently able to determine the maximum tolerated dose for an i.v. bolus injection: 5 g/m² per day [2]. Dose-limiting toxicities were leukopenia and stomatitis. The Swiss Group for Clinical Cancer Research (SAKK) started several phase II trials of doxifluridine with this schedule of administration. Target tumors were breast cancer, pancreas and colorectal carcinoma. In the latter tumor, doxifluridine had definite therapeutic activity.

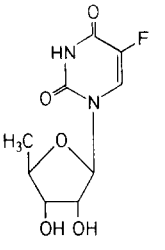

Fig. 1. Chemical structure of 5'-deoxy-5-fluorouridine.

Drug-induced toxicity consisted mainly in leukopenia, gastrointestinal intolerance, mucositis and neurotoxicity [3]. This paper summarizes our experience with doxifluridine in advanced head and neck carcinoma.

MATERIALS AND METHODS

Doxifluridine was administered daily for 5 days by an intravenous bolus injection of 4 g/m² per day as a solution (100 mg/ml in distilled water for injection) of a 10% sodium salt in patients with advanced squamous cell carcinoma of the head and neck. Paranasal sinus and nasopharynx primary tumors and prior fluoropyrimidine administration excluded patients from this trial. Skin nodule, cervical lymph node, lung nodule surrounded by aerated lung or directly measurable lesion of the oral cavity were considered as measurable disease. Patients were required to have normal serum creatinine and

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bilirubin levels, as well as leukocyte and platelet counts $\geqslant 4.0$ and $100 \times 10^9/l$ respectively. Courses were repeated every 3 weeks or after recovery from drug induced toxic effects. Patients were considered evaluable for response if they received at least 2 courses of doxifluridine. WHO criteria were used for response definition. Early death was defined as any death occurring during the first 6 weeks of treatment.

RESULTS

A total of 20 eligible patients entered this trial (Table 1). Patients in this series had aggressive disease, since median disease duration from histological diagnosis was 10 months. Fifteen patients were previously treated with palliative chemotherapy, including cisplatin, methotrexate, bleomycin, vincristine and hydroxyurea.

A total of 58 courses of doxifluridine were administered. Four patients received only 1 course of doxifluridine. Two courses were given to 8 patients, 3 courses to 3 patients and 4 courses or more to 5 patients.

Five patients were considered as early deaths: tumor-related complications were observed in 4 of them after the first course with doxifluridine and 1 patient was possibly a toxic death. This 60-yr-old patient died of a cardiogenic shock 16 days after the begin of the second doxifluridine course. Three patients were inevaluable for response because of lack of tumor parameter (2) and concomitant radiotherapy to tumor site (1). Response could thus be evaluated in only 12 patients. We observed 1 complete and 2 partial remissions, 7 patients with no change and 2 progressions (Table 2). The 3 responses were

Table 1. Patient characteristics

Total No. of patients	20		
Sex (male:female)	18:2		
Median age in years (range)	60 (53–75)		
Median WHO performance index (range)	1 (0–3)		
Median disease duration in months*	10 (0–42)		
Primary tumor location:		local relapses	metastatic
oral cavity	5	4	1
oropharynx	5†	2	0
hypopharynx	4	1	3
larynx	6	5	1
Previous treatment:			
surgery + radiotherapy + chemotherapy		6	
radiotherapy + chemotherapy		5	
chemotherapy alone		3	
surgery + radiotherapy		2	
surgery + chemotherapy		1	
none		3†	

*Calculated from initial histological diagnosis to study treatment.
†Includes untreated patients with T4N1 (2 patients) and T3N3 lesions (1 patient).

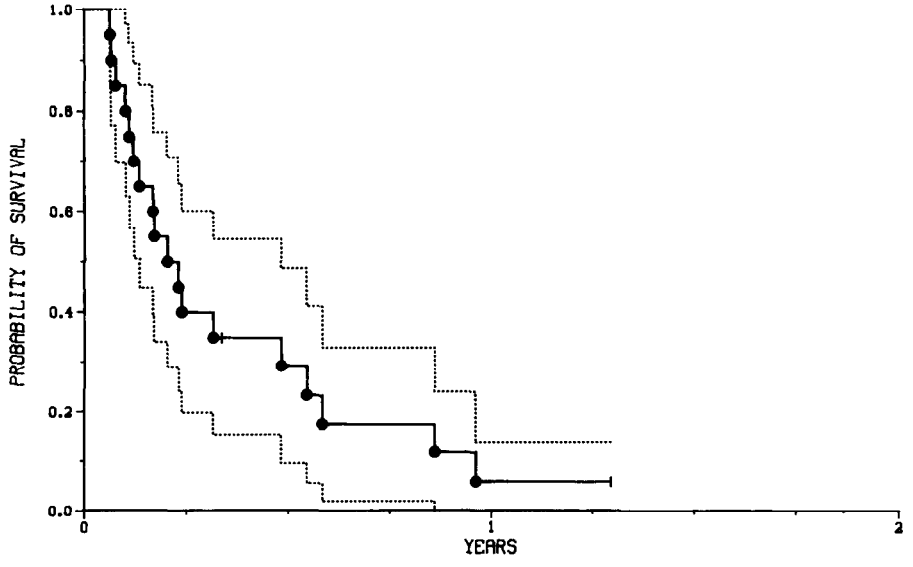

Fig. 2. Probability of survival.

Table 2. Evaluable patient characteristics

Response	No.	Median age in years (range)	Median performance index (range)	Primary site and No.	Untreated/ local relapse/ metastatic	Median disease duration in months (range)	No. of patients with prior: surgery	radiotherapy	chemotherapy	Response duration in days
Complete	1	54	0	oropharynx 1	0/1/0	33	0	1	1	365+
Partial	2	55, 65	1, 2	oropharynx 1 hypopharynx 1	1/0/1	0, 10	1	1	0	84, 100
No change	7	55 (53–70)	1 (1–2)	oral cavity 4 oropharynx 1 hypopharynx 1 larynx 1	1/5/1	11 (1–23)	3	3	5	—
Progression	2	59, 60	1, 2	larynx 2	0/2/0	11, 42	2	2	2	—

Table 3. Doxifluridine-induced toxicity

Target organ	No. of patients with WHO grade of toxicity 1	2	3	4	% toxic patients ($n=20$)
Leukocytes	1	3	2	5	55
Platelets	2	1	1	1	25
Nausea/vomiting	4	6	0	0	50
Oral mucosa	3	3	1	1	40
Central nervous system	1	3	0	1	25
Skin	2	1	0	0	15
Laryngeal edema	2	0	0	1	15
Hair	1	0	1	0	10
Local phlebitis	1	0	0	0	5
Heart	0	0	0	1	5

observed in patients previously treated with surgery (1), radiotherapy (2) and chemotherapy (1). Duration of the responses were 84, 100 and 365+ days. The 3 responding patients received 2, 4 and 7 courses with doxifluridine; treatment was then stopped because of the development of neurotoxicity (2) and refusal of further doxifluridine administration (1). Median survival was 10.6 weeks from entry into this study. For the evaluable patients only, the median survival was 12.4 weeks (Fig. 2).

Hematological toxocity consisted of myelosuppression, with a median leukocyte nadir of 3.1 $\times 10^9$/l (range 0.1–9.7) and a median thrombocyte nadir of 165 (10–337) $\times 10^9$/l (Table 3). WHO grade 4 leukopenia was observed in 5 patients, 2 of them having septicemias. Thrombocytopenia was also encountered, not related to clinical complications. Non-hematological toxicities are also shown in Table 3. Gastrointestinal tract toxicity was frequently observed and consisted of mild-to-moderate nausea and vomiting, as well as stomatitis. Central nervous system toxicity with dizziness and cerebellar ataxia was encountered in 5 patients, with one of them presenting a transient coma. There was no evidence of peripheral neuropathy. Three patients presented skin erythema and dry desquamation. Laryngeal edema, severe enough in 1 patient, who required intubation, was observed in 3 patients, all being previously irradiated on the neck. Other toxicities are shown in Table 3.

DISCUSSION

This new fluoropyrimidine derivative, doxifluridine, was studied in advanced squamous cell carcinoma of the head and neck, using a daily $\times 5$ schedule of administration with an i.v. bolus injection of 4 g/m^2 per day. Objective antitumor activity has been detected in 3/12 evaluable and adequately treated patients. With this scheme and dosage of administration, toxicity consisted in myelosuppression and other drug-induced effects, mainly nausea and vomiting, stomatitis and cerebellar signs. Toxicity, although sometimes severe, was transient. We think, however, that the rate and the intensity of these side-effects are severe enough to make changes in dosage or schedule of administration necessary, at least in patients previously treated with radiotherapy and/or chemotherapy.

5-Fluorouracil [4] and its derivatives, like ftorafur [5] or doxifluridine (this study), have antitumour activity in squamous cell carcinoma of the head and neck. In this scheme of administration of doxifluridine, toxic effects are frequently observed in patients with advanced squamous cell carcinoma of the head and neck. Other dosages or schedules might be explored for further clinical use of doxifluridine.

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REFERENCES

1. BOLLAG W, HARTMANN HR. Tumor inhibitory effects of a new fluorouracil derivative: 5'-deoxy-5-fluorouridine. *Eur J Cancer* 1980, **16**, 427–432.
2. ABELE R, ALBERTO P, SEEMATTER RJ *et al.* Phase I clinical study with 5'-deoxy-5-fluorouridine, a new fluoropyrimidine derivative. *Cancer Treat Rep* 1982, **66**, 1307–1313.
3. ABELE R, ALBERTO P, KAPLAN S *et al.* Phase II study of doxifluridine in advanced colorectal adenocarcinoma. *J Clin Oncol* In press.
4. CARTER SK. The chemotherapy of head and neck cancer. *Semin Oncol* 1977, **4**, 413–424.
5. CAMPBELL M, AL-SARRAF M. Phase II ftorafur therapy in previously treated squamous cell cancers of the head and neck. *Cancer Treat Rep* 1980, **64**, 713–715.