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Phase II study of single-agent etoposide in patients with metastatic squamous-cell carcinoma of the esophagus

Andreas Harstrick[1], Carsten Bokemeyer[1], Peter Preusser[3], Claus Henning Köhne-Wömpner[1], Hans-Joachim Meyer[1], Michael Stahl[2], Heike Knipp[1], Hans-Joachim Schmoll[1], and Hansjochen Wilke[2]

[1] Departments of Hematology and Oncology and Abdominal Surgery, University of Hannover, Hannover, FRG
[2] Department of Oncology, West German Cancer Center, Essen, FRG
[3] Department of Surgery, University of Muenster, Muenster, FRG

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Summary. A total of 26 evaluable patients presenting with advanced or metastatic squamous-cell carcinoma of the esophagus were entered in a phase II trial to assess the single-agent activity of etoposide. Etoposide was given at a dose of 200 mg/m^2 on 3 consecutive days every 3 weeks. Five patients (19%) achieved a partial response and seven (27%) experienced stabilisation of their disease. The median duration of response was 4 months (range 3–8 months). The major toxicity was leukopenia, which reached WHO grade 3 in 46% of patients and grade 4 in 11% of cases, with five instances of leukopenic fever and one therapy-associated death being recorded. Etoposide given at this dose and on this schedule seems to have considerable activity against non-pretreated metastatic esophageal carcinoma.

Introduction

The majority of patients presenting with squamous-cell carcinoma of the esophagus either exhibit or eventually develop metastatic disease and thus require systemic treatment [4]. Only a few agents have demonstrated reproducible activity against metastatic disease, including cisplatin [2, 6], mitomycin C [2], vindesine [5] and, probably 5-fluorouracil [3] with objective response rates in the range of 15%–20% being reported. Etoposide has shown some activity during phase I trials [7]. A subsequent phase II study at Memorial Sloan Kettering Cancer Center failed to confirm the activity of etoposide against esophageal cancer [1]. This study, however, mainly included heavily pretreated patients and used a quite low dose of etoposide. These two factors might have contributed to the negative results. To assess the single-agent activity of etoposide given at a maximal dose of 200 mg/m^2 to non-pretreated esophageal cancer patients, a phase II trial was initiated in February 1989 at the University Hospitals of Hannover and Muenster (FRG).

Offprint requests to: A. Harstrick, Dept. Hematology/Oncology, University of Hannover Medical School, K.-Gutschow-Strasse 8, W-3000 Hannover 61, FRG

Patients and methods

To be eligible for the study, patients had to display advanced or metastatic squamous-cell carcinoma of the esophagus that was not amenable to standard surgical or radiotherapeutic procedures, along with measurable lesions as demonstrated either by computed tomography (CT) or by X-ray. Additional requirements included no prior chemotherapy, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of <3, a WBC of >3,000/µl, a platelet count of >100,000/µl, levels of transaminases and bilirubin that were <2 times the upper limit of normal (unless caused by liver involvement of malignant disease) and the absence of active infection. Informed consent was obtained from all subjects. Initial patient evaluation included a complete history and physical examination, a whole blood count and differential, a serum chemistry study, a chest X-ray, a CT scan of the thorax and abdomen and an abdominal ultrasound examination.

Treatment consisted of 200 mg/m^2 etoposide in 250–500 ml normal saline given over 30–60 min as an infusion on 3 consecutive days, usually at the outpatient clinic. Most patients received prophylactic antiemetics. Treatment cycles were repeated every 3 weeks. Measurable lesions were evaluated prior to each cycle. In subjects showing a response or stable disease, the treatment was given for a maximum of six cycles. Patients developing progressive disease or unacceptable toxicity were removed from the study.

A complete response was defined as the disappearance of all manifestations of malignant disease for at least 4 weeks. A partial response represented a reduction by >50% in the sum of the products of the perpendicular diameters of all measurable lesions and the absence of new lesions. Patients exhibiting less than a partial response or no increase in the size of measurable lesions for at least 4 weeks were recorded as no change (NC). Toxicity was assessed at each visit of the patients and was graded according to WHO guidelines.

Results

In all 28 patients were entered in the study (Table 1), including 23 men and 5 women aged a median of 57 years (range, 42–77 years). All subjects displayed some symptoms and were ambulatory (median PS, 1). Two patients

Table 1. Characteristics and response of patients

Patients entered	28
Patients evaluable	26
Median age	57 (range 42–77) years
Sex (M/F)	23/5
Median performance status (ECOG)	1 (range, 1–2)
Prior esophageal resection	13
Prior radiotherapy	6
Sites of disease:	
Primary	13
Lymph nodes	17
Liver	11
Lung	10
Bone	4
Other	1
Number of metastatic sites (excluding primary):	
1	7
2	15
3	2
Response:	
PR	5 (19%)
NC	7 (27%)
PD	14 (53%)
Duration of response	3, 4, 4, 5, 8 months

Table 2. Toxicity assessed as the worst toxicity per patient

	Patients	
	n	%
Leukopenia		
Grade 3[a]	12	(46)
Grade 4[a]	3	(11)
Thrombocytopenia		
Grade 1[a]	11	(42)
Grade 2[a]	3	(11)
Anemia (requiring transfusion)	6	(23)
Fever/infection	5	(19)
Lethal infection	1	(4)
Nausea/vomiting		
Grade 1[a]	10	(38)
Grade 2[a]	2	(8)

[a] According to the WHO scale

were not evaluable due to early tumor-related death within 2 weeks (one case) and to violation of protocol entry criteria (PS of 3, one case). Of the evaluable patients, 13 had undergone an esophagectomy and 6 had received prior radiotherapy, with disease relapsing outside the radiation ports. The sites of metastatic disease were typical for advanced esophageal cancer.

A total of 80 cycles (median, 2; range, 1–6) were given. Five patients (19%) achieved a partial response (Table 1). The sites of disease in responding patients were the lymph nodes and the liver in one case, the lymph nodes and the lung in two subjects and the lymph nodes and the primary site in two patients. The responses lasted 3, 4, 5, 5 and 8 months. Seven additional patients (27%) showed no change for a median of 4 months (range, 2–7 months). The remaining 14 patients (53%) exhibited progressive disease.

The observed toxicity is summarized in Table 2. The major toxicity was myelosuppression, especially leukopenia, which reached WHO grade 3 in 46% of cases and grade 4 in 11%. Five episodes of fever occurred during leukopenia, resulting in one therapy-associated death due to aspiration pneumonia. Despite prophylactic antiemetics, half of the patients experienced mild to moderate nausea and vomiting. No major organ toxicity was observed.

Discussion

Only a limited number of agents that exhibit documented activity against advanced squamous-cell carcinoma of the esophagus are available. The most active drugs are cisplatin [2, 6], mitomycin [2] and vindesine [5]. Even for these drugs, the response rates have not usually exceeded 20%. The current study achieved a response rate of 19% for etoposide, with an additional 27% of patients experiencing stabilisation of their formerly progressive disease. These findings contrast with the results of a previous trial by Coonley et al. [1], who observed no objective response among 23 subjects. However, these authors gave etoposide at a quite low dose of 100–120 mg/m^2 × 3, mainly to heavily pretreated patients, which might have contributed to the negative results.

The major toxicity of etoposide was transient leukopenia and thrombocytopenia, whereas severe organ toxicity was virtually absent. In conclusion, these data suggest that etoposide given at this dose and on this schedule exerts activity against esophageal cancer. Given the known schedule dependency of etoposide, it would be interesting to determine whether etoposide might show even higher therapeutic activity when given in a greater number of fractions. Although myelosuppression was considerable at the present dose, severe organ toxicity was absent. This spectrum of toxicity makes etoposide given at lower doses a favorable component of combination protocols, especially those containing non-myelosuppressive drugs such as cisplatin.

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