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Purpose: To evaluate the response rate and toxic effects of vinorelbine (VNB) administered as a single agent in metastatic squamous cell esophageal carcinoma.

Patients and Methods: Forty-six eligible patients with measurable lesions were included and were stratified according to previous chemotherapy. Thirty patients without prior chemotherapy and 16 pretreated with cisplatin-based chemotherapy were assessable for toxicity and response. VNB was administered weekly as a 25-mg/m² short intravenous (IV) infusion.

Results: Six of 30 patients (20%) without prior chemotherapy achieved a partial response (PR) (95% confidence interval [CI], 8% to 39%). The median duration of response was 21 weeks (range, 17 to 28). One of 16 patients (6%) with prior chemotherapy had a complete response (CR) of 31 weeks’ duration (95% CI, 0% to 30%). The overall response rate (World Health Organization [WHO] criteria) was 15% (CR, 2%; PR 13%; 95% CI, 6% to 29%). The median dose-intensity (DI) was 20 mg/m²/wk. VNB was well tolerated and zero instances of WHO criteria) was 15% (CR, 2%; PR 13%; 95% CI, 6% to 29%). The median dose-intensity (DI) was 20 mg/m²/wk. VNB was well tolerated and zero instances of WHO grade 4 nonhematologic toxicity occurred. At least one episode of grade 3 or 4 granulocytopenia was seen in 59% of patients. A grade 2 or 3 infection occurred in 16% of patients, but no toxic deaths occurred. Other side effects were rare, and peripheral neurotoxicity has been minor (26% grade 1).

Conclusion: These data indicate that VNB is an active agent in metastatic esophageal squamous cell carcinoma. Given its excellent tolerance profile and low toxicity, further evaluation of VNB in combination therapy is warranted.

therapy for metastatic esophageal carcinoma. Using this combination, the European Organization for Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Cooperative Group (GITCCG), in a randomized phase II trial, achieved a 36% response rate. In the cisplatin-only arm, the response rate was only 18%. However, toxicity was higher in the combination arm, there were 11% treatment-related deaths, especially from cerebral stroke, and no advantage in survival was seen.16

Vinorelbine (VNB; Navelbine, Pierre Fabre Oncologie, Boulogne, France) is a semisynthetic vinca alkaloid (5’nor-anhydro-vinblastine) that differs from other vinca alkaloids by a modification of the catharanthine moiety of the molecule.17 VNB causes disruption of microtubules by reversible binding to tubulin, which results in mitotic spindle dissolution and metaphase arrest in dividing cells.

Based on the results of the first phase I study,18 a 30-mg/m² weekly bolus administration was recommended for phase II trials. Toxic effects in phase I and II studies have included myelosuppression, constipation, and phlebitis. Neurotoxicity greater than grade 2 is rare, but loss of deep-tendon reflexes is the most frequent event. VNB has demonstrated interesting levels of activity against breast carcinoma,19 non–small-cell lung cancer,20 and small-cell lung cancer.21 In most trials, the dose-intensity (DI) of VNB is 25 mg/m²/wk.

Our purpose was to evaluate in a phase II study the response rate, duration of response, and toxic effects of VNB in patients with metastatic squamous cell esophageal carcinoma.

PATIENTS AND METHODS

The study reported here is a phase II trial of VNB given as a weekly intravenous (IV) infusion, conducted by the EORTC GITCCG.

Eligibility and Evaluation

Eligibility criteria for this study included the following: age less than 75 years; metastatic histologically proven squamous cell carcinoma of the esophagus, previously untreated with any cytostatics or relapsing following first-line chemotherapy for locally advanced disease; World Health Organization (WHO) performance status ≤ 2; no chemotherapy within 12 weeks of study entry; at least one measurable lesion located outside of an irradiated area and clearly progressive; life expectancy greater than 3 months; peripheral neuropathy ≤ grade 1; absolute granulocyte count ≥ 2 × 10⁹/L; platelet count ≥ 100 × 10⁹/L; hemoglobin level ≥ 6.8 mmol/L; and adequate renal and hepatic function (serum creatinine, bilirubin, and alkaline phosphatase levels < 1.25 times upper limit of normal value). Exclusion criteria were as follows: prior treatment with vinca alkaloids, absence of measurable disease, brain or leptomeningeal involvement, uncontrolled infection, presence of tracheal involvement, weight loss more than 20% based on usual weight, and previous radiation therapy to the only measurable site of disease. Inclusion of patients with previous radiation therapy was allowed provided a target lesion was present outside the irradiated volume. Patients with previous head and neck carcinoma without recurrence could also be included if they had not received previous chemotherapy as part of the treatment of head and neck squamous cell carcinoma. All patients who entered the study gave oral or written informed consent according to policies followed by national legislations and to Helsinki regulations. The protocol was approved by ethics committees in France, Belgium, and the Netherlands.

Measurable disease was defined as a bidimensional tumor when measured with a ruler or calipers. Esophageal primary tumor was not considered as a measurable disease, but the response was also assessed in the primary tumor with barium swallow and computed tomographic (CT) scan. Patients with only malignant hepatomegaly were not eligible unless their disease was measured in two dimensions by ultrasound or CT scan.

Pretreatment evaluation included physical examination, complete blood cell counts, platelet count, differential blood cell count, serum chemistry analysis, serum electrolytes, calcium, chest radiograph, barium swallow in patients with an intact primary tumor, tracheobronchoscopy for cancer of the upper third, and liver ultrasound and/or CT scan of the abdomen and chest (when indicated). Determinations of complete blood cell counts, platelet counts, and creatinine level were to be performed weekly and serum chemistry analysis after at least every four injections. For response evaluation, barium studies, chest radiographs, and CT scan were repeated after every 8 administrations.

Treatment

The starting dose of VNB was 25 mg/m² in a 500-mL saline solution by 20-minute IV infusion on a weekly basis. For patients with histologically documented cirrhosis, the dose of VNB was reduced to 20 mg/m²/wk for the initial 4 weeks, then escalated to 25 mg/m²/wk in all the subsequent cycles if the drug was well tolerated. VNB was given first through a peripheral vein; however, in case of injection pain or phlebitis, insertion of a central venous line was recommended. The prophylactic use of an antiemetic was not advised, but the prophylactic use of laxatives (eg, lactulose) was recommended. Concomitant irradiation to a field as small as possible was allowed for palliation if there was at least one other measurable lesion.

Response was assessed after 8 weeks of treatment. Responding patients were treated for at least 6 months or until disease progression or unacceptable toxicity. If a patient had stable disease (SD) after the first assessment, the investigator was free to decide whether or not to continue further VNB therapy. In patients with grade 2 peripheral neurotoxicity, the dose of VNB was reduced by 20%; patients with grade 3 peripheral neurotoxicity were withdrawn. Those patients who developed a paralytic ileus had VNB postponed until a normal bowel action occurred and further injections were given at a 50% dose reduction. Complete blood cell counts and serum creatinine level were repeated after every four administrations. VNB was withheld and the start of the next cycle delayed for 1 week until granulocyte and platelet counts were greater than 1 × 10⁹/L and 50 × 10⁹/L, respectively; subsequent doses were adjusted to tolerance.

Response and Toxicity Criteria

All eligible patients were considered assessable for toxicity and response (intent-to-treat analysis). Toxicity and response criteria
were as defined according to WHO.\textsuperscript{22} Briefly, complete response (CR) was defined as the complete disappearance of all signs of active tumor and relief of all tumor-related symptoms; results had to be confirmed with a second evaluation at least 4 weeks later. Partial response (PR) was defined as a $\geq 50\%$ reduction in the sum of the products of the longest diameters of measurable disease during two evaluations separated by an interval of 4 weeks without evidence of new lesions or progression of any lesion. SD was defined as no objective change, decrease less than 50\%, or no increase of greater than 25\% of the two greatest diameters of measurable lesions. Progressive disease (PD) was defined as any evidence of progression of greater than 25\% or the appearance of new lesions. Duration of responses was dated from the start of treatment until progression. All responses were to be confirmed by external review. Overall survival was measured from the beginning of therapy to death or censored at the date when the patient was last observed. DI was calculated for each patient from the total dose of VNB administered during the entire course of treatment, and this expresses the mean drug dose in milligrams per square meter per week.

Patients were stratified before inclusion into two groups according to prior chemotherapy: patients with metastatic disease without any prior chemotherapy and patients with metastatic disease after relapse following preoperative chemotherapy or chemoradiotherapy with or without subsequent esophagectomy. For each of the two groups, we used the sequential two-step statistical design of Gehan\textsuperscript{23} to compute the number of patients required to detect a response rate $= 20\%$. If the actual response rate is $\leq 20\%$, then one additional patient had to be included. The recruitment was discontinued. The number of patients required to detect a response rate $= 20\%$ is given in Table 1.

### RESULTS

**Patient Characteristics**

A total of 49 patients were enrolled between January 1991 and December 1993. Three patients were ineligible for the following reasons: a single target lesion in a preirradiated area (one patient), uncontrolled hypercalcemia (one patient), and two lines of previous chemotherapy and grade 3 neurotoxicity at inclusion (one patient). No patient had palliative concomitant radiotherapy during treatment with VNB. Thus, data on response and toxicity are assessable for all eligible patients. Thirty patients had metastatic disease without any previous chemotherapy and 16 had metastatic disease after relapse following first-line chemotherapy (including preoperative chemotherapy and combined chemoradiotherapy). Previous chemotherapy consisted in cisplatin-based regimens (with etoposide, $n = 2$; with 5-FU, $n = 13$; with 5-FU and carboplatin, $n = 1$). The median time between primary chemotherapy and study entry was 7 months (range, 2.8 to 34.6). Patient characteristics are listed in Table 1.

<table>
<thead>
<tr>
<th>No. of metastatic sites</th>
<th>No. of patients</th>
<th>%</th>
<th>No. of patients</th>
<th>%</th>
</tr>
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<tbody>
<tr>
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<td>12</td>
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<td>4</td>
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<td>3</td>
<td>1</td>
<td>6</td>
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</tbody>
</table>

**Toxicity**

A total of 537 courses of VNB were given to 46 eligible patients. The median number of VNB administrations was eight (range, one to 53). The median DI was 20 mg/m\textsuperscript{2}/wk (range, 9 to 27). Three patients had cirrhosis and received a median dose of 16 mg/m\textsuperscript{2}/wk (range, 15.8 to 17.8).

VNB was well tolerated. However, one patient refused further therapy after one course because of neutropenia and grade 2 infection. No treatment-related deaths occurred. Table 2 lists the maximum grades of hematologic toxicity for each patient. Most patients had dose reductions (65\%) or delays (63\%) for hematologic toxicity. One cirrhotic patient had a dose escalation after 4 weeks of treatment. During the whole treatment period, 27 patients (59\%) had grade 3 or 4 granulocytopenia, but this was of short duration. The median nadir granulocyte count was $0.93 \times 10^9/L$ (range, 0.02 to 13.75 $\times 10^9/L$). There was no cumulative toxic effect. Hematologic toxicity was more severe in patients who had received previous chemotherapy, especially for granulocytopenia.
Table 2. Highest WHO Hematologic Toxicities According to Previous Chemotherapy

<table>
<thead>
<tr>
<th>Grade</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
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<td>16</td>
<td>3</td>
<td>18</td>
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Table 4. Neurotoxicity According to Previous Chemotherapy (%)

<table>
<thead>
<tr>
<th>Toxic Effect</th>
<th>Prior Chemotherapy</th>
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</tr>
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<tbody>
<tr>
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<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>No</td>
<td>57</td>
</tr>
<tr>
<td>Constipation</td>
<td>No</td>
<td>80</td>
</tr>
<tr>
<td>Peripheral neurotoxicity</td>
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<td>80</td>
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Table 3. Highest WHO Nonhematologic and Nonneurologic Toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Tissue 1</th>
<th>Tissue 2</th>
<th>Tissue 3</th>
<th>Tissue 4</th>
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<td>18</td>
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</table>

Treatment after one administration of VNB; these three patients were considered to have SD; both refused further treatment and follow-up evaluation after initial documentation of response. If we consider responses by site, two CRs of lung metastases and one in node metastases were observed. The sites of PRs were lymph nodes (four patients with metastatic nodes). Two patients also had a PR in the primary tumor, associated with a PR or CR in measurable metastatic disease. The median duration of response was 21 weeks (range, 14 to 28).

Of 16 patients with previous chemotherapy, one (6%; 95% CI, 0% to 30%) with late relapse (55 weeks) from primary chemoradiation had achieved a CR of pulmonary metastases after nine VNB administrations. The duration of response was 31 weeks.

Responses were observed after a median of six courses (range, four to eight). At the time of analysis, four patients were still alive and 42 had died. The causes of death were patient progression 9 and 16 days after first VNB administration, and another previously untreated patient refused and sudden death 6 weeks after PD (one patient). The median survival time of the entire group was 6 months and does not differ for patients with or without previous chemotherapy.

Table 5. Clinical Response
DISCUSSION

This study was performed in patients with metastatic disease at diagnosis or relapse. This trial had a slow accrual because of the rarity of occurrence of metastatic disease at diagnosis. Patients with locally advanced cancer were not eligible for this study, because rapid improvement of dysphagia can be obtained in 90% of patients, and local control in 60% of cases can be achieved with concurrent chemoradiotherapy. However, most established regimens of chemotherapy, eg, 5-FU combined with cisplatin, have resulted in PR and CR rates of approximately 55% to 60% for patients with locoregional disease and approximately 30% for patients with metastatic disease. Few compounds have been tested as single agents and the major drawback in early studies was the absence of strict response criteria, as well as the small number of patients, thus requiring the pooling of data from several studies. Mitomycin appeared to be an active agent, achieving a 42% response rate in the Eastern Cooperative Oncology Group (ECOG) study at the cost of prohibitive myelosuppression, but the response rate was lower in two other trials. Vindesine is also an active drug, yielding a 19% response rate in an overview of five compiled trials (25 responses among 129 assessable patients), but peripheral neurotoxicity occurred in 17% to 51% of the patients. Vinblastine and vincristine, which are sometimes used in combination therapy, have never been tested as single agents. Cisplatin is probably the most active drug and has been tested in seven phase II studies with a response rate of 24% (56 responses among 231 patients), but most of these trials included both metastatic and locally advanced tumors. Moreover, in locally advanced tumors, the assessment of response cannot be performed using WHO criteria and evaluation of response remains difficult. Recently, paclitaxel followed by granulocyte colony-stimulating factor was tested in 18 patients with locally advanced or metastatic squamous cell carcinoma, and five patients (28%; 95% CI, 7% to 49%) achieved a PR. The results obtained with VNB are promising. We obtained a 20% response rate in patients without prior chemotherapy. All responses were confirmed by external review. Responses were observed in all sites of disease, except liver. Two patients who showed unconfirmed PRs were evaluated as having SD, including one patient with a 55% decrease in a hepatic metastasis. Confirmation of this response was documented, but the observation was only continued for 2 weeks after the first PR assessment, because the patient refused further weekly treatment. We strictly applied the WHO criteria and considered the response to be SD. One of 16 patients with previous chemotherapy had a CR of 7 months' duration. A preliminary report from the National Institute of Tumors of Milan recently confirmed the activity of VNB in squamous cell carcinoma of the esophagus with a different schedule. They used a twice-monthly administration of 30 mg/m² and reported a response rate of 25% among 16 patients. PRs were achieved in one of six previously untreated and three of 10 previously treated patients. These results are consistent with the activity of VNB demonstrated in patients with recurrent or metastatic squamous cell carcinoma of the head and neck.

Although the results of a phase I study suggested that VNB should be given at 30 mg/m² weekly, in phase II studies the DI usually ranges from 20 to 25 mg/m². Therefore, a weekly dose of 25 mg/m² was selected for this trial, and even so, dose reductions and delays for hematologic toxicity resulted in a DI of 20 mg/m²/wk. Fifty-nine percent of patients had grade 3 or 4 granulocytopenia, but this was rarely associated with infection; only 16% of patients experienced a grade 2 or 3 infection and no toxic deaths occurred. Hematologic toxicity was more severe in patients who had received previous chemotherapy. Granulocytopenia was the dose-limiting toxicity and led to dose reduction or delay in almost all patients.

Peripheral neuropathy has been infrequent (26% grade 1), and this will allow further investigation of VNB, in combination with cisplatin. In contrast, vindesine neurotoxicity is a particular problem in patients with esophageal carcinoma treated with vindesine, cisplatin, and bleomycin, with significant peripheral neuropathy seen in almost all patients who received more than four to six doses of vindesine. A randomized study conducted in stage III and IV non–small-cell lung cancer showed that grade 3 to 4 neurotoxicity occurred twice as frequently in the vindesine-cisplatin arm as in the VNB-cisplatin arm (33% vs 15%; P < .004).

The results obtained with VNB are particularly encouraging in all respects: low toxicity, high response rate for a single agent, and at least comparable survival to other phase II regimens with active drugs such as cisplatin, vindesine, methotrexate, or 5-FU. The median survival time of patients with metastatic disease or recurrence treated with these agents was 2 to 3 months. The 6-month median survival time in this trial with a single agent is similar to that obtained with the complex drug combination of folinic acid (leucovorin), 5-FU, etoposide, and cisplatin (FLEP) in patients with metastatic disease. Moreover, both experimental models in animals and extensive clinical data in non–small-cell lung carci-
VINORELBINE IN EPIDERMOID ESOPHAGEAL CARCINOMA

In conclusion, VNB has been identified as an active agent in metastatic squamous cell esophageal carcinoma. Further evaluation of this drug in combination therapy is warranted.

REFERENCES


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