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Phase II Trial of Vinorelbine in Metastatic Squamous Cell Esophageal Carcinoma

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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 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.

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CARCINOMA of the esophagus is responsible for approximately 300,000 deaths per year and accounts for 4% of cancers worldwide.¹ It is an uncommon tumor in the United States, accounting for 10,900 estimated deaths in 1995,² and adenocarcinoma now represents the major histologic type. However, squamous cell carcinoma is still common in China, Iran, and European countries, mainly France, Hungary, Ireland, Switzerland, the United Kingdom, and Portugal.^{1,3} Despite major advances in surgery and radiation therapy, the outcome for patients with squamous cell carcinoma of the esophagus

remains poor. In the registry of gastrointestinal tract tumors established in the French County of Finistère,⁴ up to 70% of patients have advanced disease (stage T3 or T4 and node-positive lesions) and 13% have metastatic disease at diagnosis. The median survival time of 716 patients with esophageal squamous cell carcinoma diagnosed from 1984 to 1988 was 9 months. Only 15% of the patients could be treated by curative resection, with a median survival time of 22.5 months.

Combined chemotherapy and radiation therapy represents a significant advance in locally advanced disease.⁵ However, many patients develop local recurrence (17% to 67%) or distant metastases (3% to 37%).^{5,6} Autopsies of patients who die of esophageal cancer show that 51% to 82% have metastatic disease.⁷⁻⁹

A recent review outlined the results of single-agent chemotherapy for squamous cell carcinoma.¹⁰ Few drugs show evidence of response rates greater than 20%, but cisplatin, mitomycin, vindesine, and, more recently, paclitaxel¹¹ have activity at this level. Most clinical trials have been undertaken in small numbers of patients and some have also included patients with adenocarcinomas. Most trials include both locally advanced tumors and patients with metastatic disease, as well as a mixture of pretreated and untreated patients. Cisplatin is the most extensively tested drug,¹²⁻¹⁶ yielding a single-agent response rate of 6% to 40%. Cisplatin combined with fluorouracil (5-FU) by continuous infusion is the most widely used chemo-

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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 \leq 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 \leq grade 1; absolute granulocyte count $\geq 2 \times 10^9/L$; platelet count $\geq 100 \times 10^9/L$, 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 $1 \times 10^9/L$ and $50 \times 10^9/L$, 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.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 Gehan²³ to compute the number of patients required to detect a response rate $\geq 20\%$. In the first step, 14 assessable patients had to be included, and if no responses were observed, the recruitment was discontinued. The probability of observing no response in these initial 14 patients is less than 0.05 if the actual response rate is $\geq 20\%$. If one response was observed in the first stage, one additional patient had to be included, and in cases in which there were two, three, or four responses in the first 14 patients, six, nine, or 11 additional assessable patients, respectively, had to be included.

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 1. Characteristics of Eligible Patients According to Previous Chemotherapy

Variable	No Prior Chemotherapy		Prior Chemotherapy	
	No.	%	No.	%
No. of patients	30	100	16	100
Sex				
Female	3	10	2	13
Male	27	90	14	87
Age, years				
Median	60		55	
Range	40-67		40-27	
WHO performance status				
0	5	17	5	31
1	18	60	8	50
2	7	23	3	19
Prior radiotherapy				
No	20	67	2	13
Yes	10	33	14	87
Sites of disease				
Primary tumor	24	80	4	25
Lymph nodes	18	60	5	31
Lung	9	30	11	69
Liver	12	40	6	37
Bone	6	20	1	6
Other	4	13	0	0
No. of metastatic sites				
1	5	17	9	56
2	7	23	4	25
3	17	57	2	12
4	1	3	1	6

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/m²/wk (range, 9 to 27). Three patients had cirrhosis and received a median dose of 16 mg/m²/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

Nadir (WHO) Variable	Prior Chemotherapy	Grade									
		0		1		2		3		4	
		No.	%	No.	%	No.	%	No.	%	No.	%
WBCs	No	5	17	3	10	9	30	10	33	3	10
	Yes	2	13	1	6	2	12.5	6	37.5	5	31
Neutrophils	No	5	17	3	10	5	16.5	14	46.5	3	10
	Yes	2	12.5	1	6	3	19	6	37.5	4	25
Platelets	No	30	100	0	0	0	0	0	0	0	0
	Yes	13	82	1	6	1	6	1	6	0	0
Hemoglobin	No	10	34	13	43	4	13	2	7	1	3
	Yes	2	12.5	6	37.5	6	37.5	2	12.5	0	0

(25% grade 4 v 10%; $P = .21$). Grade 3 or 4 anemia occurred in five patients (11%). There was no thrombocytopenia in patients with first-line chemotherapy, but three patients who had received previous chemotherapy had grade 1, grade 2, and grade 3 thrombocytopenia (respectively, during one course). Maximum nonhematologic and nonneurologic side effects per patient are listed in Table 3. No grade 4 nonhematologic toxicity was reported.

Neurotoxicity was rare (Table 4): no peripheral neuropathy greater than grade 1 occurred. Six patients (20%) with no prior chemotherapy and six (37.5%) with previous chemotherapy had mild paresthesias (grade 1) or loss of deep-tendon reflexes. Three patients had abdominal pain (one grade 2 with diarrhea, and two grade 3 associated with severe constipation).

Response to Therapy

All eligible patients are assessable for response (Table 5). Two patients, one without and one with previous chemotherapy, died early of pulmonary lymphangitis or hepatic progression 9 and 16 days after first VNB administration, and another previously untreated patient refused

Table 4. Neurotoxicity According to Previous Chemotherapy (%)

Toxic Effect	Prior Chemotherapy	Grade				
		0	1	2	3	4
Asthenia	No	57	30	10	3	0
	Yes	69	19	12	0	0
Constipation	No	80	10	10	0	0
	Yes	75	6	6	13	0
Peripheral neurotoxicity	No	80	20	0	0	0
	Yes	62.5	37.5	0	0	0

treatment after one administration of VNB; these three patients were evaluated as having PD. Among the 30 previously untreated patients, six (20%; 95% CI, 8% to 39%) achieved a PR. Two patients had a PR not confirmed by a second evaluation and 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 of 18 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 PD (40 patients), cerebroischemic accident (one patient), 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 3. Highest WHO Nonhematologic and Nonneurologic Toxicity

Toxic Effect Variable	Grade									
	0		1		2		3		4	
	No.	%	No.	%	No.	%	No.	%	No.	%
Nausea/vomiting	29	66	9	20	4	9	2	5	0	0
Diarrhea	39	87	5	11	1	2	0	0	0	0
Liver toxicity	38	93	2	5	0	0	1	2	0	0
Renal toxicity	43	96	2	4	0	0	0	0	0	0
Pulmonary toxicity	43	96	2	4	0	0	0	0	0	0
Drug fever	40	89	4	9	1	2	0	0	0	0
Allergy	44	98	1	2	0	0	0	0	0	0
Local reaction	38	85	3	7	2	4	2	4	0	0
Cutaneous reaction	41	91	3	7	1	2	0	0	0	0
Alopecia	38	85	5	11	1	2	1	2	0	0
Infection	33	74	5	11	5	11	2	4	0	0
Mucositis	39	87	4	9	2	4	0	0	0	0
Cardiotoxicity	44	98	0	0	1	2	0	0	0	0
Flu-like syndrome	42	93	3	7	0	0	0	0	0	0

Table 5. Clinical Response

Variable	Overall		No Prior Chemotherapy		Prior Chemotherapy	
	No.	%	No.	%	No.	%
Eligible patients	46	100	30	100	16	100
CR	1	2	0	0	1	6
PR	6	13	6	20	0	0
SD	16	35	11	37	5	31
PD	20	44	11	37	9	56
Early PD	1	2	1	3	0	0
Early death due to malignant disease	2	4	1	3	1	6

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.³ 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.²⁴ 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.¹¹ 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) study¹³ at the cost of prohibitive myelosuppression, but the response rate was lower in two other trials.²⁵ Vindesine is also an active drug, yielding a 19% response rate in an overview of five compiled trials (25 responses among 129 assessable patients²⁶⁻²⁹), but peripheral neurotoxicity occurred in 17% to 51% of the patients.^{26,28-29} 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^{10,12-16}), 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.^{10,30} 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.¹¹

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 re-

sponse 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.³¹ 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.^{32,33}

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,^{10,34} with significant peripheral neuropathy seen in almost all patients who received more than four to six doses of vindesine.³⁴ 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% v 15%; $P < .004$).²⁰

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.^{12-14,26,28,35} 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.³⁶ Moreover, both experimental models in animals and extensive clinical data in non-small-cell lung carci-

noma show that addition of cisplatin to VNB may have a synergistic antitumoral effect without increased toxicity.²⁰ We are presently investigating within the EORTC GITCCG a combination of VNB and cisplatin in patients with metastatic esophageal squamous cell 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.

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REFERENCES

1. Parkin DM, Pisani P, Ferlay J: Estimates of the worldwide incidence of eighteen major cancers in 1985. *Int J Cancer* 54:594-606, 1993
2. Wingo PA, Tong T, Bolden S: Cancer statistics, 1995. *CA-A* 45:8-30, 1995
3. La Vecchia C, Lucchini F, Negri E, et al: Trends of cancer mortality in Europe, 1955-1989: I, digestive sites. *Eur J Cancer* 28:132-235, 1992
4. Calament G, Cauvin JM, Robaszkiewicz M, et al: Esophageal squamous cell carcinoma in the French county of Finistère between 1984 and 1988: Treatment and survival analysis in 716 cases. *Gastroenterol Clin Biol* 17:9-16, 1993
5. Herskovic A, Martz K, Al-Sarraf M, et al: Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 326:1593-1598, 1992
6. Kavanagh B, Anscher M, Leopold K, et al: Patterns of failure following combined modality therapy for esophageal cancer, 1984-1990. *Int J Radiat Oncol Biol Phys* 24:633-642, 1992
7. Bosch A, Frias Z, Caldwell WL, et al: Autopsy findings in carcinoma of the esophagus. *Acta Radiol Oncol* 18:103-112, 1979
8. Mandard AM, Chasle J, Marnay J, et al: Autopsy findings in 111 cases of esophageal cancer. *Cancer* 48:329-335, 1981
9. Anderson LL, Lad TE: Autopsy findings in squamous-cell carcinoma of the esophagus. *Cancer* 50:1587-1590, 1982
10. Ajani JA: Contributions of chemotherapy in the treatment of carcinoma of the esophagus: Results and commentary. *Semin Oncol* 21:474-482, 1994
11. Ajani JA, Ilson DH, Daugherty K, et al: Activity of Taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. *J Natl Cancer Inst* 86:1086-1091, 1994
12. Davis S, Shanmugathasa M, Kessler W: Cis-dichlorodiammineplatinum (II) in the treatment of esophageal carcinoma. *Cancer Treat Rep* 64:709-711, 1980
13. Engstrom PF, Lavin PT, Klassen DJ: Phase II evaluation of mitomycin and cisplatin in advanced esophageal carcinoma. *Cancer Treat Rep* 67:713-715, 1983
14. Panettiere FJ, Leichman LP, Tilchen EJ, et al: Chemotherapy for advanced epidermal carcinoma of the esophagus with single-agent cisplatin: Final report on a Southwest Oncology Group study. *Cancer Treat Rep* 68:1023-1024, 1984
15. Ravry MJR, Moore MR, Omura GA, et al: Phase II evaluation of cisplatin in squamous carcinoma of the esophagus. A Southeastern Cancer Study Group trial. *Cancer Treat Rep* 69:1457-1458, 1985
16. Bleiberg M, Jacob JH, Bedenne L, et al: Randomized phase II trial of 5-fluorouracil (5FU) and cisplatin (DDP) versus DDP alone in advanced esophageal cancer. *Proc Am Soc Clin Oncol* 10:145, 1991 (abstr 447)
17. Potier P: The synthesis of Navelbine prototype of a new series of vinblastine derivatives. *Semin Oncol* 16:2-4, 1989, suppl 4
18. Mathé G, Reizenstein P: Phase I pharmacologic study of a new vinca-alkaloid: Navelbine. *Cancer Lett* 27:285-293, 1985
19. Fumoleau P, Delgado FM, Delozier T, et al: Phase II trial of weekly intravenous vinorelbine in first-line advanced breast cancer chemotherapy. *J Clin Oncol* 11:1245-1252, 1993
20. Le Chevalier T, Brisgand D, Douillard JY, et al: Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: Results of a European multicenter trial including 612 patients. *J Clin Oncol* 12:360-367, 1994
21. Goa KL, Faulds D: Vinorelbine. A review of its pharmacological properties and clinical use in cancer chemotherapy. *Drugs Aging* 5:200-234, 1994
22. Miller AB, Hoogstraten B, Staquet M, et al: Reporting results of cancer treatment. *Cancer* 47:207-214, 1981
23. Gehan EA: The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapy agent. *J Chronic Dis* 13:346-353, 1961
24. Coia LR, Soffen EM, Schultheiss TE, et al: Swallowing function in patients with esophageal cancer treatment with concurrent radiation and chemotherapy. *Cancer* 71:281-286, 1993 (suppl 1)
25. Coia LR: The use of mitomycin in esophageal cancer. *Oncology* 50:53-62, 1993
26. Kelsen DP, Bains MS, Cvitkovic E, et al: Vindesine in the treatment of esophageal carcinoma: A phase II study. *Cancer Treat Rep* 63:2019-2021, 1979
27. Bedikian AY, Valdivieso M, Bodey GP, et al: Phase II evaluation of vindesine in the treatment of colorectal and esophageal tumors. *Cancer Chemother Pharmacol* 2:263-266, 1979
28. Bezwoda WR, Derman DP, Weaving A, et al: Treatment of esophageal cancer with vindesine: An open trial. *Cancer Treat Rep* 68:783-785, 1984
29. Japanese Esophageal Oncology Group: A phase II study of vindesine in the treatment of esophageal carcinoma. *Jpn J Clin Oncol* 19:380-383, 1989
30. Conroy T: Measurement of the primary esophageal tumor, in Wils J, Bleiberg H (eds): *Diagnosis and Treatment of Gastrointestinal Tract Cancer*. Brentwood, United Kingdom, Multiscience Publishing, 1993, pp 28-30
31. Soto Parra H, Bidoli P, Santoro A, et al: A phase II study with vinorelbine (VNB): an active new agent in squamous cell carcinoma of the esophagus (SCCE). *Ann Oncol* 5:77-78, 1994 (suppl 8, abstr P 386)
32. Gebbia V, Testa A, Valenza R, et al: A pilot study of vinorelbine on a weekly schedule in recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Eur J Cancer* 29A:1358-1359, 1993

33. Testolin A, Recher G, Pozza F, et al: Vinorelbine (VNB) in pre-treated advanced head and neck squamous cell carcinoma (AH & NSCC): A phase II study. *Proc Am Soc Clin Oncol* 13:289, 1994 (abstr 938)

34. Kelsen D, Hilaris B, Coonley C, et al: Cisplatin, vindesine, and bleomycin chemotherapy of local-regional and advanced esophageal carcinoma. *Am J Med* 75:645-652, 1983

35. Ezdinli EZ, Gelber R, Desai DV, et al: Chemotherapy of advanced esophageal carcinoma: Eastern Cooperative Oncology Group experience. *Cancer* 46:2149-2153, 1980

36. Stahl M, Wilke H, Meyer HJ, et al: 5-Fluorouracil, folinic acid, etoposide and cisplatin chemotherapy for locally advanced or metastatic carcinoma of the oesophagus. *Eur J Cancer* 30A:325-328, 1994