Acta Oncologica 27 (1988) Fasc. 6b

FROM THE DEPARTMENT OF MEDICAL ONCOLOGY OF THE UNIVERSITY HOSPITAL, AND THE ROTTERDAM CANCER INSTITUTE, ROTTERDAM, HOLLAND.

ETOPOSIDE AND CISPLATIN IN ADVANCED ESOPHAGEAL CANCER

A preliminary report

T. C. KOK, T. A. W. SPLINTER and J. VERWEIJ
For the Rotterdam Esophageal Tumor Study Group

Abstract

In order to find an effective and suitable chemotherapy regimen for preoperative treatment of esophageal cancer, patients with inoperable or metastatic disease were treated with a combination of etoposide and cisplatin. Of 27 evaluable patients, 13 had squamous cell carcinoma, 13 adenocarcinoma, and 1 muco-epidermoid carcinoma. No complete responses were noted. Nine of 13 patients with squamous cell carcinoma and only one of 13 with adenocarcinoma showed a partial response. Nine of 10 responders achieved a partial response after 2 courses, one after 4 courses. There was one toxic death, due to sepsis during leukopenia. Other toxicities were alopecia, nausea and vomiting, nephrotoxicity, thrombocytopenia and leukopenia.

Key words: Esophageal neoplasms; advanced cancer, etoposide, cisplatin.

Cancer of the esophagus has a poor prognosis. In most western countries 5-year survival rates have consistently reached a maximum of 10% in patients with seemingly localized disease at first presentation. A major cause is the fact, that in more than 50% of these cases curative resection is not possible (4). There is reasonable doubt whether preoperative radiotherapy can give higher resection rates or better long-term survival (7). Most patients who undergo surgery with curative intent will ultimately die from distant spread of tumor. Therefore, effective systemic therapy is needed to improve the survival rate. Cisplatin based multi-drug combinations result in a 25–50% response rate, but a rather high toxicity makes such a therapy less suitable for combined modality treatment (3, 6, 9). Recently, in vitro experiments have shown that etoposide (VP16–213) inhibits the enzyme topoisomerase-II, resulting in DNA strand breaks (2). Assuming that in vivo synergism between cisplatin and etoposide may depend on the continuous inhibition of the DNA strand rejoining activity of topoisomerase-II by etoposide, a combination of cisplatin and etoposide for 5 days was chosen to study its activity and toxicity in patients with advanced cancer of the esophagus. The aim is to find a regimen with a high response rate, a rapid response, and acceptable toxicity. Such a regimen might be suitable for combined modality treatment.

Material and Methods

Until October 1987, 36 consecutive patients with inoperable or metastatic cancer of esophagus or esophageal-gastric junction area were treated with a combination of cisplatin and etoposide. Histologic examination revealed squamous cell carcinoma (n=18), adenocarcinoma (n=16), undifferentiated carcinoma (n=1), and muco-epidermoid carcinoma (n=1). Major eligibility criteria were histologically proven disease, Karnofsky performance status >60%, age <70 years, adequate bone marrow and kidney function, and measurable tumor parameters. If, however, the primary tumor was the only marker lesion and not previously irradiated, the disease was considered evaluable, and monitored by barium radiogram, CT-scan and endoscopy with biopsies. In case of diminished food intake due to stenosis, a celestin tube was inserted.

The following chemotherapy regimen was used: etoposide 100 mg (fixed dose) as a 2-h infusion, immediately followed by cisplatin 80 mg/m^2 as a 4-h infusion on day 1; etoposide 100 mg (fixed dose) as a 2-h infusion on day 2; etoposide 200 mg/m^2 orally, divided over 3 equal doses on days 3 and 5. Patients were discharged at the end of day 2. Courses were repeated every 4 weeks until disease pro-

Presented at ECCO-4, Madrid, November 1–4, 1987.

gression, with a maximum of 6 courses. Cisplatin infusion was preceded and followed by adequate hydration; if necessary mannitol and low doses of furosemide were administered. Dose modifications were made according to the nadir values of leukocytes and platelets (Table 1); in this way possible differences in toxicity due to variable bio-availability of oral etoposide were counterbalanced. All patients received dexamethasone 10 mg i.v. before cisplatin infusion, and metoclopramide or domperidone and lorazepam as antiemetic treatment. To assess the response, measurements of tumor lesions were repeated after every 2 courses of therapy. Standard response criteria (10) were used, being for complete response (CR) the disappearence of all known lesions for at least 4 weeks, and for partial response (PR) a more than 50% decrease of the product of the two largest diameters of the lesion (>30% decrease unidimensionally) or an estimated 50% or more reduction of tumor bulk of an evaluable primary tumor, over a period of 8 weeks. A less than 50% decrease or less than 25% increase in total tumor size, or tumor bulk in the case of an evaluable primary tumor, for at least 4 weeks without the appearance of new lesions, was classified as stable disease (SD), and more than 25% increase in total tumor size, or the appearance of new lesions, as progressive disease (PD). Duration of response was calculated from the start of treatment to the date progressive disease was first noted.

Patients were evaluated for response after 2 courses. In case of progression after the first course, however, the patient was classified as having progressive disease. Death due to complications directly related to treatment was classified as toxic death.

Table 1

Dose modification according to the nadir number of leukocytes and/or platelets on day 14 or 21

WBC $\times 10^9$/l	Platelets $\times 10^9$/l	Etoposide day 1, 2 %	Etoposide day 3, 5 %	Cisplatin %
<1.0	<25	100	75	100
>2.0	>100	100	+25	100

Table 2

Characteristics of 27 evaluable patients

Male	21
Female	6
Median age (years)	59 (range 41–69)
Median performance status (Karnofsky)	80 (range 70–100)
Extent of disease	
locally advanced tumor	2
primary tumor and distant spread	22
primary removed, distant spread	3
Histology	
squamous cell carcinoma	13
adenocarinoma	13
muco-epidermoid carcinoma	1
Weight loss	
1–5%	8
6–10%	4
>10%	15

Table 3

Responses in 27 evaluable patients (WHO)

	CR	PR	NC	PD	Total
Squamous cell carcinoma	0	9	2	2	13
Adenocarcinoma	0	1	6	6	13
Muco-epidermoid carcinoma	0		1		1
Total	0	10	9	8	27

Results

Of 18 patients with squamous cell carcinoma, 2 have recently started chemotherapy, and 3 others were not evaluable for response; one of the last mentioned patients had a 2-month delay after the first course, due to repeated appearance of pleural fistulas after thoracotomy. Another patient with a history of alcohol abuse developed a neuropathy after the first coures. His lung metastases disappeared. The third patient received a celestin tube after the second course; perforation and mediastinitis occurred, followed by a 3-month delay without any possibility of adequately measuring the response. Of the remaining 13 patients with squamous cell carcinoma (Table 2), 9 reached PR; 8 after 2 courses and one after 4 courses. No CR was noted. Median response duration was 7 months (range 5–9).

Sixteen patients with adenocarcinoma entered the study; 3 were not evaluable for response. One refused treatment after the first course. One patient died of sepsis during leukopenia after the first course. One patient developed bacterial meningitis just before his second course. Of the remaining 13 patients with adenocarcinoma (Table 2), only one reached PR after 2 courses, with a duration of 9 months.

One patient had a large-cell undifferentiated carcinoma; she developed a broncho-esophageal fistula after the first course, probably due to tumor necrosis; enlarged supraclavicular lymh nodes disappeared. After recovery she refused further treatment, and was not evaluable for response.

One patient had a muco-epidermoid carcinoma, and showed no response to treatment.

Toxicity

There was one toxic death due to E. coli sepsis during leukopenia (0.5×10^9/l) after the first course. One patient contracted bacterial meningitis just before his planned second course, his WBC being 4.9×10^9/l. He received no

Table 4

Toxicity in 31 evaluable patients (WHO)

No. of courses	107
Dose escalation	17
Dose reduction	4
Treatment delay	4
Median WBC nadir	1.6×10^9/l (range 0.3–4.9)
Median platelet nadir	100×10^9/l (range 15–340)
Nausea and vomiting	60% (grade 2, 3)
Alopecia	84% (grade 2, 3)
Diarrhea	15% (grade 2, 3)
Neuropathy	1 (grade 2)
Toxic death	1
Leukopenia related infections	3 (grade 2, 3)
Nephrotoxicity	7 (grade 1)

further treatment at all, and died. The chemotherapy may have contributed to this fatal complication.

The experience from a total of 107 courses showed hair loss, gastrointestinal toxicity and nephrotoxicity to be the most prominent side effects (Table 4). Leukopenia and/or thrombocytopenia were demanded in the treatment protocol; in 17 courses a dose escalation of etoposide was applied. Only 4 courses required delay and dose reduction due to myelosuppression (lowest WBC nadir 0.3×10^9/l; lowest platelet nadir 15×10^9/l). In two patients pneumonia associated with broncho-esophageal fistula was seen; in both cases tumor necrosis was probably the cause, in view of regression of other tumor lesions.

Nephrotoxicity with a rise in serum creatinine of more than 50% was noted in 3 patients; 4 developed a rise of 25–50%.

Discussion

The preliminary results of this study indicate that the combination of cisplatin and etoposide has activity in squamous cell carcinoma of the esophagus. Depending on the very low activity in adenocarcinoma, further testing of the regimen in this group was discontinued. Although most adenocarcinomas of the esophageal-gastric junction area have been described in gastric cancer therapy protocols, our negative results with cisplatin and etoposide are not different from reports in the literature (5). In view of the fact that adenocarcinomas of the esophagus and esophageal-gastric junction area are occuring more frequently and may have a different biological behaviour, this group of tumors probably need to be studied as a separate entity (8). Concerning the methods for evaluation of the primary tumor, in 1 out of 28 patients the history of improved food passage was contradictory to the results of imaging studies, and 2 out of 13 CT-scans were not in agreement with the other evaluation methods. Although this study was not meant to compare evaluation techniques in esophageal cancer, it seems feasible to omit CT-scanning from the evaluation of the primary tumor during chemotherapy and rely on serial contrast radiograms as reported by Agha et al. (1), in combination with history and endoscopy. If similar response rates and toxicity continue in our on-going study, this chemotherapy regimen may be useful in squamous cell carcinoma of the esophagus, without being very toxic, and feasible as preoperative treatment.

ACKNOWLEDGEMENTS

The members of the Rotterdam Esophageal Tumor Study Group are: M. van Blankenstein MD., W. M. H. Eykenboom MD. PhD., W. C. J. Hop statistician, F. J. W. ten Kate MD., J. Lameris MD. PhD., B. L. A. M. Langenhorst MD., B. A. Reichgelt MD., H. W. Tilanus MD. PhD..

We thank Ineke van Reyswoudt and Connie Vollebregt for data management.

This study was supported by the Netherlands Cancer Foundation (KWF-CKVO 86-05).

Request for reprints: Dr T. C. Kok, Dept. of Medical Oncology, University Hospital Rotterdam/Dykzigt, Dr. Molewaterplein 40, NL-3015 GD Rotterdam, Holland.

REFERENCES

1. Agha F. P., Gennis M. A., Orringer M. B. and Forastiere A. A.: Evaluation of response to preoperative chemotherapy in esophageal and gastric cardia cancer using biphasic esophagrams and surgical–pathological correlation. Am. J. Clin. Oncol. 9 (1986), 227.
2. Chen G. L., Yang L., Rowe T. C., Halligan B. D., Tewey K. M. and Liu L. F.: Nonintercalative antitumor drugs interfere with the breakage–reunion reaction of mammalian DNA topoisomerase II. J. Biol. Chem. 259 (1984), 13560.
3. Dinwoodie W. R., Bartolucci A. A., Lyman G. H., Velez-Garcia E., Martelo O. J. and Sarma P. R.: Phase II evaluation of cisplatin, bleomycin and vindesin in advanced squamous cell carinoma of esophagus: A south eastern cancer study group trial. Cancer Treat. Rep. 70 (1986), 267.
4. Earlham R. and Cunha-Melo J. R.: Oesophageal squamous cell carcinoma: A critical review of surgery. Br. J. Surg. 67 (1980), 381.
5. Kelsen D. P., Buckner J., Einzig A., Magill G., Heelan R. and Vinciguera V.: Phase II trial of cisplatin and etoposide in adenocarcinomas of the upper gastrointestinal tract. Cancer Treat. Rep. 71 (1987), 329.
6. — Fein R., Coonley C., Heelan R. and Baines M.: Cisplatin vindesin and mitoguazone in the treatment of esophageal cancer. Cancer Treat. Rep. 70 (1986), 255.
7. Launois B., DeLarne D., Campoin J. P. and Kerbaol M.: Preoperative radiotherapy for carcinoma of the esophagus. Surg. Gynaecol. Obstet. 153 (1981), 69.
8. MacDonald W. C. and MacDonald J. B.: Adenocarcinoma of the esophagus and/or gastric cardia. Cancer 60 (1987), 1094.
9. Vogl S. E., Greenwold E. and Kaplan B. H.: Effective chemotherapy for esophageal cancer with methotrexate, bleomycine and cisdiamminedichloroplatinum II. Cancer 48 (1981), 2555.
10. WHO Handbook for Reporting Results of Cancer Treatment. Who Offset Publiction No. 48, Geneva 1979.