Pergamon

European Journal of Cancer Vol. 33, No. 13, pp. 2211–2215, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

PII: S0959-8049(97)00183-4

Original Paper

Etoposide in Malignant Pleural Mesothelioma: Two Phase II Trials of the EORTC Lung Cancer Cooperative Group

T. Sahmoud,[1] P.E. Postmus,[2] Ch. van Pottelsberghe,[1] K. Mattson,[3] L. Tammilehto,[4] T.A.W. Splinter,[5] A.S.T. Planting,[5] T. Sutedja,[2] J. van Pawel,[6] N. van Zandwijk,[7] P. Baas,[7] K.J. Roozendaal,[8] M. Schrijver,[9] A. Kirkpatrick,[1] M. Van Glabbeke,[1] A. Ardizzoni[10] and G. Giaccone[11]

[1]EORTC Data Center, Brussels, Belgium; [2]University Hospital, Groningen, The Netherlands; [3]University Hospital, Helsinki, Finland; [4]Finnish Institute of Occupational Health, Finland; [5]Academisch Ziekenhuis, Rotterdam, The Netherlands; [6]Krankenhaus Gauting, Munich, Germany; [7]Netherlands Cancer Institute, Amsterdam, The Netherlands; [8]OLV Gasthuis, Amsterdam, The Netherlands; [9]Gemini Ziekenhuis, Den Helder, The Netherlands; [10]Istituto nazionale per la ricerca sul cancro, Genova, Italy; and [11]University Hospital Vrije Universiteit, 1117 de Boelelaan, HV 1081, Amsterdam, The Netherlands

Intravenous and oral etoposide (VP 16-213) were tested in two sequential phase II trials in chemotherapy-naive patients with malignant pleural mesothelioma. In the first trial, etoposide was given intravenously (i.v.) at a dose of 150 mg/m^2 on days 1, 3 and 5 every 3 weeks. The second trial investigated a daily oral dose of 100 mg for 21 days followed by a 2-week treatment-free period, and then recycling. In both trials, the treatment was given until disease progression, intolerable toxicity or patient refusal. In the i.v. trial, 49 patients were included, 2 patients were ineligible. The oral trial recruited 45 patients, 4 patients were not eligible. In both trials, the main side-effects were moderate leucopenia, alopecia, nausea and vomiting. Two partial responses (4%) and three partial responses (7%) were reported in the i.v. and oral trials, respectively. The median survival was 29 weeks and 38 weeks in the i.v. and oral trials, respectively. In conclusion, further investigation of etoposide in malignant mesothelioma is not recommended. © **1997 Elsevier Science Ltd.**

Key words: etoposide, mesothelioma, phase II
Eur J Cancer, Vol. 33, No. 13, pp. 2211–2215, 1997

INTRODUCTION

MALIGNANT MESOTHELIOMA may originate from the pleura, peritoneum, pericardium or tunica vaginalis. Apart from the rare and early localised forms, this tumour is unresectable and most patients die within 1 year after diagnosis. Since the first description of mesothelioma in the early 1930s, the incidence based on tumour registries has steadily increased and is expected to continue to rise in the next decade [1]. Published estimates for incidence in Europe are rare. In the Nantes-Saint Nazaire region, France, the incidence during the period 1985–1992 was 10.9 per million inhabitants versus 8.7 for the period 1975–1984 and 2.6 for the period 1956–1974 [2]. In Norway, the age-adjusted incidence rate for men increased from 4 per million in the period 1960–1969 to 14 per million in the period 1980–1988 [3]. In the United States the annual incidence of mesothelioma is roughly estimated to be 2200 new cases [4–6].

Despite treatment, mesothelioma remains a rapidly progressing and lethal malignancy. Various chemotherapeutic agents have been tested in mesothelioma. A recent review of phase II trials noted that no drugs have consistently induced a response rate greater than 20% [7].

Etoposide (VP16-213), a semisynthetic podophyllotoxin derivative, is an inhibitor of DNA topoisomerase II resulting in stabilisation of DNA strand breaks [8]. Etoposide has demonstrated considerable efficacy against a broad spec-

Correspondence to G. Giaccone.
Received 6 Jan. 1997; revised 26 Mar. 1997; accepted 1 Apr. 1997.

trum of tumours [9]. The drug is thought to act in the late S and early G2 phases of the cell cycle, and is highly schedule dependent [10]. Repeated administration of etoposide has been reported to be superior to a 24 h infusion in small cell lung cancer (SCLC) [11]. The same investigators also reported that an 8-day intravenous (i.v.) regimen versus the 5-day regimen showed no improvement in efficacy [12]. Daily oral etoposide showed a 23% response rate and was well tolerated in refractory SCLC [13]. Activity of oral etoposide has also been reported in patients with germ cell tumours who previously failed on cisplatin, etoposide or both drugs [14] and heavily pretreated patients with lymphoma [15]. Interestingly, partial responses have been reported in 5 lymphoma patients out of the 9 previously treated with i.v. etoposide [15].

In mesothelioma, scanty data are available in the literature on the activity of etoposide on a small number of patients [16–18]. The EORTC LCCG initiated two consecutive phase II trials aimed at evaluating the efficacy and safety of i.v. and oral etoposide in malignant mesothelioma.

PATIENTS AND METHODS

Patient inclusion criteria for both trials were: histologically confirmed malignant pleural mesothelioma, no prior chemotherapy, no radiotherapy including all target lesions, radiologically bidimensionally or unidimensionally measurable lesions, the sole presence of pleural effusion was not acceptable as a parameter of response, no intracavitary cytotoxic drugs, ECOG performance status ≤ 2, age ≤ 75 years, white blood cell (WBC) count $\geq 3.5 \times 10^9/l$, platelets $\geq 100 \times 10^9/l$, bilirubin $\leq 25 \mu mol/l$, and informed consent. Patients should not have had any signs of chronic disease, active infection, other malignancies or symptoms of central nervous system (CNS) metastases. For responding cases, a pathology review by the EORTC mesothelioma pathology panel was mandatory. Only cases classified as definite, probable or possible mesothelioma [19] were considered eligible for these two trails.

Tumour extension was classified according to a system modified by Butchart and associates [20, 21] as follows: stage I, tumour confirmed to homolateral visceral pleura, lung or pericardium; stage IIA, tumour invading chest wall or involving mediastinum (oesophagus, heart) or presence of lymph nodes within the chest; stage IIB, involvement of contralateral pleura; stage III, tumour penetrating diaphragm to involve peritoneum directly or the presence of lymph nodes outside the chest; stage IV, distant blood-borne metastases.

In the first trial, etoposide was given i.v. at a dose of 150 mg/m^2 on days 1, 3 and 5 every 3 weeks. The drug, supplied as a 100 mg solution in ampoules, was dissolved in normal saline at a maximum concentration of 0.6 mg/ml. The infusion time was at least 30 min. The second trial investigated etoposide given orally at a daily dose of 100 mg capsules (Vepesid) for 21 days followed by a 2-week treatment-free period, and then recycle. In both trials, the treatment was given until disease progression, intolerable toxicity or patient refusal.

The drug administration was postponed by 1 week in case of incomplete haematological recovery (WBC count $\geq 3.0 \times 10^9/l$ and platelets $\geq 100 \times 10^9/l$) from the prior course. If the treatment was delayed because of myelosuppression at scheduled retreatment, or if the WBC nadir during the previous cycle was $< 1.0 \times 10^9/l$, drug dosage was reduced to 75%. If the treatment was delayed for 3 or more weeks, the treatment was discontinued. Dose escalation was not allowed.

The tumour was assessed by chest X-ray and computer tomography (CT) scan before starting the treatment and every three cycles thereafter. The response was classified according to the World Health Organization Criteria [22]. Duration of response and survival were estimated from the start of chemotherapy and the estimates at different time points were based on the Kaplan–Meier technique [23].

The sample size calculation was based on the two-stage Gehan's design [24] aiming at including 14 patients and then adding additional patients for each response seen in the first stage. This guarantees that the probability of an active treatment (real response rate $\geq 20\%$) exhibiting no response in the first 14 patients (that is, false-negative result) is 0.05 and allows estimation of the therapeutic effectiveness with a standard error of 10%.

RESULTS

Between April 1988 and October 1989, 49 patients were registered into the i.v. etoposide trial. Two patients were ineligible because histological diagnosis was considered "probably not a mesothelioma" in 1 patient and the ECOG performance status for the other patient was 3. The oral etoposide trial recruited 45 patients between April 1990 and February 1992. 4 patients were not eligible because of incorrect diagnosis (metastatic pancreatic carcinoma and thymoma) in 2, prior chemotherapy in 1 and the absence of measurable disease in another.

Patient and tumour characteristics are present in Table 1. The male/female ratio was 10:1. The i.v. trial recruited more patients with sarcomatous histological subtype than the oral etoposide trial. The majority of patients presented with a relatively early stage of the disease.

The median number of administered cycles was three in both trials and varied between 1 and 12 in the i.v. trial and between 1 and 7 in the oral trial. The median total dose of etoposide was 1350 mg/m^2 (maximum 5400 mg/m^2) and 6624 mg (maximum 14 700 mg) in the i.v. and oral trials, respectively.

In the i.v. trial, the dose was reduced because of myelosuppression in 3 cases, because of weight loss in 1 patient and because of dyspnoea in another patient. Delays were reported in 8 patients: 3 due to haematological toxicity, and 5 for reasons unrelated to toxicity. In the oral etoposide trial, dose reduction was documented in 3 patients: one because of poor general conditions and treatment-unrelated in 2 other patients. Treatment delays were reported for 5 patients in the oral etoposide trial: 2 due to haematological toxicity and 3 were considered unrelated to treatment.

In the i.v. trial, two early deaths were reported. One patient died 2 weeks after starting the treatment due to rapidly progressing disease, with no substantial toxicity. Another patient died at home 2 weeks after the start of the first cycle. During this cycle, no severe toxicity was reported. No autopsy was performed and a precise cause of death could not be established.

The most common side-effects were leucopenia, nausea, vomiting and alopecia (Table 2). In the i.v. trial, the median nadir values for leucocytes and platelets were $3.5 \times 10^9/l$ (range 0.5–9.0) and $255 \times 10^9/l$ (range 119–

Table 1. Patient and tumour characteristics at entry

Characteristic	Etoposide i.v. n	($n = 47$) (%)	Oral etoposide n	($n = 41$) (%)
Age (years)				
median	55		57	
(range)	(40–72)		(30–73)	
Sex				
male	45	(96)	35	(85)
female	2	(4)	6	(15)
ECOG performance status				
0	11	(23)	13	(32)
1	26	(55)	21	(51)
2	10	(21)	7	(17)
Histological subtype				
epithelial	18	(38)	18	(44)
sarcomatous	21	(45)	6	(15)
mixed	3	(6)	5	(12)
undefined	5	(11)	12	(29)
Clinical stage				
I	15	(32)	12	(29)
IIA	23	(49)	18	(44)
IIB	1	(2)	2	(5)
III	3	(6)	7	(17)
IV	3	(6)	2	(5)
unknown	2	4	0	
Disease measurability				
bidimensionally	19	(40)	27	(66)
unidimensionally	28	(60)	14	(34)

639), with 6% and 0% grade 3–4 toxicity, respectively. In the oral trial, the median nadir values for leucocytes and platelets were $4.0 \times 10^9/l$ (range 0.9–12.6) and $274 \times 10^9/l$ (range 24–778), with 12% and 2% grade 3–4 toxicity, respectively. Hair loss was complete in 17% and 24% in the i.v. and oral trials, respectively. Nausea and vomiting were observed in 55% (grade 3–4 in 4%) and 66% (grade 3–4 in 10%) of the patients in the i.v. and oral trials, respectively. Drug fever was reported in a total of 7 patients; 2 in the i.v. trial and 5 in the oral trial. Mucositis, local phlebitis, diarrhoea and allergy were observed infrequently and were not severe.

In the i.v. trial, partial responses were documented in 2 patients (4%, 95% exact confidence interval: 1–15%). Stable disease was observed in 15 patients and 25 patients progressed on treatment. 2 patients died after only one cycle (see above). The response was not assessable in 3 other patients because they had received only one cycle: due to poor performance status in 1 patient, hypotension and pulmonary oedema (possibly due to cardiac toxicity) in another patient, and the third patient suffered from severe anaphylactic reaction (dyspnoea and bronchial spasm 2 min after the first infusion). One response lasted for 32 weeks and the other patient was lost to follow-up after 28 weeks with no progression. The median survival for all eligible patients was 29 weeks (Figure 1).

In the oral etoposide trial, 3 patients achieved partial response (7%, 95% exact confidence interval: 2–20%), 14 patients had stable disease, 22 progressed on treatment, 1 patient died after one cycle due to malignant disease and the response could not be evaluated in another patient, who received only one cycle due to severe thrombocytopenia leading to a haemorrhage. The three partial responses lasted

Table 2. Side-effects: worst grade reported during the treatment period

Side-effect	Etoposide i.v. ($n = 47$)		Any toxicity grade 3–4		Oral etoposide ($n = 41$)		Any toxicity grade 3–4	
	n	(%)	n	(%)	n	(%)	n	(%)
Leucopenia	27	(57)	3	(6)	20	(49)	5	(12)
Thrombocytopenia	0	(0)	0	(0)	3	(7)	1	(2)
Nausea/vomiting	26	(55)	2	(4)	27	(66)	4	(10)
Diarrhoea	4	(9)	0	(0)	5	(12)	1	(2)
Liver toxicity	0	(0)	0	(0)	5	(12)	0	(0)
Drug fever	2	(4)	0	(0)	5	(12)	0	(0)
Allergy	3	(6)	1	(2)	1	(2)	0	(0)
Cutaneous reaction	0	(0)	0	(0)	1	(2)	1	(2)
Alopecia	22	(47)	8	(17)	29	(71)	10	(24)
Infection	2	(4)	0	(0)	3	(7)	0	(0)
Mucositis	2	(4)	1	(2)	2	(5)	0	(0)

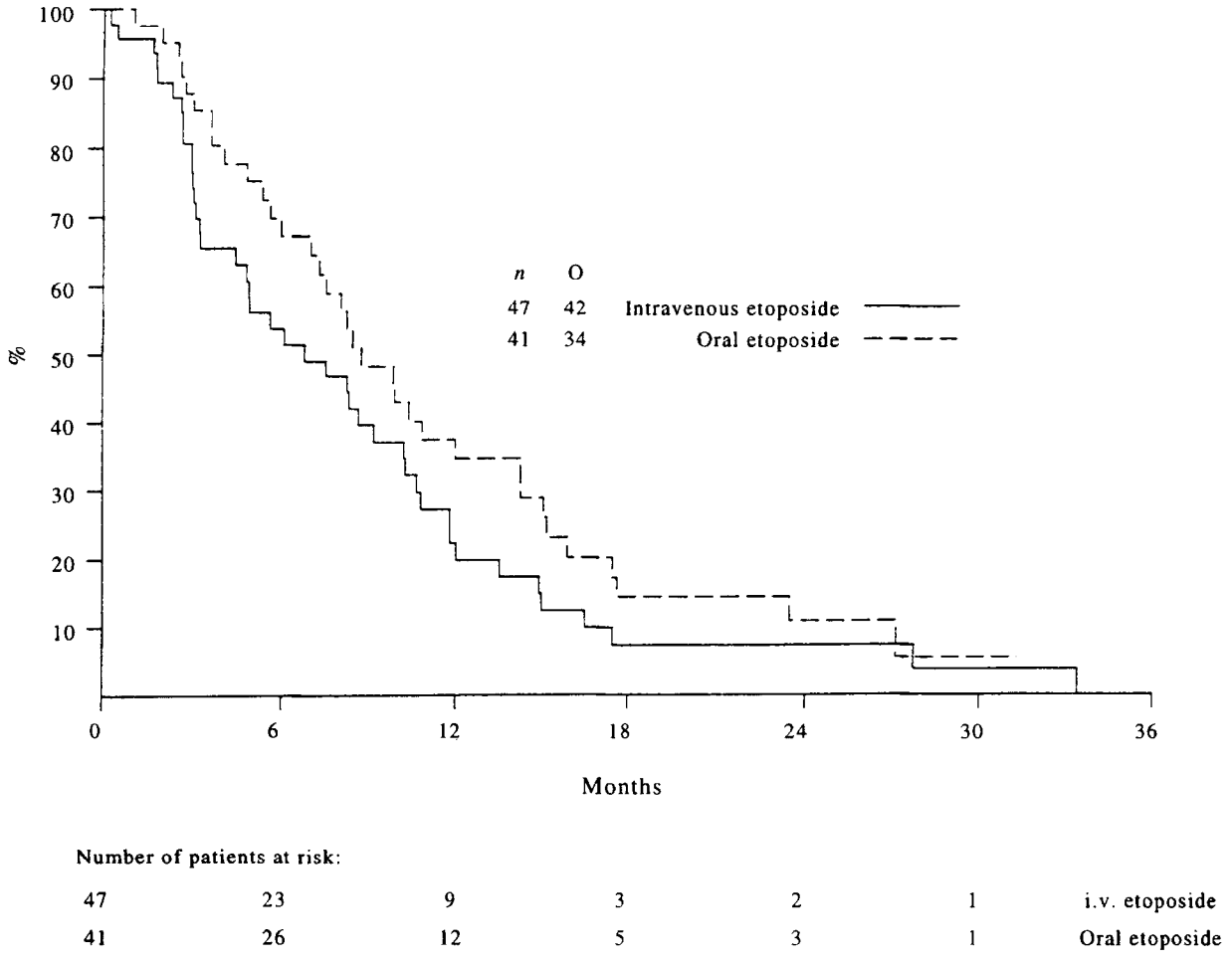

Figure 1. Duration of survival (*n*, number of patients; O, observed number of events).

for 26, 30 and 52 weeks. The median survival for eligible patients was 37 weeks (Figure 1).

DISCUSSION

Both trials demonstrate a low activity of etoposide in mesothelioma when given i.v. for three alternative days or with chronic oral route. We could not prove any advantage of giving oral etoposide for a prolonged period. Oral etoposide is known to yield a considerable intrapatient and interpatient variation in drug bioavailability [25]. Assuming a 40–50% oral bioavailability, the average actually delivered total dose in the oral etoposide trial was roughly equivalent to that in the i.v. trial (6624 mg and 1350 mg/m^2, respectively).

Toxicity in general was similar for the two different routes of administration. However, the relatively modest leucopenia, especially in the oral route trial, could be partially explained by the protocol requirement for haematological evaluation. In the i.v. trial, blood cell counts were required weekly during the first two cycles and were thereafter mandatory only prior to starting the next cycle. In the oral trial, a complete blood count was required only at days 22, 29 and 36 of each cycle.

The accrual of both trials was higher than initially planned, because some partial responses were not subsequently confirmed by the study coordinator. These unconfirmed responses led to the continuation of recruitment to over 40 patients in both trials, in accordance with the study design.

We observed a difference in survival in favour of the oral route. However, one should not overinterpret the apparent difference in the duration of survival because of the lack of randomisation, and because of the poor activity of the treatment. This difference could be simply due to an imbalance in some prognostic factors such as sex (4% females in the i.v. trial versus 15% in the oral trial) or having a purely sarcomatous histological subtype (50% in the i.v. trial versus 21% in the oral trial).

Because etoposide combined with cisplatin has been shown to be synergistic in animal models [26] and has proven efficacious in other tumours, two studies investigated this combination in malignant pleural mesothelioma. This combination gave only three partial responses in 27 eligible patients (11%) in a Canadian study [27]. In another small study of 25 patients, oral etoposide for 15 days was associated with high-dose weekly cisplatin [28]; a response rate of 24% (one complete response and five partial responses) was observed. This somewhat encouraging result may well be explained by the intensive cisplatin dosing but because of the small number of patients enrolled, the confidence intervals of this study are rather large.

In conclusion, we do not think that further investigation of etoposide alone in mesothelioma is to be recommended in the dose and schedule administered in our two studies.

1. De Klerk NH, Armstrong BK. The epidemiology of asbestos and mesothelioma. In Henderson DW, Shelkin KB, Langlois SLP, Whitaker D, eds. *Malignant mesothelioma.* New York, Hemisphere, 1992, 223–243.
2. Chailleux E, Pioche D, Chopra S, *et al.* Epidemiologie du mesotheliome pleural malin dans la region de Nantes-Saint Naziare. Evolution 1956–1992. *Rev Mal Respir* 1995, **12**, 353–357.
3. Mowe G, Andersen A, Osvoll P. Trends in mesothelioma incidence in Norway 1960–1988. *Toxicol Ind Health* 1991, 7, 47–52.
4. Connelly RR, Spirtas R, Myers MH, *et al.* Demographic patterns for mesothelioma in the United States. *J Natl Cancer Inst* 1987, **78**, 1053–1560.
5. Enterline PE, Henderson VL. Geographic patterns for female pleural mesothelioma deaths for 50 states. *J Natl Cancer Inst* 1987, **79**, 31–37.
6. Walker AM, Loughlin JE, Freidlander ER, *et al.* Projections of asbestos-related disease 1980–2009. *J Occup Med* 1983, **25**, 409–425.
7. Ong ST, Vogelzang NJ. Chemotherapy in malignant mesothelioma: A review. *J Clin Oncol* 1996, **14**, 1007–1017.
8. Chen GL, Yang L, Rowe TC, *et al.* Non-intercalative antitumor drugs interfere with the breakage–reunion reaction of mammalian DNA topoisomerase II. *J Biol Chem* 1984, **259**, 9182.
9. O'Dwyer PJ, Leyland-Jones B, Alonso MT, *et al.* Etoposide (VP16-213). Current status of an active anticancer drug. *N Engl J Med* 1985, **312**, 692–700.
10. Clark PI, Slevin ML. The clinical pharmacology of etoposide and tenoposide. *Clin Pharmacokinet* 1987, **12**, 223–252.
11. Slevin ML, Clark PI, Joel SP, *et al.* A randomized trial to evaluate the effect of schedule on the activity of etoposide in small cell lung cancer. *J Clin Oncol* 1989, **7**, 1333–1340.
12. Clark PI, Slevin ML, Joel SP, *et al.* A randomized trial of two etoposide schedules in small-cell lung cancer: the influence on efficacy and toxicity. *J Clin Oncol* 1994, **12**, 1427–1435.
13. Einhorn LH, Pennington K, McClean J. Phase II trial of daily oral VP-16 in refractory small cell lung cancer: a Hoosier Oncology Group study. *Semin Oncol* (Suppl 2) 1990, **17**, 32–35.
14. Miller JC, Einhorn LH. Phase II study of daily oral etoposide in refractory germ cell tumors. *Semin Oncol* (Suppl 2) 1990, **17**, 36–39.
15. Hainsworth JD, Johnson DH, Frazier SR, Greco FA. Chronic daily administration of oral etoposide in refractory lymphoma. *Eur J Cancer* 1990, **26**, 818–821.
16. Nissen NI, Larson V, Petersen H, Thompson K. Cancer chemotherapy. *Chemother Rep* 1972, **56**, 769–777.
17. Falkson G, Van Dijk JJ, Van Eden EB, Van Merwe AM, Van den Berg JA, Falkson H. A clinical trial of the oral form of 4'-demethyl-epipodophyllotoxin-beta-D ethylidene glucoside (NSC 141540) VP16-213. *Cancer* 1975, **35**, 1141–1144.
18. Nissen NI, Dombernowsky P, Hansen H, Larson V. Phase I clinical trial of an oral solution of VP-16-213. *Cancer Treat Rep* 1976, **60**, 943–945.
19. Van Gelder T, Hoogsteden HC, Vandenbroucke JP, Van der Kwast TH, Planteydt HT. The influence of the diagnostic technique on the histopathological diagnosis in malignant mesothelioma. *Virchows Arch A Pathol Anat* 1991, **418**, 315–317.
20. Butchart EG, Aschcroft T, Barnsley WC, *et al.* Pleuropneumonectomy in the management of diffuse malignant mesothelioma of the pleura. Experience with 9 patients. *Thorax* 1976, **31**, 15–24.
21. Mattson K. Natural history and clinical staging of malignant mesothelioma. *Eur J Resp Dis* 1982, **63**, 87.
22. World Health Organization. *Handbook for Reporting Results of Cancer Treatment.* Geneva, WHO Offset Publication number 48, 1979.
23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
24. Gehan EA. The determination of the number of patients required in a preliminary and follow-up trial of a new therapeutic agent. *J Chron Dis* 1961, **13**, 346–353.
25. Harvey VJ, Slevin ML, Joel SP, *et al.* Variable bioavailability following repeated oral doses of etoposide. *Eur J Cancer Clin Oncol* 1985, **21**, 1315–1319.
26. Schabel FM, Trader MW, Laster WR, *et al.* Cis-dichlorodiammineplatinum (II): combination chemotherapy and cross resistance studies with tumors in mice. *Cancer Treat Rep* 1979, **63**, 1459–1473.
27. Eisenhauer EA, Evans WK, Murray N, *et al.* A phase II trial of VP-16 and cisplatin in patients with unresectable malignant mesothelioma. *Investigational New Drugs* 1988, **6**, 329.
28. Planting AST, van der Burg MEL, Goey SH, *et al.* Phase II study of a short course of weekly high-dose cisplatin combined with long-term oral etoposide in pleural mesothelioma. *Ann Oncol* 1995, **6**, 613–615.

Acknowledgements—This publication was supported by grant numbers 5U10-CA11488-20–5U10-CA11488-26 from the National Cancer Institute (Bethesda, Maryland, U.S.A.). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.