Combined Cisplatin, Doxorubicin, and Mitomycin for the Treatment of Advanced Pleural Mesothelioma

A Phase II FONICAP Trial

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BACKGROUND. In a previous FONICAP trial, the combination of doxorubicin (D) and cisplatin (P) yielded an objective response rate of 25% and a subjective response rate of 50% in patients with mesothelioma. In human mesothelioma cell lines, mitomycin (M) showed a synergic activity with P and in a recent randomized study, the combination of M and P showed slightly superior activity when compared with the PD regimen.

METHODS. The authors tested the activity and toxicity of a combination chemotherapy regimen including P, 60 mg/m^2, D, 60 mg/m^2, and M, 10 mg/m^2, all by intravenous infusion on Day 1 every 28 days in a Phase II study.

RESULTS. Twenty-four chemotherapy-naive mesothelioma patients were enrolled in the study. Patient characteristics were the following: the median age was 58 years; the median performance status was 1; there were 6 Stage I patients, 15 Stage II patients, 2 Stage III patients, and 1 Stage IV patient; and 10 patients had previous asbestos exposure. All patients had pretreatment symptoms: 13 had chest pain, 9 had pleural effusion, and 7 had dyspnea. A total of 78 cycles of chemotherapy were administered. The only significant side effect was myelosuppression, with only 9.5% of patients having Grade 4 toxicity. Among 23 patients evaluable for response, 5 achieved a partial response (20.8%; 95% confidence interval, 7.1–42.1%), 9 had stable disease, and 9 had progressive disease (including 1 early death). One patient was not evaluable because of treatment refusal. A clinical improvement was observed in 7 of 24 patients (29%).

CONCLUSIONS. The combination of PDM in patients with pleural mesothelioma is feasible and moderately active. However, the observed level of activity is similar to that obtained with other two-drug regimens. ***Cancer* 1997;79:1897–902.**
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Malignant pleural mesothelioma is a relatively rare neoplasm deriving from pleural mesothelium that causes approximately 0.4% of all cancer deaths.[1] Approximately 2000 new cases of pleural mesothelioma are diagnosed in the U. S. each year; in Italy, 910 deaths were recorded in 1991. In addition, epidemiologic data from the United Kingdom indicate that mesothelioma deaths will continue to increase in the next 20 years.[2]

Epidemiologic studies have shown an association between asbestos exposure and pleural mesothelioma.[3] The latency period from asbestos exposure to development of disease ranges from 20 to 40 years.[4] Therefore, although exposure to asbestos in the workplace has been greatly reduced with recent legislation, oncologists will continue

to face this disease for many decades. The prognosis of malignant mesothelioma is bleak and, despite a prevalently local evolution, the median survival time from diagnosis ranges from only 6 to 15 months.[5] Local treatments such as aggressive surgery or radical radiotherapy are feasible only in a minority of patients, are burdened by high morbidity and mortality rates, and yield long term survival in <25% of cases.[6,7] Because the majority of patients present at diagnosis with locally advanced disease, making them unsuitable for regional treatment, systemic therapy is often the only available therapy for patients with mesothelioma.

Antineoplastic drug activity has been tested in many Phase II studies but, due to the small number of patients enrolled and the difficulty in response assessment typical of this neoplasm, results are inconclusive.

Data from many studies, recently reviewed by Hansen and Vogelzang,[8,9] show that systemic chemotherapy results in an objective response in <20% of cases. Doxorubicin and cisplatin (as single agents or in combination) are the most widely tested drugs, resulting in a 15–20% response rate. In a previous FONICAP study, the authors reported an activity of 25% using a combination of cisplatin and doxorubicin; notably, nearly 50% of patients experienced a symptomatic improvement.[10] Mitomycin as a single agent showed a 21% response rate.[11] Interestingly, when tested in vitro on human mesothelioma cell lines, mitomycin showed a synergic activity with cisplatin.[12] In vivo, the combination of mitomycin and cisplatin has activity similar to that of the cisplatin-doxorubicin regimen.[13] On this basis, the authors designed a Phase II study with the aim of testing the toxicity and activity of a three-drug regimen including cisplatin, doxorubicin, and mitomycin in patients with advanced pleural mesothelioma.

PATIENTS AND METHODS

Patients with histologically proven malignant mesothelioma of the pleura were considered for this study. Surgery, thoracoscopy, or fine-needle biopsy were all considered acceptable techniques to obtain tumor tissue adequate for diagnosis. Cytologic diagnosis alone was not considered adequate. Histologic diagnosis had to be supported by appropriate immunohistochemical stainings including Carcinoembryonic antigen+, vimentin+, and keratin+. Specimens and slides were centrally reviewed. Other eligibility criteria included: age ≤ 75 years, performance status (PS) ≤ 2, measurable or evaluable disease according to World Health Organization (WHO) criteria,[14] normal renal, hepatic, and cardiac function, and no previous systemic chemotherapy. Due to the uncertain impact of chemotherapy on the survival of pleural mesothelioma patients, only symptomatic patients were enrolled. Pretreatment workup included history, physical examination, thoracic computed tomography (CT) scan and chest X-ray, abdominal CT scan or ultrasound, baseline blood tests (complete blood cell counts and chemistry), and electrocardiogram. The staging system proposed by Butchart et al.[7] was used in this study. Patients with Stage II–IV disease were eligible; patients with Stage I were also eligible if their tumors were judged to be inoperable by a thoracic surgeon. All Stage I patients had to have bulky disease with diffuse pleural thickening of at least 1 cm. Patients with pleural effusion as the only evidence of disease were not eligible.

Tumor assessment was made according to the WHO criteria[14] by repeating thoracic CT scan after two or three cycles of chemotherapy. Any other previously abnormal tests was also repeated at the same time. Objective responses had to be reviewed by a panel of experts including a radiologist (C.F.).

Eligible patients received cisplatin, 60 mg/m^2, doxorubicin, 60 mg/m^2, and mitomycin, 10 mg/m^2 given by intravenous infusion on Day 1 every 4 weeks. No dose reduction was applied. In case of incomplete hematologic recovery on Day 28, chemotherapy was postponed by 1 week.

In the absence of clinical or radiologic evidence of progression and severe toxicity, chemotherapy was continued for a maximum of six cycles. Toxicity was evaluated according to WHO criteria[14] and survival analysis was made by means of the Kaplan–Meier method.

Simon's minimax two-stage design for Phase II clinical trials was used to calculate the sample size.[15] The sample size was calculated based on the following assumptions: alpha error = 0.5, beta error = 0.20, P0 (clinically uninteresting true response rate) = 10%, and P1 (sufficiently promising true response rate) = 30%. Fifteen patients had to be accrued in the first stage; if no responses were observed, the trial was stopped. Otherwise, accrual continued until 25 patients were evaluable for response and a second test was performed. The drug combination had to be accepted with ≥5 responses in 25 evaluable patients.

RESULTS

From April 1990 to April 1995, a total of 24 patients with pleural malignant mesothelioma were enrolled in the study.

The patient characteristics are shown in Table 1. All but one patient were male; the median age was 58 years and the median PS was 1; 6 patients were Stage 1, 15 were Stage II, 2 were Stage III, and 1 was Stage

TABLE 1
Patient Characteristics

Entered	24
Median age (range) (yrs)	58 (44–66)
M/F	23/1
Median PS	1
Stage	
I	6
II	15
III	2
IV	1
Histology subtype	
Epithelial	18
Mixed	4
Undifferentiated	2
Asbestos exposure	
Yes	10
No	14
Symptoms	
Pain	13
Dyspnea	7
Fever	2
Cough	4
Pleural effusion	
Yes	9
No	15

M: male; F: female; PS: performance status.

IV. Histologic subtype was defined for all patients: 18 epithelial, 4 mixed, and 2 undifferentiated. All patients had uni- or bidimensionally measurable disease. Only four patients underwent surgery prior to chemotherapy (three underwent decortication and one underwent exploratory thoracotomy) and two patients received prior treatment with systemic interferon. Prior asbestos exposure was demonstrable in ten patients. Pretreatment symptoms included thoracic pain (13 patients), dyspnea (7 patients), cough (4 patients), and fever (2 patients). Nine patients had a significant pleural effusion at presentation. A total of 78 cycles of chemotherapy were administered and all patients received a mean of 3 cycles. All patients were evaluable for toxicity and all but one were evaluable for response. Five patients (20.8%, 95% confidence interval, 7.1–42.1%) obtained a >50% tumor reduction (Table 2). Two examples of those responses are illustrated in Figure 1. Stable disease was observed in nine patients and eight patients had progressive disease; one patient died early after the first cycle of chemotherapy and one patient was not evaluable because of treatment refusal after the first cycle. All responding patients had a clinical improvement and only two patients with stable disease had a symptom reduction during treatment (giving an overall clinical improvement rate of 29%). Duration of response was 8+, 8, 7, 7, and 6 months, respectively. Median survival time was 45.5 weeks and the probability of survival at 1 and 2 years was 30% and 0.6%, respectively.

TABLE 2
Response to Treatment

	No. of patients	%
Entered	24	
PR	5	20.8
SD	9	37.5
P	8	33.3
ED	1	4.2
Refused treatment	1	4.2
Clinical improvement	7	29.2

PR: partial response; SD: stable disease; P: progression; ED: early death.

The chemotherapy regimen was generally well tolerated; no toxic death occurred and only 2 patients (8%) developed Grade IV hematologic toxicity (both patients had Grade IV leukopenia and Grade IV thrombocytopenia). Only one patient had Grade 1 neuropathy (Table 3). Chemotherapy had to be suspended in the two patients with Grade IV toxicity after the second and fifth cycle, respectively. No dose reduction was applied.

DISCUSSION

A standard treatment for mesothelioma patients has not been clearly identified and the results of treatment with surgery, radiotherapy, and chemotherapy are still disappointing. Doxorubicin and cisplatin are among the most active drugs; however, they yield a response rate of < 20%. The Eastern Cooperative Oncology Group studied the activity of doxorubicin in 51 patients and observed a response rate of 14%.[16] Of 39 patients treated with cisplatin in 3 different studies, 13% obtained a partial response.[17–19] The combination of cisplatin and doxorubicin was first tested by Zidar et al. who reported four partial responses among six patients treated.[20] Results from additional trials using this combination were less encouraging. Henss et al. treated 19 mesothelioma patients and achieved 6 partial responses (32%).[21] The authors previously reported a 25% objective response rate among 26 patients along with a 50% rate of subjective improvement (mainly improvement of pain score).[10] In a recent cancer and leukemia group B (CALGB) trial, Chahinian et al. showed only a 14% response rate with the same combination.[13] The overall survival appears similar in all studies, ranging from 9 to 12 months. A preclinical study conducted by Chahinian et al. showed that the combination of mitomycin and cisplatin was the most

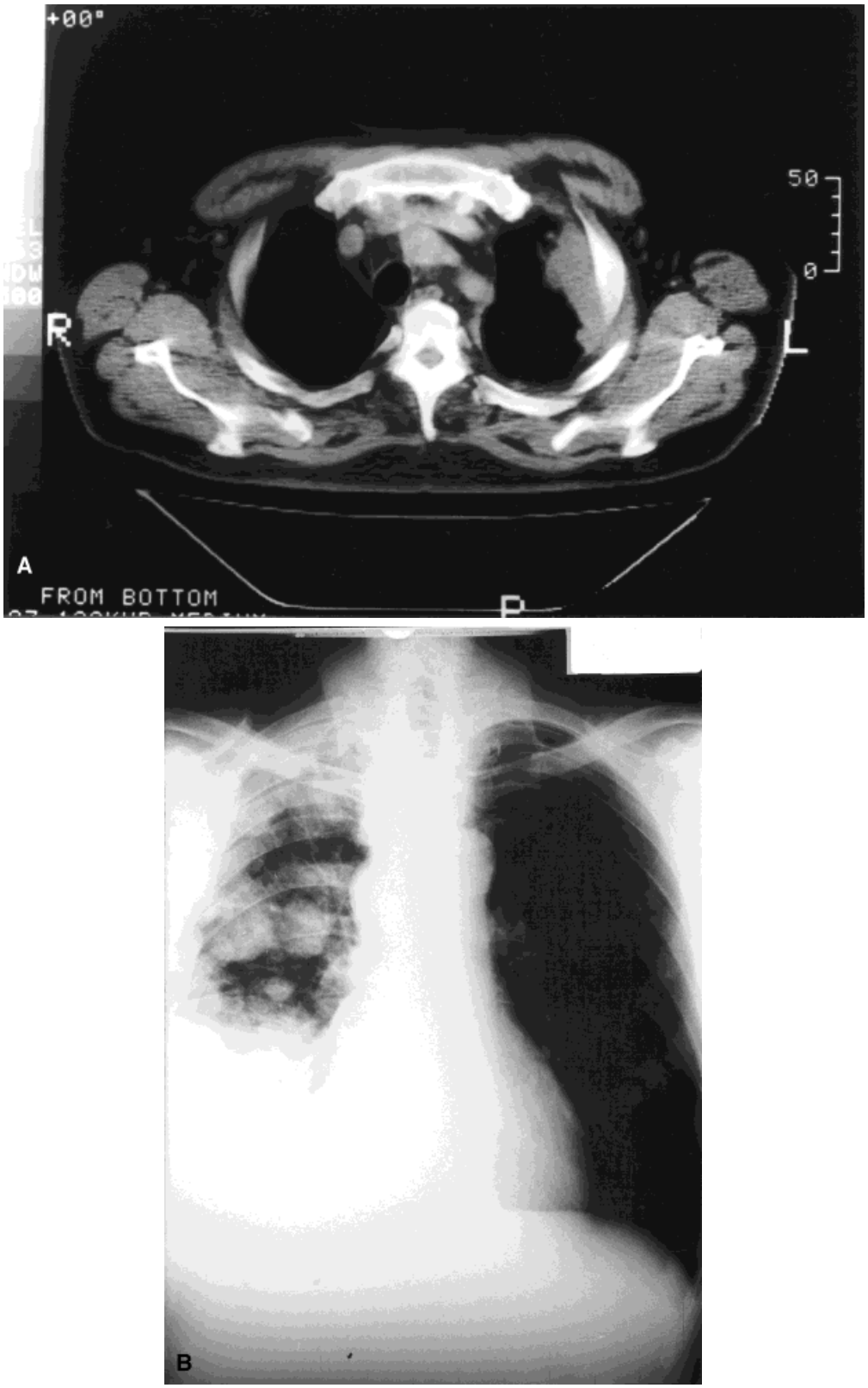
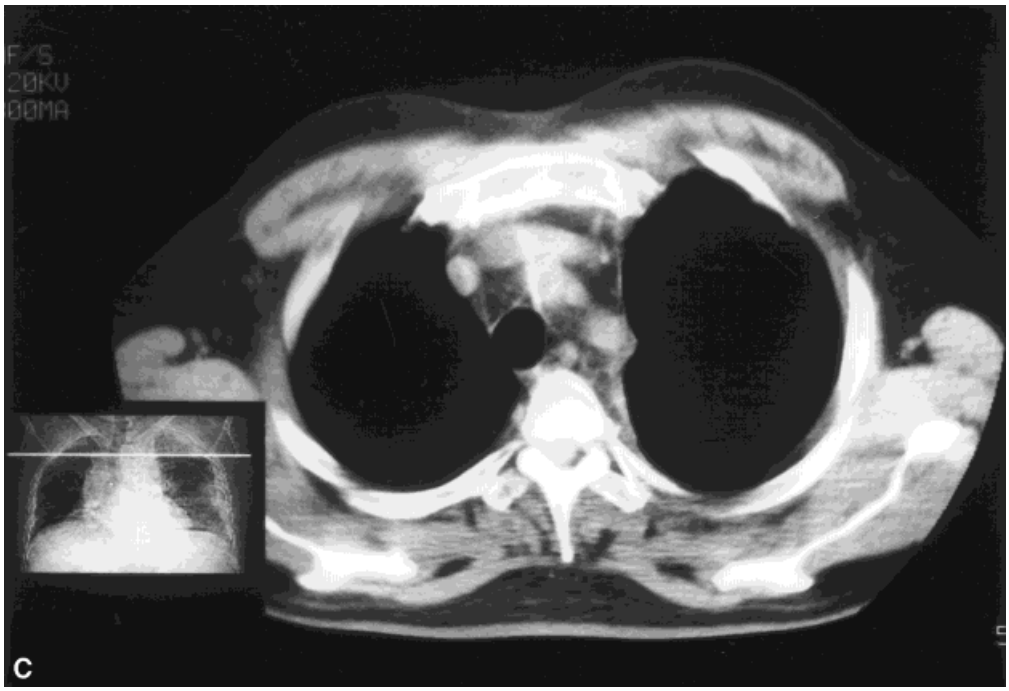


FIGURE 1. Computed tomography scan and X-ray of the chest from two patients who achieved a partial response. (A) First patient before treatment. (B) Second patient before treatment. (C) First patient after treatment. (D) Second patient after treatment.



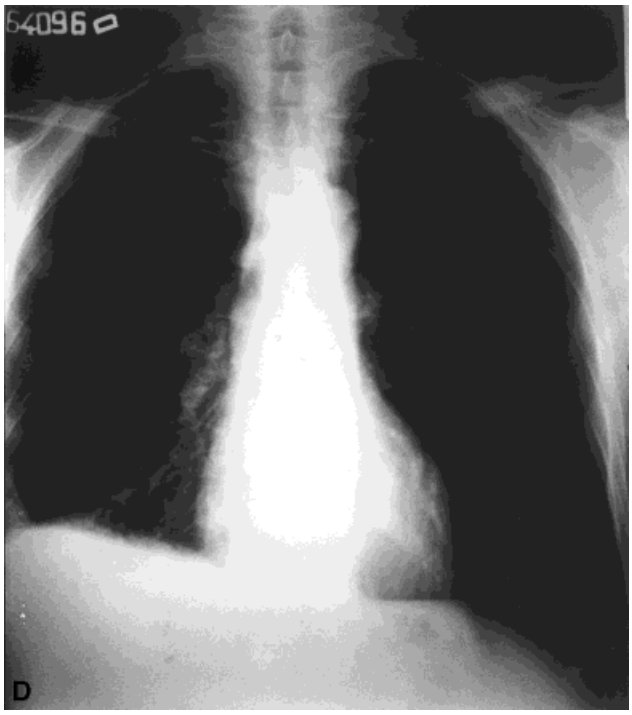


FIGURE 1. *(continued)*

effective regimen for xenografted human mesothelioma cell lines and the same authors reported a 33% response rate in a preliminary clinical trial.[12] In the CALGB study, 35 patients were treated with a combination of cisplatin and mitomycin and 26% obtained an objective partial response.[13]

In the current trial, mitomycin was added to a combination of cisplatin and doxorubicin. To the authors' knowledge, this is the only available study with this combination chemotherapy regimen for the treatment of pleural mesothelioma. The results of the current study show that the combination of cisplatin, dox-

TABLE 3
Toxicity

	Grade I		Grade II		Grade III		Grade IV	
Toxicity	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Leukopenia	1/25	4	2/25	8	1/25	4	2/25	8
Anemia	2/25	8	4/25	16	1/25	4	—	
Thrombocytopenia	—		—		1/25	4	2/25	8
Nausea and Emesis	8/25	32	5/25	20	—		—	
Neuropathy	1/25	4	—		—		—	

orubicin, and mitomycin is feasible and moderately active in mesothelioma patients. However, the response rate obtained (20.8%) and the overall survival are not different from those reported by other studies using two-drug regimens such as cisplatin-doxorubicin or cisplatin-mitomycin.

Based on these data, it can be concluded that cisplatin-containing two-drug regimens remain advisable when the decision to initiate a chemotherapy challenge is made in mesothelioma patients outside clinical trials. With regard to clinical research, testing new drugs should be considered a high priority in the study of malignant pleural mesothelioma.

REFERENCES

1. Silverberg E. Cancer statistics 1985. *CA Cancer J Clin* 1985; 351:19–35.
2. Peto J, Hodgson JT, Matthews FE, Jones JR. Continuing increase in mesothelioma mortality in Britain. *Lancet* 1995;345:535–9.
3. Doll R, Peto J. Asbestos. Effects of early exposure to asbestos. Health & Safety Commission. London: Her Majesty's Stationery Office, 1985.
4. Antman KH, Li FP, Osten R, Sugarbaker DJ, Herman T, Weissman C, et al. Mesothelioma: update to 3rd edition. In: DeVita VT Jr., Helleman S, Rosenberg SA, editors. (Cancer: principles and practice of oncology. 3rd edition.) Philadelphia PA: J.B. Lippincott, 1989:1–16.
5. Antman KH. Current concepts: malignant mesothelioma. *N Engl J Med* 1980;303:200–2.
6. Brady LW. Mesothelioma: the role of radiation therapy. *Semin Oncol* 1981;8:329–34.
7. Butchart E, Ashcroft T, Barnsky W, Holden MP. Pleuropneumonectomy in the management of diffuse malignant mesothelioma of the pleura: experience with 29 patients. *Thorax* 1976;31:15–24.
8. Hansen AK, Hansen HH. Chemotherapy in malignant mesothelioma: a review. *Cancer Chemother Pharmacol* 1991; 28:319–30.
9. Vogelzang NJ. Malignant mesothelioma: diagnostic and management strategies foe 1992. *Semin Oncol* 1992; 19(Suppl 11):64–71.
10. Ardizzoni A, Rosso R, Salvati F, Fusco V, Cinquegrana A, DePalma M, et al: Activity of doxorubicin and cisplatin combination chemotherapy in patients with diffuse malignant mesothelioma. *Cancer* 1991;67:2984–7.
11. Bajorin D, Kelsen D, Mintzer DM. Phase II trial of mitomycin in malignant mesothelioma. *Cancer Treat Rep* 1987;71:857–8.
12. Chahinian AP, Norton L, Holland JF, Szrajer L, Hart RD. Experimental and clinical activity of mitomycin C and cis-diamminedicloroplatinum in malignant mesothelioma. *Cancer Res* 1984;44:1688–92.
13. Chahinian AP, Antman K, Gautsou M, Carson JM, Suzuki Y, Modeas C, et al. Randomized phase II trial of cisplatin with mitomycin or doxorubicin for malignant mesothelioma by the Cancer and Leukemia Group B. *J Clin Oncol* 1993; 11:1559–65.
14. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1990;47:207–14.
15. Simon R. Optimal two stage design for phase II clinical trials. *Control Clin Trials* 1989;10:1–10.
16. Lerner HJ, Schoenfeld DA, Martin A. Malignant mesothelioma. The Eastern Cooperative Group (ECOG) experience. *Cancer* 1983;52:1981–5.
17. Samson MK, Baker LH, Benjamin RS, Lane M, Plager C. cis-Dichlorodiamminoplatinum in advanced soft tissue and bony sarcomas: a Southwest Oncology Group study. *Cancer Treat Rep* 1979;63:2027–9.
18. Dabouis G, Mevel BL, Corroller J. Treatment of diffuse pleural malignant mesothelioma by cis dichloro diammine platinum (CDDP) in nine patients. *Cancer Chemother Pharmacol* 1981;5:209–10.
19. Mintzer DM, Kelsen D, Frimmer D, Heelan R, Gralla R. Phase II high-dose cisplatin in patients with malignant mesothelioma. *Cancer Treat Rep* 1985;69:711–2.
20. Zidar BL, Pugh RP, Schiffer LM, Raju RN, Vaidya KA, Bloom RL, et al. Treatment of six of mesothelioma with doxorubicin and cisplatin. *Cancer* 1983;52:1788–91.
21. Henss H, Fiebig HH, Schildge J, Arnold H, Hasse J. Phase II study with the combination of cisplatin and doxorubicin in advanced malignant mesothelioma of the pleura. *Onkologie* 1988;11:118–20.