Acta Oncologica 29 (1990) Fasc. 8

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FIVE-DAY CONTINUOUS INFUSION OF CISPLATIN AND ETOPOSIDE IN NON-SMALL CELL LUNG CANCER

A phase II trial

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Abstract

Cisplatin (CDDP) and etoposide are synergistic in vitro: the aim of this study was to evaluate the efficacy of a continuous infusion (C.I.) of these 2 drugs in inoperable non-small cell lung cancer. Patients were to receive 3 courses of CDDP 20 mg/m^2/d in 1 l saline × 5d and etoposide 50 mg/m^2/d in 2 l saline × 5d —both in C.I.— every 3–4 weeks. Thirty patients have entered the study. Four were inevaluable for response. One patient got complete remission, 15 partial remission, 8 no change and 2 progressive disease. The response rate was 53.3% overall (95% confidence interval: 35–71%), and 61.5% for 26 assessable patients. Toxicity appeared to be acceptable despite 52% transient neutropenia — one patient died during aplasia— and 78% grade 1 to 3 nausea or vomiting. Treatment was stopped in only one case, and modified in 6 others. The high response rate that we observed, supports the idea of potentiation of the antineoplastic effect of CDDP and etoposide by C.I., in non-small cell lung cancer. These results must be confirmed in larger series before definitive conclusions can be drawn.

Key words: Chemotherapy, cisplatin, etoposide, phase II, non-small cell lung cancer.

Cisplatin (CDDP) and etoposide have significant therapeutic activity against advanced non-small cell lung cancer (NSCLC). Despite a response rate of only 10–19% in previously untreated patients (1), when used as a single agent, CDDP is one of the most active available agents for treatment of NSCLC. Etoposide gives a major response rate in only 7–11% when used as a single agent (2). The demonstration by Schabel et al. (3) of synergism between the 2 compounds in an experimental system has given rise to a number of clinical trials using their combination. Also, some clinical data suggest that CDDP and etoposide may act synergistically: in phase II trials, response rates in NSCLC varying from 18–52% have been published (4).

In clonogenic assays, these 2 drugs appear to be schedule-dependent (5). As suggested by a terminal half-life of approximately 11.5 h, the cell-cycle dependency and some preclinical schedule studies, divided doses of etoposide over several days appear to be more active than a single dose. Opinions concerning the stability of etoposide in solution have varied considerably between different studies. Clark et al. (6) stated that etoposide was found to be stable for 24 h at room temperature at a maximal concentration of 0.5 g/l in 0.9% NaCl or 5% dextrose. Continuous infusion of etoposide is well tolerated, but so far no clinical advantage has been found over fractionated daily doses (7). Earhart's experiment demonstrated that CDDP is stable in physiologic saline for at least 24 h (8). Phase I trials have demonstrated that continuous infusions of CDDP at a rate of 20–25 mg/m^2/d × 5 days are well tolerated, provided that at least 3 l of 0.9% NaCl solution per day are added to prevent nephrotoxicity (9–13).

Despite the obvious practical inconveniences and economic burden of hospitalization, a phase II trial was carried out in order to evaluate the efficacy of a 5-day, continuous infusion (C.I.) of these 2 drugs, in patients with advanced non-small cell lung cancer.

Material and Methods

Patients were required to have previously untreated, inoperable, biopsy-proven non-small cell lung cancer, evaluable or measurable tumour, life expectancy of more

Submitted 2 October 1989.
Accepted for publication 15 February 1990.

than 2 months, Karnofsky index $\geqslant 50$, WBC count $>4 \times 10^9$/l, platelet count $>100 \times 19^9$/l, serum creatinine <120 mmol/l), and no cardiac insufficiency. Oral informed consent was required.

Pretreatment evaluation included a complete history and physical examination, chest radiography, thoracic CT-scan, abdominal ultrasonography, bone scan and bronchoscopy. Staging was done according to the UICC recommendations (14).

Treatment schedule. According to the protocol, the patients should receive 3 courses (with one course every 3–4 weeks) of the following schedule: CDDP 20 mg/m^2/d in 1 l saline × 5d (d1 to d5) in C.I. and etoposide 50 mg/m^2/d in 2 l saline × 5d (days 1–5) in C.I. Two volumetric pumps were used. Furosemide 20 mg i.v. was given on day 1 to day 5. Non-metastatic patients were planned to receive thoracic irradiation after 3 courses of chemotherapy, while patients with metastases should continue with repeated courses till progression or unacceptable toxicity.

Methods for evaluation. The response was evaluated (15) 3 weeks after the end of the third course. All assessments of tumour response included at least clinical examination, chest radiography, chest CT-scan and fiberoptic bronchoscopy. Complete response (CR) was defined as complete disappearence of clinical evidence of disease, including endoscopic normalization with negative biopsies and aspirations; partial response (PR) as 50% or greater reduction of all target lesions without evidence of new lesions; no change (NC) as a $<50\%$ decrease in total tumour size or as a $>25\%$ increase in the size of one or more measurable or evaluable lesions; and progression (PD) as a 25% progression at any site and/or the appearence of new lesion(s). The toxicity was evaluated after each course according to WHO criteria (15). Weekly blood cell counts were obtained after the first course. Survival was analysed with the Kaplan-Meier method, from the first day of treatment.

Results

Patients' characteristics are shown in Table 1. Thirty previously untreated, male patients entered the study. All

Table 1

Patients' characteristics

No.	Age (years)	Karnofsky index	Histology	TNM	WHO grade toxicity		Response rate	Survival (weeks)
					PMN	vomiting		
1	51	70	LC	T4N2M0	0	2	PR	15
2	50	90	LC	T2N3M0	ineval	ineval	ineval	1
3	77	70	EPI	T4N0M0	3	3	PR	28
4	44	50	EPI	T4N1M1	3	2	PR	18
5	63	90	LC	T4N0M0	0	2	NC	97
6	56	70	EPI	T3N1M0	3	2	NC	21
7	65	90	EPI	T1N3M0	3	1	CR	98
8	56	80	ADN	T4N1M1	1	2	PR	43
9	58	70	EPI	T3N3M1	2	2	PR	48
10	67	70	LC	T4N3M1	3	2	PR	19
11	54	90	EPI	T3N2M0	3	2	PR	73
12	62	70	ADN	T3N3M1	ineval	1	ineval	3
13	71	80	EPI	T2N1M0	4	2	PR	55
14	65	70	ADN	T2N0M1	2	2	PR	63
15	60	70	EPI	T4N2M0	3	0	NC	45
16	41	70	ADN	T1N3M1	0	0	PROG	7
17	50	70	LC	T4N3M0	3	2	PR	19
18	57	70	ADN	T2N3M1	ineval	0	ineval	2
19	45	90	EPI	T3N2M0	0	2	NC	27
20	41	90	EPI	T3N2M0	0	2	PR	34
21	36	70	ADN	T1N0M1	4	2	PR	29
22	53	80	EPI	T4N3M0	0	0	NC	26
23	57	90	EPI	T2N3M0	2	0	PR	27
24	62	70	EPI	T4N2M0	3	3	PR	16
25	46	80	ADN	T4N1M0	3	1	PROG	11
26	47	70	ADN	T4N1M1	2	0	NC	17
27	55	90	EPI	T2N3M1	3	2	PR	21
28	65	50	EPI	T2N2M1	4	2	ineval	3
29	59	90	ADN	T4N2M0	0	2	PR	10
30	56	90	EPI	T2N0M0	0	0	NC	9

Abbreviations: ADN: adenocarcinoma; EPI: squamous cell carcinoma; LC: large cell carcinoma; ADS: adenosquamous carcinoma; CR: complete response; PR: partial response; NC: no change; PROG: progression.

Table 2

Toxicity, number of cases

WHO scale	Leukocyte*	P.M.N.**	Platelet	GI-Tract vomiting	GI-Tract diarrhea	Hair
0	10	8	25	6	23	3
1	4	1	0	3	1	5
2	4	4	0	16	2	6
3	7	11	0	2	0	10
4	2	3	1	0	0	0
9	3	3	3	3	4	6

Nadir of leukocytes (*) and polymorphonuclears (**).

patients were inoperable: there were 1 stage I and 1 stage II patient (their pulmonary function tests contraindicated operation), 4 stage IIIa, 12 stage IIIb, and 12 stage IV patients. The median Karnofsky index was 70 (50–90). There were 16 squamous cell carcinomas, 8 adenocarcinomas, 5 large cell carcinomas and 1 adenosquamous carcinoma. Only 26 patients are fully evaluable for response: one patient had a fatal grade IV leukopenia with sepsis, and 3 patients died during the first two months of treatment without progressive disease. The recorded efficacy was high: one CR, 15 PR, 8 NC and 2 PD. Inevaluable patients were classified as treatment failures. The major response rate was then 53.3% overall (95% confidence interval 35–71%), and 61.5% for 26 assessable patients. The response rate was similar in non-metastatic patients (55.5%) and metastatic patients (50%). At present (October 1989), the median survival time is 35 weeks overall. Twelve patients are alive with a median follow-up time of 22 weeks.

Toxicity (Table 2) was acceptable despite 52% transient neutropenia (nadir $< 10^9$/l for polymorphonuclears), 33% grade 3 or 4 leukopenia, 4% grade-4 thrombopenia, 78% grade 1 to 3 nausea or vomiting, and 11.5% grade 1–2 diarrhea, A reversible grade 1 to 3 alopecia was common (87.5%). Acute mucositis was not observed. Treatment was stopped in only one case (general condition), and modified in 6 others due to increase of serum creatinine ($n = 1$), transient aplasia ($n = 3$), GI tract intolerance ($n = 1$) and anasarca ($n = 1$). There was one septic death related to severe neutropenia. Transient hypertension easily controlled with furosemide was observed in a few patients.

Discussion

The benefit from chemotherapy in patients with NSCLC is difficult to evaluate. Table 3 shows the results of 19 phase II-III trials of the combination CDDP-etoposide in NSCLC published since 1981; C.I. trials are excluded. In these studies, the dose of CDDP per course varied from 60 mg/m^2 to 120 mg/m^2 and that of etoposide from 200 mg/m^2 to 480 mg/m^2. Major response rates varied from 0% to 58%. Our results (53% major response rate) matches the results reported by Splinter et al. (23). However, we observed only one CR among 26 fully evaluable patients. Many factors can influence response to chemotherapy and survival in NSCLC (34), and the small number of patients in our series must also be taken into account. The previous schedule used in our department (35) was a five-drug schedule including CDDP: the major response rate was only 31%, which, however, is not statistically different from the response rate in the present C.I. trial.

The problem of dosage and schedule may be crucial, and it is possible that some of the inconsistencies observed in the phase II studies are related to differences in dosage and treatment schedule. Responses in patients treated with CDDP appear to be dose-dependent and related to filterable (non-protein bound) drug levels (36–38). In the present trial, the dose of CDDP (100 mg/m^2) was close to the one used in bolus schedules. It has been shown that continuous infusion of CDDP at a dose rate of 25 mg/m^2/d gives increased exposure to non-protein bound drug levels as measured by the bioavailability. At the present time, it is unclear whether C.I. of CDDP increases its efficacy or not.

The gastrointestinal toxic effects of CDDP do not seem to be reduced by the C.I.: emesis appears to be less intense but to last for a longer time, and 78% of our patients experienced nausea or vomiting. The dose-limiting toxicity for C.I. schedules of CDDP and etoposide is myelosuppression. Continuous infusion of CDDP is said to be associated with more myelosuppression and magnesium wasting. A pharmacokinetic and toxicologic comparison of 5-day C.I. versus bolus CDDP in head and neck cancer patients showed more frequent myelosuppression and hypomagnesemia in the continuous-infusion patients, suggesting that the total exposure to free platinum contributes more to these toxicities than the peak levels (39).

Experimental and clinical studies suggest a marked dose and schedule dependency for etoposide: frequent administration appears to be more active than intermittent. In

Table 3

Cisplatin-etoposide in non-small cell lung cancer (1981–1989)

Ref. No.	Schedule (mg/m²/d × d)		Number of patients		Response rate			Survival (weeks)
	CDDP	etoposide	total	evaluable	PR	CR	%PR + CR	
(16)	60	120 × 3	107	94	32	4	38	30
(17)	60	120 × 3	108	—	19	—	17	30
(18)	60	120 × 3	41	37	5	2	17	36
(19)	60	120 × 3	16	16	0	0	0	32
(20)	60	120 × 3	30	30	4	2	20	52
(21)	80	80 × 3	40	40	8	1	28	32
(22)	40 × 2	100 × 3	52	47	11	—	21	14
(23)	80	100 d1–2 200 po d3–5	60	51	27	8	58	52
(24)	90	100 × 3	46	46	9	1	22	28
(25)	100	80 × 3	23	18	7	0	30	22
(26)	100	80 × 3	77	63	21	—	27	38
(27)	100	125 × 3	42	33	10	2	36	47
(28)	20 × 5	75 × 5	37	33	10	1	30	30
(29)	20 × 5	75 × 5	71	55	19	2	38	27
(30)	100	240 × 2	39	33	8	0	24	32
(17)	120	120 × 3	87	—	26	—	30	25
(31)	60 × 2	120 × 3	50	46	14	1	30	33
(32)	60 × 2	120 × 3	103	103	20	4	24	33
(33)	120	100 × 2	69	69	18	3	30	36

vitro data suggested a correlation between the dose of etoposide and its cytotoxicity, and between the dose × duration of exposure and the cytotoxicity (40). Early phase I trials have shown the optimal dose rate for 5-day infusion of etoposide as a single agent to be between 60 and 100 mg/m²/d (41, 42). Vogelzang (7) observed pronounced toxicity at 60 mg/m²/d × 5d and above that made further testing prohibitive due to granulocytopenic fever. Bennett et al. (43) recommended an etoposide dose for phase II trials of 150 mg/m²/d in 72-h infusion for patients with good performance status. In our study, only 250 mg/m² etoposide was administered per course, which is lower than the dose in the short-term infusion schedules reported in Table 3. Out of 27 patients fully evaluable for haematologic toxicity, we observed 3 grade IV neutropenia (including one septic death), and 11 grade III transient neutropenia. Our results thus indicate a greater haematologic toxicity of the concomitant C.I. of CDDP and etoposide. According to our data and data in the literature, an increase in the dose of CDDP and/or etoposide to 10–20% above our schedule should lead to major toxicity. Creagan et al. (44) recommend 20 mg/m²/d for CDDP and only 30 mg/m²/d for etoposide. Glynn et al. (45) observed a good tolerance and a comparable efficacy in 21 patients with the same dosage of CDDP and etoposide, but with a shorter C.I.

The solubility of etoposide makes C.I. of this drug inconvenient for an outpatient program. Furthermore, hydration with 3 l 0.9% saline is mandatory to prevent CDDP induced renal toxicity (10, 12). For the convenience of the patients it may be preferable to mix the 2 drugs as described by Lokich et al. (46) in a phase I clinical investigation. The high response rate that we observed in the present small series supports the idea that C.I. potentiates the antineoplastic effect of CDDP and etoposide, in NSCLC. However, our results must be confirmed in larger series before any definitive conclusion can be drawn.

ACKNOWLEDGMENT

The authors wish to thank the 'Comités Départementaux de l'Aisne, des Ardennes et de la Marne de la Ligue Française Centre le Cancer' for their financial contribution to this study.

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REFERENCES

1. Loehrer PJ, Einhorn LH. Cisplatin. Ann Intern Med 1984; 100: 704–13.
2. O'Dwyer PJ, Leyland-Jones B, Alonso MT, Marsoni S, Wittes RE. Etoposide (VP16-213). Current status of an active anticancer drug. New Eng J Med 1985; 312: 692–700.
3. Schabel FM, Tradel MW, Laster WR, Corbet TH, Griswold DP. Cis-dichlorodiammineplatinum(II): combination chemotherapy and cross-resistance studies with tumors of mice. Cancer Treat Rep 1979; 63: 1459–73.

4. Klastersky J. VP-16 and cisplatin in the treatment of non-small cell lung cancer. Semin Oncol 1985; 12 (Suppl. 2): 17–20.
5. Matsushima Y, Kanzawa F, Hoshi A, et al. Time-schedule dependency of the inhibiting activity of various anticancer drugs in the clonogenic assay. Cancer Chemother Pharmacol 1985; 14: 104–7.
6. Clark PI, Slevin ML. The clinical pharmacology of etoposide and teniposide. Clin Pharmacokinet 1987; 12: 223–52.
7. Vogelzang NJ. Continuous infusion chemotherapy: a critical review. J Clin Oncol 1984; 2: 1289–304.
8. Earhart RH. Instability of cis-dichlorodiammineplatinum in dextrose solution. Cancer Treat Rep 1978; 62: 1105–6.
9. Salem P, Hall SW, Benjamin RS, Murphy WK, Wharton JT, Bodey GP. Clinical phase I-II study of cis-dichlorodiammineplatinum(II) given by continuous IV infusion. Cancer Treat Rep 1978; 62: 1553–5.
10. Lokich JJ. Phase I study of cis-diamminedichloroplatinum(II) administered as a constant 5-day infusion. Cancer Treat Rep 1980; 64: 905–8.
11. Salem P, Khalyl M, Jabboury K, Hashimi L. Cis-diamminedichloroplatinum(II) by 5-day continuous infusion. A new dose schedule with minimal toxicity. Cancer 1984; 53: 837–40.
12. Posner MR, Skarin AT, Clark J, Ervin TJ. Phase I study of continuous-infusion cisplatin. Cancer Treat Rep 1986; 70: 847–50.
13. Posner MR, Ferrari L, Belliveau JF, et al. A phase I trial of continuous infusion cisplatin. Cancer 1987; 59: 15–8.
14. TNM Classification of malignant tumours. Fourth fully revised edition. International Union Against Cancer. Helmanek P, Sobin LH, eds. Berlin: Springer-Verlag, 1987.
15. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207–14.
16. Longeval E, Klastersky J. Combination chemotherapy with cisplatin and etoposide in bronchogenic squamous cell carcinoma and adenocarcinoma. A study by the EORTC Lung Cancer Working Party (Belgium). Cancer 1982; 50: 2751–6.
17. Klastersky J, Sculier JP. Chemotherapy of non-small cell lung cancer. Semin Oncol 1985; (Suppl. 6): 38–48.
18. Dhingra HM, Valdivieso M, Booser DJ, et al. Chemotherapy for advanced adenocarcinoma and squamous cell carcinoma of the lung with etoposide and cisplatin. Cancer Treat Rep 1984; 68: 671–3.
19. Pallares C, Piera JM, Barnadas A, Izquierdo A, Lopez Lopez JJ. Phase II trial of chemotherapy with cisplatin and etoposide in non-small cell lung cancer. Cancer Treat Rep 1986; 70: 677.
20. Cox JD, Samson MK, Herskovic AM, Abrams R, Koehler M. Cisplatin and etoposide before definitive radiation therapy for inoperable squamous carcinoma, adenocarcinoma and large cell carcinoma of the lung: a phase I-II study of the Radiation Therapy Oncology Group. Cancer Treat Rep 1986; 70: 1219–20.
21. Joss RA, Alberto P, Obrecht JP, et al. Combination chemotherapy for non-small cell lung cancer with doxorubicin and mitomycin or cisplatin and etoposide. Cancer Treat Rep 1984; 68: 1079–84.
22. Areco A, Chiesa G, Moreso J, et al. A randomized study of cisplatin (CDDP) etoposide (VP-16) with or without mitomycin C (MitoC) in advanced non-small cell lung cancer. Proceedings of ASCO, 1989; 8: 240.
23. Splinter T, Kok T, Kho S, et al. A multicenter phase II trial of cisplatin and oral etoposide (VP-16) in inoperable non-small cell lung cancer. Semin Oncol 1986; 13 (Suppl. 3): 97–103.
24. Mitrou PS, Graubner M, Berdel WE, et al. Cis-platinum (DDP) and VP 16-213 (etoposide) combination chemotherapy for advanced non-small cell lung cancer. A phase II clinical trial. Eur J Cancer Clin Oncol 1984: 20: 347–51.
25. Goldhirsch A, Joss RA, Cavalli F, Sonntag RW, Brunner KW. Cis-dichloro-diammineplatinum(II) and VP 16–213 combination chemotherapy for non-small cell lung cancer. Med Pediatr Oncol 1981; 9: 205–8.
26. Ceci G, Elonardi F, Bertusi M, et al. Randomized trial of cisplatin plus etoposide vs CAMP in advanced non-small cell lung cancer. Proceedings of ASCO, 1989; 8: 246.
27. Paccagnella A, Brandes A, Pappagallo GL, et al. Cisplatin plus vindesine versus cisplatin plus VP-16 versus doxorubicin plus cytoxan in non-small cell carcinoma of the lung. A randomized study. Tumori 1986; 72: 417–25.
28. Veronesi A, Zagonel V, Santarossa M, et al. Cis-platinum and etoposide combination chemotherapy of advanced non-oat cell bronchogenic carcinoma. Cancer Chemother Pharmacol 1983; 11: 35–7.
29. Veronesi A, Magri MD, Tirelli U, et al. Chemotherapy of advanced non-small cell lung cancer with cyclophosphamide, adriamycin, methotrexate and procarbazine versus cisplatin and etoposide: a randomized study. Am J Clin Oncol 1988; 11: 566–71.
30. Focan C, Le Hung L, Frere MH, Schallier D. Ambulatory combination chemotherapy with oral etoposide and cisplatin for advanced non-small cell lung carcinoma patients. A phase II study. Anticancer Res 1986; 6: 977–82.
31. Ardizzoni A, Canobbio L, Pronzato P, et al. Etoposide and high dose cisplatin in good risk patients with advanced squamous cell carcinoma and adenocarcinoma of the lung. Cancer Treat Rep 1986; 70: 891–2.
32. Rosso R, Ardizzoni A, Salvati F, et al. Etoposide vs etoposide and cisplatin in the treatment of advanced non-small lung cancer: a FONICAP randomized study. Semin Oncol 1988; 15 (Suppl. 7): 49–51.
33. Crino L, Darwish S, Corgna E, et al. Treatment of advanced non-small cell lung cancer (NSCLC): the 'UMBRIA' Cooperative study. Semin Oncol 1988; 15 (Suppl. 7): 52–5.
34. Aisner J, Hansen HH. Commentary: current status of chemotherapy for non-small cell lung cancer. Cancer Treat Rep 1981; 65: 979–86.
35. Maréchal F, Incatasciato C, Cattan C. Results of a five-drug combination chemotherapy in non-small cell lung cancer. A phase II trial. Acta Oncol 1988; 27: 537–9.
36. Belliveau JF, Posner M, Ferrari L, et al. Cisplatin administered as a continuous 5-day infusion: plasma platinum levels and urine platinum excretion. Cancer Treat Rep 1986; 70: 1215–7.
37. Gandara DR, Wold H, Perez EA, et al. Cisplatin dose intensity in non-small cell lung cancer: phase II results of a day 1 and day 8 high-dose regimen. J Natl Cancer Inst 1989; 81: 790–4.
38. Livingston RB. Cisplatin in the treatment of solid tumours: effect of dose and schedule. J Natl Cancer Inst 1989; 81: 724–5.
39. Forastiere AA, Belliveau JF, Goren MP, Vogel WC, Posner MR, O'Leary GP Jr. Pharmacokinetics and toxicity evaluation of five-day continuous infusion versus intermittent bolus cis-diamminedichloroplatinum(II) in head and neck cancer patients. Cancer Res 1988; 48: 3869–74.
40. Wolff SN, Grosh WW, Prater K, Hande KR. In vitro pharmacodynamic evaluation of VP-16-213 and implications for chemotherapy. Cancer Chemother Pharmacol 1987; 19: 246–9.

41. Lokich J, Corkery J. Phase I study of VP16-213 (etoposide) administered as a continuous 5-day infusion. Cancer Treat Rep 1981; 65: 887–9.
42. Aisner J, Van Echo DA, Whitacre M, Wiernick PH. A phase I trial of continuous infusion VP16-213 (etoposide). Cancer Chemother Pharmacol 1982; 7: 157–60.
43. Bennett CL, Sinkule A, Schilsky RL, Senekjan E, Choi KE. Phase I clinical and pharmacological study of 72-hour continuous infusion of etoposide in patients with advanced cancer. Cancer Res 1987; 47: 1952–6.
44. Creagan ET, Richardson RL, Kovach JS. Pilot study of a continuous five-day infusion of etoposide concomitant with cisplatin in selected patients with advanced cancer. J Clin Oncol 1988; 6: 1197–201.
45. Glynn P, Ficalora M, Higby D, et al. Etoposide/cisplatin infusion in non-small cell lung cancer: a well-tolerated, effective regimen. Proceedings of ASCO, 1989; 8: 230.
46. Lokich J, Anderson N, Bern M, Wallach S, Moore C, Williams D. Etoposide admixed with cisplatin. Phase I clinical investigation of 72-hour infusion. Cancer 1989; 63: 818–21.