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## Original Paper

# Evaluation of a Prediction Model of Cisplatin Dose Based on Total Platinum Plasma Concentration

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**The aim of this study was to validate prospectively a model of cisplatin dose adjustment. 27 patients (63 courses) with lung cancer were treated by a 5 day continuous infusion of cisplatin and etoposide. The dose of cisplatin was adjusted in order to reach a target plasma concentration of total platinum (TP) of 2000 μ/l at the end of the infusion. The target concentration was reached with a mean bias of 2.7% and a precision of 7.8%. The results were compared with those of a population of 38 patients (97 courses) with lung cancer and treated with the same protocol of chemotherapy, but without dose adjustment. The average dose adjustment was an increase of cisplatin dose of 20.2%. This augmentation was most important during the first course, decreasing during the following courses. There was also an increase in the etoposide AUC, although its dose was not modified. Toxicity to polymorphonuclear cells was significantly increased and was linked to etoposide AUC.** 

**Key words: cisplatin, dose adjustment, clinical pharmacokinetics, etoposide, clinical toxicity**
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## INTRODUCTION

THE RECOMMENDED doses of anticancer drugs are determined according to a compromise between efficacy and toxicity. Doses are usually standardised according to the patient's body surface area. This policy may actually increase the variability of the pharmacological response, since clearance of anticancer drugs is often not correlated to body surface area [1–3]. Given substantial interindividual variability [4–6], the standardised dose exhibits two pitfalls. Some patients will achieve high plasma drug concentration which can increase side-effects, whilst other patients have only low plasma drug concentration with reduced likelihood of clinical response [4]. Hence, when patients are in good physiological condition apart from their tumour, and they are able to eliminate anticancer drugs more quickly, their probability of responding to chemotherapy could be reduced. Unfortunately, the frequency of such 'underdosing' is not known, but it seems more appropriate to individualise the dose to the patient's ability to eliminate the drug [5, 6].

We evaluated the clearance of cisplatin with the plasma concentration of total platinum (TP), since TP is related to both toxicity [4, 7, 8] and efficiency [4, 7, 9–11]. Other investigators prefer to consider the platinum in ultrafilterable plasma, but there are several methodological objections to this measurement. Firstly, ultrafilterable platinum is an ill-defined mixture, including the parent compound, metabolites and platinum bound to low molecular weight species. The relative proportions of this mixture may vary with time, since cisplatin still reacts with protein in the test tube after the blood is drawn. Secondly, the ultrafiltration of plasma platinum is not reproducible between laboratories, since different groups use different filters and different protocols for cooling the blood samples.

In this study, we prospectively validated a model of cisplatin dose adjustment. This model has already been successfully tested retrospectively [12]. Our purpose was to achieve a plasma concentration of TP of 2000 μg/l at the end of a 120 h continuous infusion of cisplatin and etoposide. In previous studies, this concentration was associated with an increased likelihood of response to treatment, in the absence of toxicity. An evaluation of the prospective dose-adaptation method and its effect on toxicity is reported.

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## PATIENTS AND METHODS

*Patients and treatment*

To date, 27 new patients with lung cancer have entered the study and constitute the prospective evaluation population. The pharmacokinetic profile of cisplatin was followed during the first three courses. A total of 63 courses was studied. The reference group consisted of 38 previously untreated patients with non-small cell lung cancer (NSCLC). As in the evaluation group, the first three courses were known (total of 97 courses). These patients were treated identically to the evaluation group, but without the cisplatin dose adjustment. The characteristics of the patients of both populations are shown in Table 1. Cisplatin and etoposide (20 and 50 mg/m$^2$/day, respectively) were infused continuously over 5 days using volumetric pumps. The time interval between two cycles was 3–4 weeks. Blood was collected in heparinised tubes before the infusion, after 48 h and at the end of the infusion, quickly centrifuged and the plasma frozen until assayed.

*Drug assays and pharmacokinetic analyses*

Platinum assays were performed using flameless atomic absorption spectrophotometry [13]. The intra-assay coefficient of variation was 3.2% ($n = 10$) and the inter-assay coefficient of variation was 8.6% ($n = 20$). Etoposide was assayed as previously described [14]. The intra- and inter-assay coefficient of variation was 3.9% ($n = 10$) and 5.0% ($n = 13$), respectively. These assays are periodically checked by an interlaboratory quality control organised by the Groupe de Pharmacology Clinique (GPCO, Fédération Nationale des Centres de Lutte Contre le Cancer, 101 rue de Tolbiac, 75654 Paris cedex 13, France).

The pharmacokinetic parameters were calculated by using 'MicroPharm' software [15]. For cisplatin, a one compartmental model was fitted to the data using a Bayesian analysis [12]. The area under the concentration–time curve (AUC) was calculated by extrapolation to infinity. For etoposide, the AUC was calculated by multiplying the mean plasma concentration of etoposide by the infusion time (120 h). It is assumed that the overestimate of AUC made between time zero and the plateau (approximately 17–24 h after the beginning of the infusion) was balanced by the underestimate of AUC after the end of the infusion [16].

*Dose adjustment procedure*

The dose-adjustment procedure has been described previously [12]. Briefly, TP concentrations at times 0 and 48 h were used to calculate the patient pharmacokinetic parameters, using a Bayesian analysis. Then the dose of cisplatin to be infused from 72 to 120 h was calculated, based on the estimate of clearance. The dose for the following course was calculated using the data points 0, 48 and 120 h. All computations were performed with the MicroPharm program. Since we have observed significant intrasubject variation of TP clearance [12], pharmacokinetic parameters were verified during the subsequent course at times 0 and 48 h and the dose modified when necessary. In the adapted population, 26, 23 and 14 patients were included in the 1st, 2nd and 3rd courses respectively. 1 patient was not adapted during the first course by error. Toxicity was evaluated according to WHO criteria [17]. Patients were especially asked for paresthesis and hearing problems. An audiogram was usually performed in case of hearing problem, but no hearing/neurological problem was noticed during the first three courses.

*Statistical analysis*

The predicted and observed plasma TP concentrations were compared by calculating the mean, standard deviation (S.D.), bias (mean percentage of error) and precision (mean absolute percentage error). Patients' parameters were compared using the Student's $t$-test (age, weight and body surface area) and Fisher's exact test (two-tail; gender, histology, stage

*Table 1. Patients' characteristics*

| Parameters | Reference ($n = 38$) | Adapted ($n = 27$) | $P$ |
|---|---|---|---|
| Age (years ± S.D.) | 58.7 ± 9.3 | 60.0 ± 9.6 | ns |
| Weight (kg) | 64.1 ± 11.0 | 67.8 ± 12.9 | ns |
| Body surface area (m$^2$) | 173 ± 15 | 179 ± 18 | ns |
| Gender: M/F | 31/7 | 25/2 | ns |
| Histology | | | ns |
| Squamous carcinoma | 20 | 11 | |
| Adenocarcinoma | 14 | 10 | |
| Large cell carcinoma | 4 | 4 | |
| Small cell carcinoma | 0 | 2 | |
| Staging | | | ns |
| 1 | 1 | 0 | |
| 2 | 2 | 1 | |
| 3A | 10 | 4 | |
| 3B | 5 | 5 | |
| 4 | 20 | 17 | |
| Karnofsky index | | | 0.014 |
| 100–80 | 26 | 12 | |
| 70–50 | 7 | 14 | |
| 40–00 | 5 | 1 | |

Parameters of the reference and the dose-adjusted population were compared with the Student $t$-test (age, weight and body surface area) and Fisher's exact (two-tail) for the other parameters.

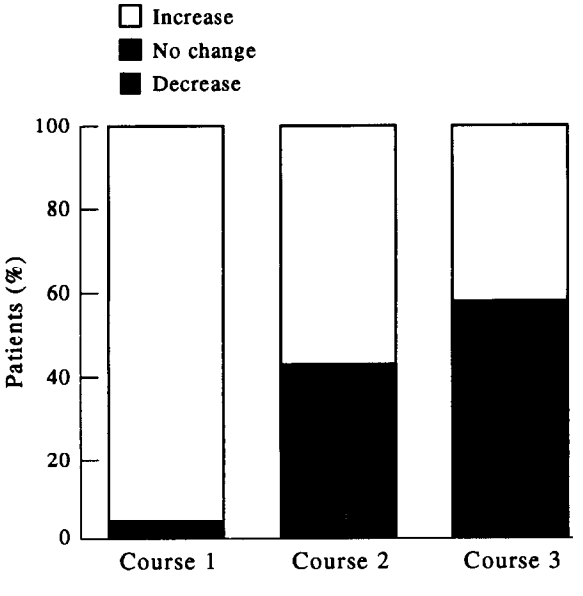


**Figure 1. Frequency of patients requiring a dose of cisplatin adjustment (more than 5%) and those whose dose remained unchanged in achieving a target TP concentration of 2000 µg/l.**

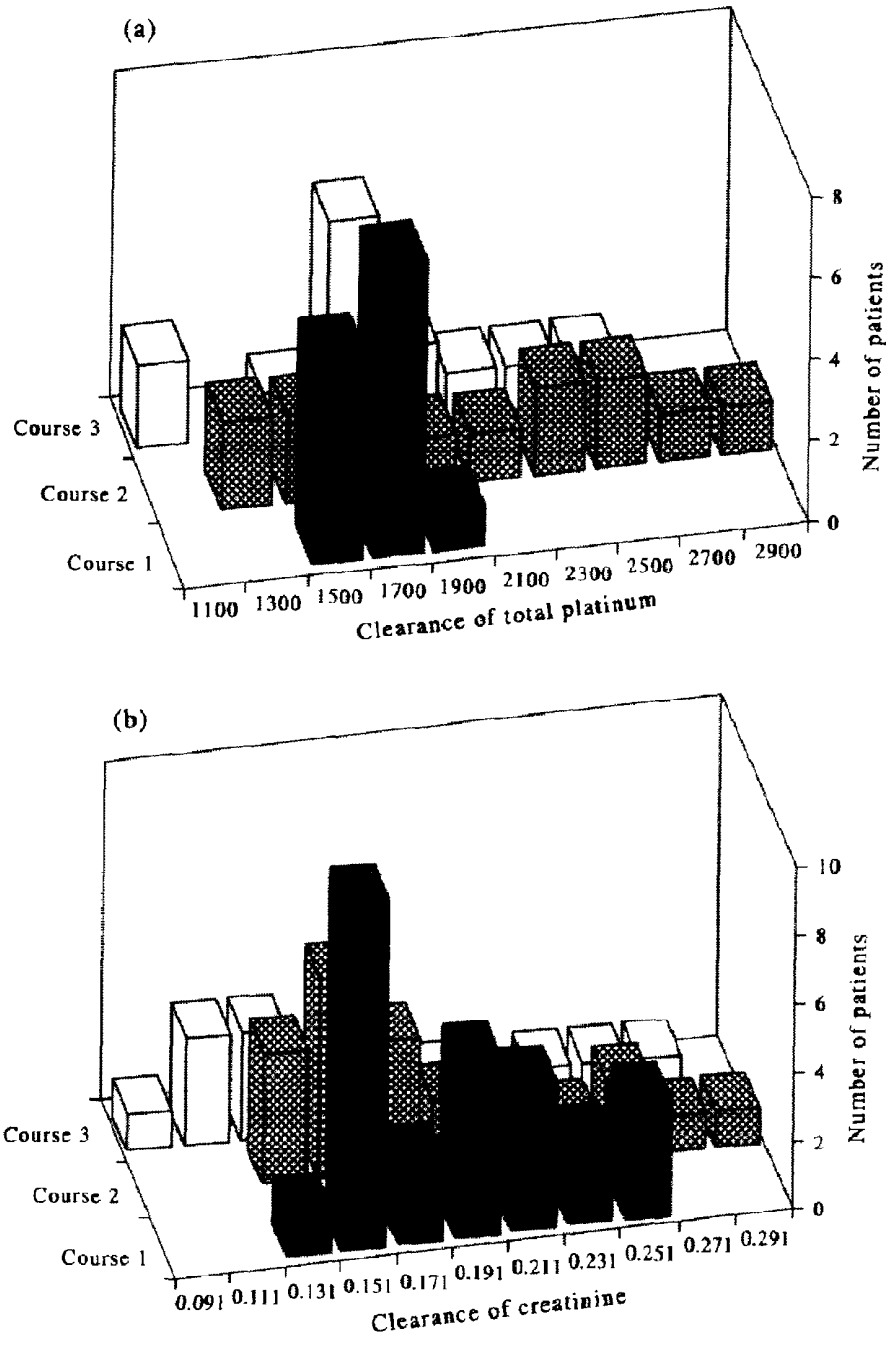


**Figure 2. The distribution of TP clearance (a) and creatinine clearance (b) (Cockroft index) in the first three courses.**

and Karnofsky index). Grades of toxicity were compared using the Fisher's exact test (two-tail).

## RESULTS

*Pharmacokinetic data analysis*

The cisplatin dose was individualised for 27 patients during 63 courses. On average, the observed TP concentration was equal to 97.3% of the target TP. The overall bias was 2.7% and the overall precision 7.8%. Bias improved after the first course: 5.2, 0.2 and 2.2% for the 1st, 2nd and 3rd courses, respectively. The coefficient of variation of observed TP was 10.6, 9.6 and 9.1, respectively for the three courses. The ratio of the highest to the lowest TP concentration for all courses was 1.6. In the reference group, the average TP concentration at 120 h was 1689 μg/l for the 97 courses, with a minimum of 832 μg/l and a maximum of 2988 μg/l, giving a ratio of 3.6.

Compared with the original protocol, i.e. to the patient reference group, the mean dose of cisplatin was increased by an average of 20.2%. The doses were increased (>105% of the original dose) in 44 courses out of 63 (70%), not modified in 13 courses (21%) and decreased (<95% of the original dose) in 6 courses (9%). Dose augmentations were more important during the first courses, 25 of 26 patients had a dose increase of cisplatin (greater than 5%) during the first course. During the 2nd and 3rd courses, the proportion of dose increases was lower (Figure 1). The mean dose increases were 31, 16 and 7% during the 1st, 2nd and 3rd courses, respectively. The time between cycles was 27.0 ± 4.6 days

*Table 2. Toxicity for each course (expressed in per cent); 38 patients—97 courses and 27 patients—63 courses for the reference and the dose-adjusted populations, respectively*

| | Toxicity | No toxicity | Low toxicity (grade 1+2) | High toxicity (grade 3+4) |
|---|---|---|---|---|
| Toxicity in reference population | Creatininaemia | 98 | 2 (2+0) | 0 |
| | Haemoglobin* | 20 | 36 (13+23) | 44 (21+23) |
| | Platelets | 87 | 9 (4+5) | 4 (1+3) |
| | Leucocytes | 58 | 34 (22+12) | 8 (6+2) |
| | PMN | 57 | 26 (16+10) | 17 (7+10) |
| Toxicity in dose-adjusted population | Creatininaemia | 87 | 13 (13+0) | 0 |
| | Haemoglobin | 21 | 63 (25+38) | 16 (16+0) |
| | Platelets | 74 | 16 (8+8) | 10 (5+5) |
| | Leucocytes† | 40 | 44 (19+25) | 16 (11+5) |
| | PMN‡ | 40 | 17 (11+6) | 43 (27+16) |

Fisher's exact test (two-tail), *$P = 0.0004$; †$P = 0.044$; ‡$P = 0.001$.
PMN, polymorphonuclear neutrophils.

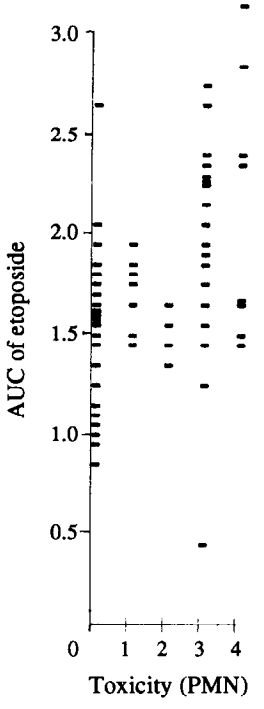


**Figure 3. The relationship between AUC of etoposide and toxicity to PMN is statistically significant ($n = 63$, df = 1, $\chi^2 = 4.61$, $P = 0.032$).**

in the dose-adjusted population and 26.7 ± 5.8 days in the reference population.

The distribution of TP clearance in the patient population seemed to be Gaussian during the first course (Figure 2), but changed markedly for the subsequent courses. The distribution of creatinine clearance, evaluated by the Cockroft index, was more heterogeneous in the first course, but similar for the two other courses (Figure 2).

The dose of etoposide was strictly adjusted to the body surface area for all patients and all courses. Nevertheless, compared with the patient reference group, the AUC of etoposide was increased by 41, 21 and 36% for the 1st, 2nd and 3rd courses, respectively. The AUCs were respectively 456, 458 and 497 μmol/l/h.

*Toxicity analysis*

The dose-adjusted and the reference populations were comparable for gender, age, weight, body surface area, histology and staging, but the Karnofsky index was significantly lower in the dose-adjusted population (Table 1), therefore the interpretation in comparing the toxicity in both populations is restricted. The most interesting difference in toxicity between the two groups concerned polymorphonuclear neutrophils (PMN; Table 2, chi-square = 13.82, $P = 0.001$). 1 patient died between two courses with a deficiency of PMN, even though his TP AUC was below the average and the etoposide AUC was equal to the average. No pharmacokinetic parameter of TP was correlated with toxicity. However, the AUC of etoposide was linked to the grade of toxicity on PMN ($n = 63$, df = 1, $\chi^2 = 4.61$, $P = 0.032$, Figure 3).

## DISCUSSION

The TP target concentration was achieved with relatively low bias (less than 1% for the second course), compared with that in the retrospective evaluation which was only 5.0% [12]. The distribution of patients' TP clearance, compared to that of creatinine clearance, was very narrow during the first course. This distribution appeared to broaden for subsequent courses. This could be due to a toxic effect of cisplatin on renal function, since we have previously shown that TP seems to be cleared by glomerular filtration [12]. These results indicate that cisplatin may modify its own clearance.

It has already been reported that cisplatin and etoposide act synergistically and that the etoposide dose must be decreased when administered with cisplatin [18]. Pflüger and coworkers [19] reported that etoposide AUC was increased by prior cisplatin administration. Later, McLeod and colleagues [20] and Relling and colleagues [21] reported that cisplatin decreased etoposide clearance. A pharmacokinetic interaction between cisplatin and etoposide could explain the effect of an increase in cisplatin dose on etoposide AUC in this study. There was no significant correlation between etoposide and TP pharmacokinetic parameters.

It has been reported that etoposide AUC is related to myelotoxicity [21–23]. Since a similar relationship was observed in the present study, the pharmacokinetic interaction between cisplatin and etoposide could be the cause of increased haematological toxicity. Differences in myelotoxic-

ity between the two groups in the present study could be due, at least in part, to the difference in Karnofsky index. Nevertheless, it appears that when the dose of cisplatin is individualised, the dose of etoposide should be adjusted as well. The increase of cisplatin dose did not increase its own specific toxicity, as evaluated by plasma creatinine concentration and according to WHO criteria.

The mean cisplatin dose increase was significant in the majority of courses. This would indicate that in the regular protocol, without individualisation of dose, many patients would have been underdosed. This effect was especially important for the first course. It has been reported that dose intensification during the initial course has a beneficial effect on the efficacy of chemotherapy [24, 25], which could explain, at least in part, the improvement of efficacy. The largest decrease of cisplatin dose, compared with the non-adjusted population, was −25%, and the most important increase was +64%. The ratio between the extreme doses, indicating the range of individualisation necessary, was 2.2. Our results demonstrate that an important proportion of patients appeared to be underdosed by using conventional therapy with cisplatin. Thus, intensification of cisplatin dose could be achieved in clinical practice, provided that the TP plasma concentration is monitored. Monitoring and individualisation of dose is not expensive compared with the cost of some new cancer treatments which yield comparable improvement in efficacy.

The preliminary results of this study are promising and may be further improved by controlling the associated increase in toxicity. A randomised clinical trial is planned to confirm these results and to determine if a decrease of etoposide dose in patients achieving a high AUC will diminish the toxicity on PMN, while retaining efficacy.

In conclusion, our results show that (i) the dose of cisplatin can be individualised to achieve a target plasma concentration, (ii) the dose of cisplatin is consequently intensified without specific toxicity and (iii) the dose of etoposide, administered simultaneously, should also be adjusted.


1. Grochow LB, Baraldi C, Noe D. Is dose normalisation to weight or body surface area useful in adults? *Natl Cancer Inst* 1990, **82**, 323–325.
2. Gilles E. Is dose adjustment for body surface area valid? *Proc Am Assoc Cancer Res* 1992, **33**, 529 (Abstract).
3. Reilly JJ, Workman P. Normalisation of anticancer drug dosage using body weight and surface area: is it worthwhile? A review of theoretical and practical considerations. *Cancer Chemother Pharmacol* 1993, **32**, 411–418.
4. Desoize B, Robert J. Individual dose adaptation of anticancer drugs. *Eur J Cancer* 1994, **30A**, 844–851.
5. Kobayaschi K, Ratain MJ. Individualizing dosing of cancer chemotherapy. *Semin Oncol* 1993, **20**, 30–42.
6. Galpin AJ, Evans WE. Therapeutic drug monitoring in cancer management. *Clin Chem* 1993, **39**, 2419–2430.
7. Desoize B, Maréchal F, Millart H, Cattan A. Correlation of clinical pharmaco-kinetic parameters of cisplatin with efficacy and toxicity. *Biomed Pharmacother* 1991, **45**, 203–207.
8. Collery P, Morel M, Millart H, *et al.* Oral administration of gallium in conjunction with platinum in lung cancer treatment. In Collery P, Poirier LA, Manfait M, eds. *Metal Ions in Biology and Medicine*. London, John Libbey, 1990, Vol. 1, 437–442.
9. Campbell AB, Kalman SM, Jacobs C. Plasma platinum levels: relationship to cisplatin dose and nephrotoxicity. *Cancer Treat Rep* 1983, **67**, 169–172.
10. Kelsen DP, Alcock N, Young CW. Cisplatin nephrotoxicity. Correlation with plasma concentrations. *Am J Clin Oncol* 1985, **8**, 77–80.
11. Crom W, Mauer E, Greene W, *et al.* Relation between cisplatin ototoxicity and platinum accumulation in plasma. *Proc Am Soc Clin Oncol* 1984, **3**, 28 (Abstract).
12. Desoize B, Dumont P, Manot L, Dufour R, Berthiot G. Comparison of two dose prediction models for cisplatin. *Anticancer Res* 1994, **14**, 2285–2290.
13. Bannister SJ, Chang Y, Sternson LA, Repta AJ. Atomic absorption spectrophotometry of free circulating platinum species in plasma derived from cis-dichlorodiammineplatinum(II). *Clin Chem* 1978, **24**, 877–880.
14. Desoize B, Woirin V, Legros M, Coninx P. Reduced oral etoposide bioavailability in patients with advanced head and neck cancer. *J Natl Cancer Inst* 1992, **5**, 348–350.
15. Urien S. MicroPharm-K microcomputer interactive program for the analysis and simulation of pharmacokinetic processes. *Pharm Res* 1995, **12**, 1225–1230.
16. Desoize B, Marechal F, Cattan A. Clinical pharmacokinetics of etoposide during 120 h continuous infusions in solid tumours. *Br J Cancer* 1990, **62**, 840–841.
17. Miller A, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
18. Creagan ET, Richardson EL, Kovach JS. Pilot study of a continuous 5-day intravenous infusion of etoposide concomitant with cisplatin in selected patients with advanced cancer. *J Clin Oncol* 1988, **6**, 1197–1201.
19. Pflüger KH, Schmidt L, Merkel M, Jungclas H, Havemann K. Correlation of pharmacokinetic parameters to clinical and biochemical data from patients receiving etoposide. *Cancer Chemother Pharmacol* 1987, **20**, 40–66.
20. McLeod HL, Santana VM, Bowman LC, Furman WL, Relling MV. Etoposide pharmacokinetics are influenced by acute but not chronic exposure to cisplatin. *Proc Am Assoc Cancer Res* 1992, **33**, 531 (Abstract).
21. Relling MV, McLeod HL, Bowman LC, Santana VM. Etoposide pharmacokinetics after acute and chronic exposure to cisplatin. *Clin Pharmacol Ther* 1994, **56**, 503–511.
22. Miller AA, Tolley EA, Niell HB, Stewart CF, Griffin JP. Pharmacodynamics of three daily infusion of etoposide in patients with extensive-stage small-cell lung cancer. *Cancer Chemother Pharmacol* 1992, **31**, 161–166.
23. Joel SP, Shah R, Slevin ML. Etoposide dosage and pharmacokinetics. *Cancer Chemother Pharmacol* 1994, **34** (Suppl.), S69–S75.
24. Arriagada R, Le Chevalier T, Pignon JP, *et al.* Initial chemotherapy doses and survival in patients with limited small-cell lung cancer. *N Engl J Med* 1993, **329**, 1848–1852.
25. De Vathaire F, Arriagada R, De The H, *et al.* Dose intensity of initial chemotherapy may have an impact on survival in limited small cell lung carcinoma. *Lung Cancer* 1993, **8**, 301–308.


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