Anti-Cancer Drugs 1998, 9, pp. 759–764

Research paper

Corticosteroid co-medication does not reduce the incidence and severity of neurotoxicity induced by docetaxel

LC Pronk, PHE Hilkens,[1] MJ van den Bent,[1] WLJ van Putten,[2] G Stoter and J Verweij
Departments of Medical Oncology, [1]Neuro-Oncology and [2]Biostatistics, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital, 3008 AE Rotterdam, The Netherlands.

Docetaxel is a new antimicrotubule agent that induces a predominantly sensory neuropathy that is mild in most patients. This prospective study was performed to determine if corticosteroid co-medication reduces the incidence and severity of docetaxel-induced neuropathy. Two groups of patients treated with docetaxel in subsequent cohorts were prospectively analyzed for neurotoxicity. Group A consisted of 38 patients with a variety of solid tumors, who were treated in studies before corticosteroid co-medication was recommended, while 49 female patients in group B with metastatic breast cancer were treated after co-medication with corticosteroids was introduced as a routine. Neuropathy was evaluated by a clinical sum-score for symptoms and signs, and by measurement of the vibration perception threshold (VPT). The severity of neuropathy was graded according to NCI Common Toxicity Criteria. In 42% of patients of group A and in 65% of patients of group B a mainly mild neuropathy was documented. There was no statistically significant difference in neurotoxicity between group A and B. The cumulative dose of docetaxel showed a significant correlation with post-treatment scores of VPT, sensory sum-score, grade of paresthesias, and grade of neurosensory and neuromotor toxicity. Corticosteroid co-medication does not reduce the development of docetaxel-related neuropathy.

Key words: Corticosteroids, docetaxel, neuropathy.

Introduction

Docetaxel (Taxotere; Rhône-Poulenc Rorer, Antony, France) is a new semi-synthetic taxoid that is prepared from 10-deacetyl baccatin III, a non-cytotoxic precursor extracted from the needles of the European yew, *Taxus baccata*. Like paclitaxel (Taxol), docetaxel acts as an antimicrotubule agent that enhances polymerization of the tubulin into stable microtubules and inhibits microtubule depolymerization. This leads to a disruption of the equilibrium within the microtubule system and ultimately to cell death.[1-4]

In phase I studies on single-agent docetaxel the major dose-limiting toxicity (DLT) was neutropenia that appeared to be short lasting, dose dependent, schedule independent and non-cumulative.[5-10] Based on these phase I studies the recommended single-agent dose and schedule for docetaxel was 100 mg/m^2 given as a 1 h infusion every 3 weeks. Phase II studies on docetaxel showed activity in breast cancer,[11-15] non-small cell lung cancer,[16-18] head and neck cancer,[19] gastric cancer,[20] melanoma,[21] soft tissue sarcoma,[22] and pancreatic cancer.[23] The most important side effect was an early short-lasting neutropenia which in 20% of the patients was complicated by infection.[1] Other side effects included alopecia, nausea, vomiting, diarrhea, mucositis, asthenia, infrequent hypersensitivity reactions, skin reactions, nail changes, fluid retention and a mild sensory neuropathy.[1,24-26]

We prospectively assessed neurotoxicity in 41 patients treated with docetaxel as first- or second-line chemotherapy. Docetaxel induced a predominantly sensory neuropathy in 20 of 41 patients that was mild in most patients. However, at cumulative doses above 600 mg/m^2, three of 15 patients developed a moderate and one of 15 patients a severe neuropathy.[24] Most of these patients did not receive corticosteroid co-medication. In the present study we prospectively assessed neurotoxicity in patients with metastatic breast cancer who were treated in a multicenter study of docetaxel and who routinely received corticosteroid co-medication during 5 days. The results of this prospective study were compared with those of the previous study,[24] with the aim to determine if corticosteroid co-

Correspondence to LC Pronk, Servicio de Oncologia Medica, Hospital Universitario '12 de Octubre', Avda Cordoba, km 54, 28041 Madrid, Spain. Tel: (+34) 91 390 83 49; Fax: (+34) 91 460 33 10

medication reduces and/or delays docetaxel-induced neurotoxicity.

Patients and methods

Neurotoxicity was assessed prospectively in two groups of patients with metastatic or locally advanced cancer. Group A included patients with metastatic or locally advanced cancer who participated to one of four different multicenter phase II trials on the activity of docetaxel as first- or second-line chemotherapy as described before.[22] The patients with breast cancer who were randomized to receive prophylactic corticosteroids were excluded from the analyses. Group B consisted of patients with histologically or cytologically proven breast cancer who had not responded to conventional chemotherapy and participated to a compassionate use programme. Eligibility criteria for all studies included: (i) age $\geqslant 18$ years; (ii) WHO performance status 0–2; (iii) adequate hematological (granulocytes $\geqslant 2.0 \times 10^9$/l), renal (serum creatinine $\leqslant 1.5\times$ upper normal limit) and hepatic function (total serum bilirubin $\leqslant 1.25\times$ upper normal limit); (iv) no clinical signs of symptomatic peripheral neuropathy grade 2 or more according to the NCI Common Toxicity Criteria (CTC).[27] All patients had given informed consent.

Drug administration

Docetaxel was supplied by Rhône-Poulenc Rorer and administered as a 1 h infusion at a dose of 100 mg/m^2 every 3 weeks. In six patients of group A the dose per cycle was divided and given on days 1 and 8 every 3 weeks.[28] In group B all patients received co-medication consisting of 8 mg of dexamethasone orally 13, 7 and 1 h before docetaxel infusion, followed by dexamethasone 8 mg orally twice a day during 96 h after docetaxel administration. In group A no corticosteroids were given because these patients were treated in studies before corticosteroid co-medication was recommended. No other neurotoxic drugs were used during the study or follow-up period.

Methods

The severity of neuropathy was evaluated by a questionnaire for neurologic symptoms, by standardized neurological examination and by measurements of the vibration perception threshold (VPT) before start of treatment, after every two cycles, at 2 weeks after the last dose of docetaxel and every 3 months thereafter. The questionnaire established separately absence (0) or presence (1) of paresthesias, numbness, loss of dexterity and unsteadiness of gait. On sensory examination, position sense, vibration sense, pin-prick sensation, Romberg's sign, Romberg's sign with heel-to-toe stand and tendon reflexes of the legs were each scored as normal (0) or abnormal (1). A sum-score for these signs and symptoms was calculated (minimum 0, maximum 11). The severity of paresthesias was graded on a 5-point scale (0, no; 1, temporary; 2 continuous light; 3, severe; 4, unbearable). Sensory loss was defined as an abnormal test on either position sense, vibration sense or pin-prick sense. Patients were asked whether they experienced Lhermitte's sign or pain. Distal muscle strength in the lower extremities was tested. Motor signs were defined as the presence of objective weakness. The severity of neuropathy was scored according to the NCI-CTC[27] for sensory neuropathy (0, no symptoms or signs; 1, mild paresthesias, loss of deep tendon reflexes; 2, moderate paresthesias, objective sensory loss; 3, severe paresthesias, sensory loss interfering with function). VPT was measured at the dorsum of the second metacarpal bone of the left hand with a Vibrameter type IV (Somedic, Stockholm, Sweden) and recorded in micrometers of skin displacement. This Vibrameter uses a vibratory frequency of 100 Hz and corrects for pressure-induced alterations of vibratory amplitude. The mean value of three measurements of the VPT determined with the method of limits was considered the actual VPT.[29] The VPT has been shown to be a reliable technique to monitor cisplatin neuropathy and shows a good correlation with the sum-score of neuropathic signs and symptoms as observed previously.[30–32] It has been used to quantify paclitaxel-induced neuropathy.[33]

Since a relation was suggested between docetaxel-induced toxicity and cumulative dose given, the post-treatment evaluation on day 90 was chosen as primary endpoint for the assessment of neurotoxicity. Cycles of docetaxel given after the last neurologic evaluation, which occurred in 27 patients, were not counted in the analysis and excluded from the calculation of the cumulative dose.

Statistical methods

Primary endpoints for the analysis were the VPT, the sensory sum-score, the grade of paresthesias, the CTC neurosensory grade and the CTC neuromotor grade. Because of the skewed distribution of VPT the natural logarithm was used for statistical analysis. The post-

treatment grade of patients with pre-existing paresthesias, CTC neurosensory or CTC neuromotor with grade ≥ 1 was considered 0 if it was not increased at post-treatment evaluation. Analysis of covariance was applied to test for a difference between the two treatment groups in post-treatment sensory sum-score and log VPT while adjusting for pre-treatment values, age and the cumulative dose of docetaxel (log transformed). Ordinal logistic regression analysis, according to the proportional odds model,[34] was applied to compare the two groups with respect to post-treatment grade of paresthesias, neurosensory and neuromotor, adjusted for age and cumulative dose of docetaxel. The p values reported in Results for the comparison of groups A and B are all based on these adjusted analyses.

Results

A total of 87 patients were evaluable for neurotoxicity. Patient characteristics are given in Table 1. The two groups we studied differed in several ways; group A consisted of patients with various tumor types of whom nine patients had received cisplatin as prior antitumor therapy, whereas all patients of group B were females with metastatic breast cancer of whom most were pretreated with non-neurotoxic chemotherapy. The patients with breast cancer in group A did not receive corticosteroid co-medication. In both groups there was one patient with diabetes mellitus and two patients of group A reported alcohol abuse.

Table 2 represents the number of cycles and the cumulative dose of docetaxel administered for both groups. All patients started treatment at a dose of 100 mg/m^2 every 3 weeks, but in some patients dose reductions were required because of various adverse effects. In the six breast cancer patients of group A the dose per cycle was divided, and given on day 1 and 8 every 3 weeks. The cumulative dose of docetaxel was below 300 mg/m^2 in 15 patients of group A and in 10 patients of group B, 300-600 mg/m^2 in nine patients of group A and in 15 patients of group B, and above 600 mg/m^2 in 14 and 24 patients of group A and B, respectively.

Before the start of treatment four patients in group A and three patients in group B showed a mild sensory neuropathy. The four patients in group A were pretreated with cisplatin. In Table 3 the increase in sensory sum-score, VPT, paresthesias, and grade of neurosensory and neuromotor toxicity are shown at post-treatment evaluation in relation to treatment group. According to CTC criteria 16 patients of group A (42%) and 32 patients of group B (65%) developed a sensory neuropathy. There was no statistically significant difference between groups A and B in the post-treatment scores of VPT (p=0.87), sensory sum-score (p=0.83), paresthesias (p=0.62) and CTC neuromotor (p=0.53). In group B somewhat higher CTC neurosensory grades were found compared to group A (p=0.04).

Table 4 represents the mean increase in sensory sum-score, the mean VPT ratio, the increase in severity of paresthesias, the CTC neurosensory grade and the CTC neuromotor grade at post-treatment evaluation classified by cumulative dose. At a cumulative dose of docetaxel below 600 mg/m^2 six of 24 patients in group A showed a mild sensory neuropathy, while in group B eight of 25 patients developed a mild and five of 25 patients a moderate sensory neuropathy. At a cumulative dose of 600 mg/m^2 or above 10 of 14

Table 1. Patient characteristics

	Group A	Group B
No. of patients	38	49
Mean age (years) (range)	52 (28–73)	50 (31–73)
Sex		
male	15	–
female	23	49
WHO performance status		
0	16	13
1	19	33
2	3	3
Prior treatment		
cisplatin	9	1
oncovin	–	–
other chemotherapy	15	45
Tumor type		
breast	6	49
ovarian	10	–
sarcoma	7	–
bladder	7	–
head and neck	5	–
melanoma	2	–
colorectal	1	–

Table 2. Number of cycles and cumulative dose of docetaxel

	Group A	Group B
No. of cycles		
median	4	6
range	2–11	1–20
Cumulative dose of docetaxel (mg/m^2)		
median	363	575
range	100–1100	100–1700

patients in group A developed a sensory neuropathy that was mild in eight patients and moderate in two patients. In group B 19 of 24 patients who had received a cumulative dose of 600 mg/m^2 or above developed a sensory neuropathy that was mild in 13 patients, moderate in four patients and severe in two patients. Neuromotor toxicity was reported in four patients of group A and in seven patients of group B.

Table 3. Increase in neurotoxicity in relation to treatment group

	Group A		Group B	
Number of assessable patients	38		49	
Sensory sum-score increase (mean ± SD)	2.5 ± 2.7		2.7 ± 2.2	
VPT ratio post/pre-treatment (mean ± SD)	1.2 ± 0.7		1.5 ± 0.9	
	N	%	N	%
Paresthesias				
no increase	18	47	28	57
grade 1	9	24	6	12
grade 2	9	24	6	12
grade 3	1	3	7	14
grade 4	1	3	2	4
CTC neurosensory				
no increase	22	58	17	35
grade 1	14	37	21	43
grade 2	2	5	9	18
grade 3	0	0	2	4
CTC neuromotor				
no increase	34	89	42	86
grade 1	3	8	4	8
grade 2	0	0	3	6
grade 3	1	3	0	0

Table 4. Increase in neurotoxicity in relation to cumulative dose of docetaxel

Group	< 300 mg/m^2		300–600 mg/m^2		> 600 mg/m^2	
	A	B	A	B	A	B
No. of patients	15	10	9	15	14	24
Sensory sum-score increase[a]	1.2 ± 1.1	0.6 ± 1.1	2.2 ± 2.2	3.3 ± 2.4	4.0 ± 3.4	3.1 ± 1.9
VPT ratio[b]	1.3 ± 0.9	1.1 ± 0.6	1.0 ± 0.2	1.3 ± 0.7	1.3 ± 0.8	1.8 ± 1.3
Paresthesias[c]						
no increase	9	8	4	6	5	14
grade 1	5	1	2	3	2	2
grade 2	1	0	3	3	5	3
grade 3	0	1	0	1	1	5
grade 4	0	0	0	2	1	0
CTC neurosensory[c]						
no increase	13	10	5	2	4	5
grade 1	2	0	4	8	8	13
grade 2	0	0	0	5	2	4
grade 3	0	0	0	0	0	2
CTC neuromotor[c]						
no increase	15	9	9	13	10	20
grade 1	0	1	0	1	3	2
grade 2	0	0	0	1	0	2
grade 3	0	0	0	0	1	0

[a]Difference between post-treatment and pre-treatment score. Values are means ± SD.
[b]Ratio of post-treatment and pre-treatment score. Values are means ± SD.
[c]Incidence at post-treatment evaluation; in case of pre-existing graded toxicities, only higher grades are counted.

Neurotoxicity was a reason to stop docetaxel treatment in three patients (8%) of group A and in six patients (12%) of group B.

The cumulative dose of docetaxel showed a positive association with all post-treatment scores when adjusted for pretreatment score, age and treatment group: VPT (p=0.02), sensory sum-score ($p<0.001$), grade of paresthesias (p=0.11), CTC neurosensory ($p<0.001$) and CTC neuromotor (p=0.09).

Discussion

Docetaxel is a new antimicrotubule agent that has shown activity in a variety of solid tumors.[11-23] It induces a frequent dose-dependent, predominantly sensory neuropathy that is mild in most patients.[24-26] New *et al.*[25] reported a sensorimotor neuropathy in 11% of 186 patients that were treated with docetaxel at a wide range of cumulative doses (50-720 mg/m^2) and dose levels (10-115 mg/m^2). Hilkens *et al.*[24] documented a sensory neuropathy in 20 (49%) of 41 patients that was mild in most patients, but at cumulative doses of docetaxel higher than 600 mg/m^2 three patients developed a moderate and one patient a severe neuropathy. The clinical characteristics of severe peripheral neuropathy were described in detail.[35] Disabling and painful paresthesias, loss of tendon reflexes, loss of dexterity and steadiness of gait, and proximal weakness dominated the clinical picture in these patients. In some patients Lhermitte's sign was observed.[35,36] Freilich *et al.*[37] reported motor neuropathy due to treatment with docetaxel in seven of 60 patients (12%). The motor weakness was predominantly proximal; it seemed idiosyncratic as it occurred at any stage of treatment and had a variable course. Motor neuropathy appeared to be reversible upon cessation of docetaxel therapy.

The present study was performed to determine if corticosteroid co-medication reduces the incidence and/or severity of docetaxel-related neuropathy. In the early studies on docetaxel corticosteroid co-medication was not given routinely. However, in a phase II study of the EORTC Breast Cancer Study Group in which patients treated with docetaxel were randomized between prophylactic oral antihistamine with or without methylprednisolone, corticosteroids appeared to decrease the severity of docetaxel-related fluid retention.[28] Furthermore, the application of corticosteroid co-medication markedly reduced the incidence of hypersensitivity reactions induced by docetaxel.[38] Considering these observations it was recommended to administer corticosteroid co-medication routinely in later studies on docetaxel.

Hilkens *et al.* performed a prospective study in which patients treated with docetaxel were assessed for neurotoxicity.[24] Most of these patients did not receive corticosteroid co-medication, except for some patients with breast cancer who participated in a phase II study in which patients were randomized to receive premedication with or without methylprednisolone.[28] In the present analysis we deleted the patients who were randomized to receive corticosteroid co-medication (group A) and compared these data with the results of a study that prospectively assessed patients for neurotoxicity who were treated with docetaxel and received corticosteroid co-medication (group B). The two groups differed in several ways; the patients in group A had a variety of tumor types and nine of 38 patients were pretreated with cisplatin. The patients in group B, however, were all females with metastatic breast cancer who were pretreated with non-neurotoxic chemotherapy.

There was no statistically significant difference in the post-treatment scores of VPT (p=0.87), sensory sum-score (p=0.83), paresthesias (p=0.62) and CTC neuromotor (p=0.53) when adjusted for pretreatment score, age, treatment group and cumulative dose of docetaxel. In group B somewhat higher CTC neurosensory grades were reported compared to group A (p=0.04). This could be explained by the fact that the median number of cycles administered and the cumulative dose of docetaxel were higher in group B than in group A. The cumulative dose of docetaxel was strongly associated with all post-treatment neurotoxicity scores.

Conclusion

We conclude that corticosteroid co-medication does not reduce the incidence or severity of docetaxel-related neuropathy. Nevertheless there is a role for corticosteroids since they do reduce the incidence of hypersensitivity reactions and docetaxel-related fluid retention.

References

1. Pronk LC, Stoter G, Verweij J. Docetaxel (Taxotere): single agent activity, development of combination treatment and reducing side-effects. *Cancer Treat Rev* 1995; **21**: 463-78.
2. Rowinsky EK, Donehower RC. The clinical pharmacology and use of antimicrotubule agents in cancer chemotherapeutics. *Pharmacol Ther* 1991; **52**: 35-84.
3. Gueritte-Voegelein F, Guenard D, Lavelle F, Le Goff MT, Mangatal L, Potier P. Relationships between the structure of taxol analogues and their antimitotic activity. *J Med Chem* 1991; **34**: 992-8.

4. Ringel I, Horwitz SB. Studies with RP 56976 (Taxotere): a semi-synthetic analog of Taxol. *J Natl Cancer Inst* 1991; **83**: 288–91.
5. Extra JM, Rousseau F, Bruno R, Clavel M, Le Bail N, Marty M. Phase I and pharmacokinetic study of Taxotere (RP 56976; NSC 628503) given as a short intravenous infusion. *Cancer Res* 1993; **53**: 1037–42.
6. Tomiak E, Piccart MJ, Kerger J, *et al.* Phase I study of Docetaxel administered as a 1-hour intravenous infusion on a weekly basis. *J Clin Oncol* 1993; **112**: 1458–67.
7. Burris H, Irvin R, Kuhn J, *et al.* Phase I clinical trial of Taxotere administered as either a 2-hour or 6-hour intravenous infusion. *J Clin Oncol* 1993; **11**: 950–8.
8. Bisset D, Setanoians A, Cassidy J, *et al.* Phase I and pharmacokinetic study of Taxotere (RP 56976) administered as a 24-hour infusion. *Cancer Res* 1993; **53**: 523–7.
9. Pazdur R, Newman RA, Newman BM, *et al.* Phase I trial of Taxotere: five-day schedule. *J Natl Cancer Inst* 1992; **84**: 1781–8.
10. Aapro MS, Zulian G, Albert P, Bruno R, Oulid-Aissa D, Le Bail N. Phase I and pharmacokinetic study of RP 56976 in a new ethanol-free formulation of Taxotere. *Ann Oncol* 1992; **3** (suppl 5): 208.
11. Chevallier B, Fumoleau P, Kerbrat P, *et al.* Docetaxel is a major cytotoxic drug for the treatment of advanced breast cancer: a phase II trial of the Clinical Screening Cooperative Group of the European Organization for Research and Treatment of Cancer. *J Clin Oncol* 1995; **13**: 314–22.
12. Seidman AD, Hudis C, Crown JPA, *et al.* Phase II evaluation of Taxotere (RP56976, NSC628503) as initial chemotherapy for metastatic breast cancer. *Proc Am Soc Clin Oncol* 1993; **12**: 63.
13. Trudeau ME, Eisenhauer E, Lofters W, *et al.* Phase II study of Taxotere as first line chemotherapy for metastatic breast cancer: a National Cancer Institute of Canada Clinical Trial Group study. *Proc Am Soc Clin Oncol* 1993; **12**: 64.
14. ten Bokkel-Huinink WW, Prove AM, Piccart M, *et al.* A phase II trial with Docetaxel (Taxotere™) in second line treatment with chemotherapy for advanced breast cancer. A study of the EORTC Early Clinical Trials Group. *Ann Oncol* 1994; **5**: 527–32.
15. Valero V, Esparza L, Holmes F, *et al.* Phase II study of Taxotere in refractory metastatic breast cancer. *Proc Am Soc Clin Oncol* 1993; **12**: 96.
16. Cerny T, Kaplan S, Pavlidis N, *et al.* Docetaxel (Taxotere™) is active in non-small-cell lung cancer: a phase II trial of the EORTC Early Clinical Trials Group. *Br J Cancer* 1994; **70**: 384–7.
17. Fossella FV, Lee JS, Shin DM, *et al.* Phase II study of docetaxel for advanced or metastatic platinum-refractory non-small cell lung cancer. *J Clin Oncol* 1995; **13**: 645–51.
18. Miller VA, Rigas JR, Francis PA, *et al.* Phase II trial of a 75 mg/m^2 dose of docetaxel with prednisone premedication for patients with advanced non-small cell lung cancer. *Cancer* 1996; **4**: 968–72.
19. Catimel G, Verweij J, Mattijsen V, *et al.* Docetaxel (Taxotere): an active drug for the treatment of patients with advanced squamous cell carcinoma of the head and neck. *Ann Oncol* 1994; **5**: 533–7.
20. Sulkes A, Smyth J, Sessa C, *et al.* Docetaxel (Taxotere™) in advanced gastric cancer: results of a phase II clinical trial. *Br J Cancer* 1994; **70**: 380–3.
21. Aamdal S, Wolff I, Kaplan S, *et al.* Docetaxel (Taxotere) in advanced malignant melanoma: a phase II study of the EORTC Clinical Trials Group. *Eur J Cancer* 1994; **30A**: 1061–4.
22. van Hoesel QGCM, Verweij J, Catimel G, *et al.* Phase II study with Taxotere (RP 56976) in advanced soft tissue sarcomas of the adult. *Ann Oncol* 1994; **5**: 539–42.
23. De Forni M, Rougier Ph, Adenis A, *et al.* Phase II study of Taxotere in locally advanced and/or metastatic pancreatic cancer. *Ann Oncol* 1994; **5** (suppl): 509.
24. Hilkens PHE, Verweij J, Stoter G, Vecht ChJ, van Putten WLJ, van den Bent MJ. Peripheral neurotoxicity induced by Docetaxel. *Neurology* 1996; **46**: 104–8.
25. New PZ, Jackson CE, Rinaldi D, Burris H, Barohn RJ. Peripheral neuropathy secondary to Docetaxel (Taxotere). *Neurology* 1996; **46**: 108–11.
26. Apfel SC. Docetaxel neuropathy. *Neurology* 1996; **46**: 2–3.
27. Brundage MD, Pater JL, Zee B. Assessing the reliability of two toxicity scales: implications for interpretating toxicity data. *J Natl Cancer Inst* 1993; **85**: 1138–48.
28. Piccart MJ, Klijn J, Paridaens R, *et al.* Corticosteriods significantly delay the onset of Docetaxel-induced fluid retention: final results of a randomized study of the European Organization for Research and Treatment of Cancer Investigational Drug Branch for Breast Cancer. *J Clin Oncol* 1997; **15**: 3149–55.
29. Goldberg JM, Lindblom U. Standardised method of determining vibratory perception threshold for diagnosis and screening in neurological investigation. *J Neurol Neurosurg Psychiatry* 1979; **42**: 793–803.
30. Gispen WH, Jennekens FGI. Vibration perception and thermoperception as quantitative measurements in the monitoring of cisplatin induced neurotoxicity. *J Neurol Sci* 1989; **93**: 167–74.
31. Gerritsen van der Hoop R, Vecht ChJ, Van der Burg MEL, *et al.* Prevention of Cisplatin neurotoxicity with an ACTH(4-9) analogue in patients with ovarian cancer. *N Engl J Med* 1990; **322**: 89–94.
32. Hovestadt A, Van der Burg MEL, Verbiest HBC, Van Putten WLJ, Vecht ChJ. The course of neuropathy after cessation of cisplatin treatment, combined with org 2766 or placebo. *J Neurol* 1992; **239**: 143–6.
33. van Gerven JMA, Moll JWB, van den Bent MJ, *et al.* Paclitaxel (Taxol) induces cumulative mild neurotoxicity. *Eur J Cancer* 1994; **30A**: 1074–7.
34. Green WH. *Econometric analysis*, 2nd edn. New York: Macmillan 1995.
35. Hilkens PHE, Verweij J, Vecht ChJ, Stoter G, van den Bent MJ. Clinical characteristics of severe peripheral neuropathy induced by docetaxel (Taxotere). *Ann Oncol* 1997; **8**: 187–90.
36. van den Bent MJ, Hilkens PH, Sillevis Smit PAE, van Raaij-van den Aarssen VJM, Bontenbal M, Verweij J. Lhermitte's sign following chemotherapy with docetaxel. *Neurology* 1998; **50**: 563–4.
37. Freilich RJ, Balmaceda C, Seidman AD, Rubin M, DeAngelis LM. Motor neuropathy due to docetaxel and paclitaxel. *Neurology* 1996; **47**: 115–8.
38. Schrijvers D, Wanders J, Dirix L, *et al.* Coping with toxicities of docetaxel (Taxotere). *Ann Oncol* 1993; **4**: 610–1.

(Received 4 July 1998; accepted 14 July 1998)