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Clinical trials of nimodipine as a potential neuroprotector in ovarian cancer patients treated with cisplatin

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Abstract Our previous randomised trial in patients with advanced ovarian cancer indicated a significant response and survival advantage for those receiving high-dose (100 mg/m^2) as compared with low-dose (50 mg/m^2) cisplatin in combination with cyclophosphamide (750 mg/m^2). However, this was accompanied by more toxicity; peripheral neuropathy was troublesome, with 32% of patients experiencing ≥ WHO grade 2 at the cisplatin dose of 100 mg/m^2. Nimodipine is a calcium-channel antagonist that has provided protection from cisplatin-induced neurotoxicity in a rat model system. We performed a pilot study in 50 patients that demonstrated the feasibility of co-administration of nimodipine in a chronic oral dosing schedule with cisplatin-based chemotherapy in an open-label non-randomised trial. This led us to initiate a double-blind, placebo-controlled, randomised trial in patients with ovarian cancer, which was prematurely discontinued because of problems with nausea and vomiting, leading to poor patient compliance, that were not predicted by the pilot study. These studies did not demonstrate a neuroprotective effect for nimodipine. The primary efficacy variable, i.e, the neurotoxicity score at the end of treatment, gave a significantly lower mean for placebo patients than for nimodipine patients. This report details our experience and discusses the reasons for premature termination of the randomised trial.

Key words Neurotoxicity · Nimodipine
Ovarian cancer

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Introduction

In ovarian cancer, controversy exists over the optimal treatment schedule for patients with advanced disease, though most investigators would accept that platinum compounds are superior [3]. Active debate surrounds the issues of the choice of platinum analogue and the optimal dose intensity for single-agent or combination chemotherapy. Our group performed a large randomised trial of two doses of cisplatin given in combination with cyclophosphamide to patients with advanced ovarian cancer [1]. This study confirmed that a dose-effect relationship exists for cisplatin therapeutic activity but also demonstrated that the same was true of toxicity. The most troublesome side effect was a typical cisplatin-induced peripheral neuropathy; this was present at WHO grade II or above in 32% of patients receiving cisplatin at 100 mg/m^2. Nausea and vomiting was also troublesome, but the introduction of 5-hydroxytryptamine$_3$ (5-HT$_3$) antagonist therapy has vastly improved anti-emetic control in patients receiving high-dose cisplatin [4].

Although the precise pathophysiological mechanism that gives rise to cisplatin neuropathy is unknown [5–7], the search for protective agents has been aided by the development of a rat model system. Several compounds have shown promise in this system and are currently at various stages of clinical evaluation. These include a radioprotector, WR 2721 [6]; an adrenocorticotropic hormone (ACTH) analogue, ORG 2766 [8]; and glutathione [9].

Nimodipine is a dihydropyridine calcium antagonist with a relatively specific capacity for dilatation of cerebral arterioles, causing increased cerebral blood flow. This accounts for its use in a range of cerebrovascular disorders, particularly those associated with cerebral vasospasm [10]. In the United Kingdom it is licensed for use in the prevention and treatment of ischaemic neurological deficit following sub-arachnoid haemorrhage, with the recommended oral dose being 60 mg of 4 h (total dose 360 mg/day). Nimodipine may have a more

fundamental cellular mode of action, conferring protection on neural tissue exposed to ischaemia by limiting cellular calcium overload [11]. This may also account for the in vivo neuroprotective effect of this agent against cisplatin neuropathy in a rat model system [2]. The use of nimodipine in cancer patients may also have important additional benefits, such as inhibition of metastasis by blockage of tumour-cell platelet-endothelial interactions and circumvention of the multi-drug resistance phenotype in some human tumours [12].

Our initial pilot study was designed to demonstrate the feasibility of chronic oral dosing of nimodipine in conjunction with cisplatin-based chemotherapy. This was followed by a placebo-controlled, double-blind randomised trial that aimed to recruit 150 evaluable patients to have an 80–90% chance of detecting a change of 2 points (approximately half a standard deviation) in the mean neurotoxicity score recorded for the two groups. This study was prematurely terminated, mainly due to poor compliance with study medication.

Patients and methods

Patients

Patients aged less than 70 years who had histologically confirmed epithelial ovarian cancer of FIGO stages Ic–IV were eligible. Evidence of adequate renal function (creatinine clearance ≥ 60 ml/min), hepatic function (normal bilirubin levels, transaminase values less than twice the upper limit of normal) and bone marrow function (WCC > 3 for the pilot study and > 4 for the randomised trial, platelets > 100 for the pilot study and > 120 for the randomised trial) were required prior to entry. No patient had received prior chemotherapy, and all gave fully informed consent for the studies. Patients on concomitant calcium antagonist or beta-blocker therapy were specifically excluded to reduce the possibility of postural hypotension.

Chemotherapy schedule

The intended chemotherapy for all patients was 750 mg/m^2 cyclophosphamide and 100 mg/m^2 cisplatin given at 3-weekly intervals for a total of six cycles. A dose delay of 1 week occurred if the day-of-treatment leukocyte count was < 3 or the platelet count was < 100. The cisplatin dose was reduced by 25% if the creatinine clearance was ≤ 59 ml/min and the drug was discontinued if the creatinine clearance fell to < 40 ml/min. All patients had adequate pre- and post-hydration with cisplatin administration (sufficient to achieve a urine ouput of > 100 ml/h, and prophylactic anti-emetics were given routinely.)

Nimodipine dose schedules

Nimodipine 30-mg tablets and matching placebos were supplied by Bayer UK Limited. In the pilot study, increasing doses of nimodipine were given to sequential cohorts of patients for the assessment of tolerance. The treatment was given orally, commencing 24 h prior to the first pulse of chemotherapy, and was continued without planned interruption for 27 weeks, i.e. for 12 weeks following the last scheduled dose of cisplatin. We chose to give nimodipine in this chronic fashion rather than for just a few days around the time of chemotherapy because of the extremely prolonged tissue retention of cisplatin and because of the tendency for delayed-onset neuropathy in some patients receiving cisplatin. Patients were entered at the following dose schedules: 30 mg qds, 60 mg tds, 60 mg qds and 90 mg qds. Dosing at a frequency greater than four times daily was not attempted, as it was felt this would cause an unacceptable fall in compliance and patient acceptability. The maximal dose achieved (360 mg/day) was identical to that recommended for cerebrovascular disease.

In the randomised trial, nimodipine/placebo was commenced on the day following the first cycle of chemotherapy and was continued for 12 weeks following the end of cisplatin therapy (i.e., planned 27 weeks). Nimodipine/placebo tablets could be omitted on the day of chemotherapy in patients with severe emesis. The dose of nimodipine was initially fixed at 90 mg qds, but a few patients at the latter part of the study had dose reductions in an attempt to salvage poor compliance. A dose reduction was also permissible in patients with documented symptomatic postural hypotension (defined as a > 20-mmHg drop in systolic BP as determined from a lying to a standing position).

In both studies, compliance with study medication was checked by tablet counts and comparison of the recorded dates of discontinuation of medication with those predicted by the protocol.

General toxicity assessment

In the pilot study, toxicity was recorded using WHO criteria. In the randomised trial, toxicity was graded using the NCI common toxicity scale. This change was made because of a change in our group policy and to allow the data generated to be used for registration purposes by the study sponsors. Assessment visits in both studies were scheduled every 3 weeks and involved haematology and biochemistry profiles, history, clinical examination and lying/standing BP measurements.

Neurological toxicity

In the high-versus low-dose cisplatin study [1] we perceived that the WHO grading of this toxicity was not optimal and, in our opinion, tended to underestimate the true incidence and severity of this problem. Changes between grades are subjective and crude estimates of clinically important, more subtle changes. The WHO grading is given in Table 1. We therefore designed a structured questionnaire and neurological examination protocol for use in these two studies. A patient scores $+1$ for each of the following symptoms or signs that she has at that assessment: tingling or numbness of the feet, tingling or numbness of the fingers, burning or discomfort in the feet, burning or discomfort of the fingers, weakness of feet, weakness of hands, both sides of the body affected, continual symptoms, sleep disturbed by symptoms, difficulty in feeling small objects, restricted activity, extra medication needed for symptoms of neuropathy, inability to distinguish caliper points 4 mm apart on the pulp of the index finger, failure on Rombergs' test, decreased patellar reflex, decreased ankle reflex and inability to recognise vibration from a 128-mHz tuning fork at the terminal MP joint of the left hallux.

The neurotoxicity score can take a minimal value of 0 and a maximal value of 17. As far as possible this was administered by the same physician at each visit and, with experience, took less than 10 min to perform. In the pilot study this was performed at around 6 months from the initiation of chemotherapy; it was not performed at baseline as we used this cohort of patients to devise and validate the scoring system. It was compared with the WHO grades and both physician and patient estimates of neurotoxicity and was

Table 1 WHO grading of neurotoxicity

Grade 0	None
Grade 1	Paraesthesia and/or decreased tendon reflexes
Grade 2	Severe paraesthesia and/or mild weakness
Grade 3	Intolerable paraesthesia and/or marked motor loss
Grade 4	Paralysis

found to be in agreement with these cruder estimators whilst allowing numerical evaluation (data not shown). In the randomised study we intended to validate further the scoring system against formal neurophysiological evaluations, but this was not completed in view of the premature cessation of that trial.

In the randomised study this assessment was performed at baseline, at week 27 in patients completing six cycles of chemotherapy or at 12 weeks following the last cisplatin dose in those prematurely discontinuing protocol therapy. Assessments were thereafter performed at 6-monthly intervals.

Ototoxicity

Audiometry was performed at baseline and repeated at week 27. Hearing loss in decibels was measured in both ears at 4000 and 8000 cps and was scored as follows: 0 = >60, 1 = >50–60, 2 = >40–50, 3 = >30–40, 4 = >20–30, 5 = >10–20, 6 = >0–10 and 7 = <0. The maximal difference in this score (for either ear or either frequency) was taken as a secondary end point for the trial.

Antitumour efficacy

Tumour bulk was assessed at entry to the trials by the most appropriate means (usually CT or ultrasound), and this estimation was repeated after three and six cycles of chemotherapy. Patients with objective evidence of tumour progression received alternative chemotherapy at the investigators' discretion, but nimodipine was continued as specified above.

Randomisation and statistical methods

Random assignment to treatment groups was performed using a computer-generated randomisation schedule provided by the Biometrics group, Bayer UK Limited. Separate schedules were provided for each centre/stratum with a blocking factor that was a multiple of 2. Nine centres participated and, within each centre, further stratification was made according to the bulk of residual disease post-laparotomy (<2 cm versus ≥2 cm). Patient numbers were allocated in sequence within a centre/stratum, with no number being missed or substituted. We aimed to recruit 75 evaluable patients (patients were deemed to be unevaluable if they died before 27 weeks or were too ill for the neurotoxicity questionnaire to be completed) into each arm of the study. This would give an 80–90% power for detection of a 2-point change (approximately half a standard deviation) in the mean neurotoxicity score recorded for the two treatment arms. Four interim analyses were also planned using an O'Brien-Fleming sequential procedure. Before the first interim analysis took place, recruitment to the trial was stopped because of poor compliance. The neurotoxicity score at 27 weeks was compared between the two arms using analysis of variance techniques; the centre and extent were used as blocking factors and the initial neurotoxicity score served as a co-variate. A check was made for interactions and residuals were checked for approximate normality. Other data were compared between the treatment arms using either Pearson's chi-square test (qualitative variables), the Mann-Whitney *U*-test (ordinal categorical data) or Student's two-sample *t*-test (data with an approximately normal distribution). *P* values for the chi-square test and the Mann-Whitney *U*-test were obtained from the package StatXact.

Results

Pilot study

A total of 50 patients were entered on study; 1 patient was excluded because of incorrect diagnosis. The median age was 55 (range 35–68) years, and 55% of the patients had FIGO stage III disease (17% stage 1c, 9% stage II, 19% stage IV). No patient had pre-existing evidence of neuropathy. In all, 6 patients received nimodipine at 30 mg qds; 10, 60 mg tds; 7, 60 mg qds; and 26, 90 mg qds, which was the planned maximal dose tested.

In all 67% of patients received the planned six cycles of chemotherapy, with a total of 41% not requiring any dose delay or modification. The commonest toxicities cited as bringing about alteration of therapy were haematological, renal, ototoxicity, nausea and vomiting and peripheral neuropathy. Peripheral neuropathy of WHO grade II or above occurred in 8% of patients and was the cause of treatment withdrawal in only four patients in this study.

The incidence and severity of most non-neurological toxicities during chemotherapy was similar to that seen in our previous randomised trial [1]. There was a suggestion of less ototoxicity in the present study (WHO grade 2/3 14% versus 32%). There was an increase in the recording of grade 1–2 neurotoxicity during chemotherapy (51% versus 33%), which probably reflects an increased sensitivity to patients' neurological problems by participating clinicians. There was an unexpected and unexplained increase in gastrointestinal toxicity (nausea and vomiting grades 3–4 65% versus 39%), with eight patients being withdrawn from study for that reason. Postural hypotension was unusual, with only three patients requiring dose reduction for this problem. The results of this pilot study suggested that chronic oral dosing of nimodipine was feasible in conjunction with cisplatin-based chemotherapy.

Randomised study

A total of 51 patients were entered on this trial. One patient declined to take any trial medication of any sort on the day following randomisation and is therefore not considered further in this analysis. Demographic details are given for both groups in Table 2. Histological subtypes, degree of differentiation and sites of disease were well balanced between the groups (data not shown).

General chemotherapy toxicity

Toxicity was recorded as the worst CTC grade experienced in any cycle of therapy. No statistically significant difference between the nimodipine and placebo groups was found in the degree of anaemia, thrombocytopaenia, neutropaenia or nausea and vomiting.

Neurological toxicity

The primary efficacy variable in this study was the neurotoxicity score at week 27. Of the 50 patients who

Table 2 Patients' characteristics

		Nimodipine (n = 24)	Placebo (n = 26)	P value
Mean age (SD) in years		57.2 (8.1)	52.7 (11.4)	0.109
ECOG performance status:	0	63%	38%	
	1	21%	54%	
	2	17%	8%	0.279
FIGO stage:	1c	13%	12%	
	II	13%	8%	
	III	58%	69%	
	IV	17%	12%	0.995
Residuum > 2 cm		38%	50%	0.374

Table 3 Neurotoxicity scores recorded for 40 patients

	Nimodipine (n = 19)	Placebo (n = 21)	Estimated difference in adjusted means from ANOVA	P value
Week 27 mean neurotoxicity score (SE)	10.4 (1.0)	6.4 (0.8)	5.3 (1.1)	< 0.001

entered the trial and took the study drug, 40 provided data for this end point. Four patients died before they could complete the neurotoxicity questionnaire (two receiving nimodipine, two receiving placebo) and were therefore unevaluable. Two patients completed the questionnaire, but outwith the limit of ± 50 days (one receiving nimodipine, one receiving placebo); two patients (one receiving nimodipine, one receiving placebo) did not have adequate baseline assessments; one patient (nimodipine) did not complete the questionnaire; and for one other patient (placebo) the assessment was substantially incomplete. For a further 6 patients (5 receiving nimodipine, 1 receiving placebo) a single item was omitted from the assessment; for these patients the score on the missing item was taken to be their average score over the other 16 items. The results of neurotoxicity scoring are given in Table 3. If the analysis is restricted to patients who continued to take their nimodipine beyond their last cycle of chemotherapy, a further nine patients are lost from the nimodipine group and a further seven, from the placebo group. Most of these patients stopped the study drug early because of a combination of nausea, vomiting and the number of tablets they had to take. The results recorded for this more compliant group are given in Table 4. Altogether, 22 cycles were dose-modified on the placebo arm: 9 for haematological toxicity, 6 for renal toxicity, 3 for a combination of renal and marrow toxicity, 1 for vomiting, 1 for an allergic reaction to drug and 2 due to errors.

Table 4 Neurotoxicity scores of patients taking nimodipine after their last chemotherapy cycle

	Nimodipine (n = 10)	Placebo (n = 14)	Estimated difference in adjusted means from ANOVA	P value
Week 27 mean neurotoxicity score (SE)	10.7 (1.7)	6.1 (0.9)	6.5 (1.8)	0.002

Discussion

Ovarian cancer is increasing in incidence and is presently responsible for approximately 6% of cancer deaths in women in the western world [13]. Most investigators would accept that platinum combinations are superior in terms of the survival of patients with advanced disease [3], but this often results in marked emesis, peripheral neuropathy, ototoxicity and renal damage (from cisplatin). Our group performed a randomised trial of two doses of cisplatin given in combination with cyclophosphamide to patients with advanced ovarian cancer [1]. The results confirmed a dose-response relationship for cisplatin in the range of 50–100 mg/m^2 but also demonstrated an unacceptably high incidence of neurotoxicity for high-dose cisplatin.

At the time of initiation of the pilot study, two other compounds had been identified as potential neuroprotectors and were just about to enter clinical trials with other groups [8, 9]. We elected to pursue the possible benefits of nimodipine because of the promising preclinical data [2]; also, the drug had been licensed (and found safe), albeit in a different patient population.

The pilot study was designed to test the feasibility of combining chronic oral nimodipine with cisplatin/cyclophosphamide chemotherapy and to establish a safe dose regimen for the subsequent randomised trial. We found no evidence of compliance problems in the pilot study. An unexpected observation in this pilot study was the apparent increase in gastrointestinal toxicity. At the time,

we attributed this to our anti-emetic policy, since not all patients received a 5-HT_3 antagonist, and we therefore recommended this class of anti-emetic for the randomised trial patients. However, in the randomised trial, problems arose with nausea and vomiting that led to an unacceptably high dropout rate and eventually led us to abandon further patient entry. A large number of patients defaulted from study medication in the belief that the tablets exacerbated nausea and vomiting in the post-chemotherapy phase. Our results indicate that although there was a trend for patients on placebo to experience worse nausea and vomiting, this did not reach statistical significance ($P = 0.075$ in both cases). It is possible that group investigators (aware of the pilot data) in some subtle way influenced patients' perceptions or expectations of the trial medication. A more likely explanation is that in the pilot study all patients received an "active" drug that may have had neuroprotective effects, whereas in the placebo-controlled trial, subjects were aware that half of them would be on placebo. Thus, the patients' perception of potential benefit was altered between the studies to the detriment of the randomised trial. A further possibility is that patients who experience significant post-chemotherapy nausea may be unwilling to comply with any frequently given oral co-medication. We felt incapable of continuing the randomised trial as it was clear that the drop-out rate would make it impossible to accrue our target number of fully evaluable patients within a reasonable time scale.

Despite the premature cessation of the randomised trial we could detect a difference between the groups, given that the magnitude of effect is roughly 3 times greater than the one we set out to detect. The most important result is that this effect is exerted in the *reverse direction*, the conclusion being that nimodipine exacerbates neurotoxicity in this group of patients. The explanation for this observation is not clear, and it is not possible to exclude the possibility of neuroprotection by a different dose/schedule of nimodipine. It is also possible that nimodipine may have an effect on the timing of onset of or recovery from cisplatin-induced neuropathy. We assessed neurotoxicity only at baseline and 27 weeks later, by which time it is possible that any delayed-onset neuropathy may have become manifest. We continue to follow the neurotoxicity scores of all patients, but it is unlikely (in view of the small numbers) that we will be capable of drawing any definitive conclusions on any potential difference in recovery rates between the two treatment arms in the randomised trial.

A potential criticism of any agent designed to reduce the toxic effects of chemotherapy is that it may also reduce the anti-tumour efficacy. We found no evidence of this in the present trial, and the patients continue to be followed for detection of any longer-term differences in response time and overall survival. There was also no evidence that the relative dose intensity, total drug doses or treatment duration were significantly different between the nimodipine and placebo groups. There was also no difference in the other groups of toxicities on which data were collected. It is possible that nimodipine altered the pharmacokinetics of cisplatin or cyclophosphamide, thus exacerbating neurotoxicity, but this was not evident in other toxicity differences.

At the time that we commenced these studies, no compound had shown proven benefit in clinical trials of modulation of cisplatin neurotoxicity. Recent reports on two agents have been promising: glutathione given as a 3-g/m^2 single dose together with cisplatin has resulted in reduced toxicity in two trials, allowing a higher total dose of cisplatin to be given, with a suggestion of improved anti-tumour efficacy [14,15]; and amifostine (WR 2721) seems to be capable of modulating both cisplatin and carboplatin toxicities [16] and has some clinical utility [17]. The Org 2766 compound [8,18], on the other hand, has been shown to be ineffective in a double-blind randomised trial [19] despite promising preclinical activity and early clinical experience. None of the compounds above has been rigorously tested to ensure that it does not reduce cisplatin anti-tumour effect in addition to reducing its side effects. In the present study we could show no clear difference in anti-tumour response, which is not surprising in view of the small numbers evaluated in our randomised trial.

The introduction of Taxol into ovarian cancer chemotherapy has increased the potential utility of a neuroprotective agent, since this drug also causes a neuropathy, albeit with some important differences in its characteristics. If cisplatin is combined with Taxol as in the GOG study [20] or the current Scottish-EORTC-NCI Canada Intergroup trial (in which we are participants), the potential exists for limitation of therapeutic benefit because of neuropathy [21], even though the currently recommended cisplatin dose of 75 mg/m^2 reduces the number of patients with severe problems. Further studies of potential neuroprotectors are therefore clearly warranted, and we would recommend that such studies utilise clinical non-invasive assessments of neurotoxicity (such as ours) in conjunction with more complex neurophysiological testing.

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References

1. Kaye SB, Paul J, Cassidy J, et al. (1996) Mature results of a randomised trial of two doses of cisplatin for the treatment of ovarian cancer. J Clin Oncol 14: 2113–2119
2. Hamers FPT, Gerritsen van der Hoop R, Traber J, Neijt JP, Jennekens FGI, Gispens WH (1990). The calcium antagonist nimodipine in cisplatin induced neuropathy in the rat. Eur J Pharmacol 183: 1710–1711
3. Vermorken JB, Bokkel Huinink WW ten, Eisenhauer EA, Favalli G, Belpomme D, Conte PF, Kaye SB (1993) Carboplatin versus cisplatin. Ann Oncol 4 [Suppl 4]: 41–48
4. Soukop M (1990) A comparison of two dose levels of granisetron in patients receiving high-dose cisplatin. Eur J Cancer 26 [Suppl 1]: 15–19

5. Thompson SW, Davis LE, Kornfield M, Hilgers RD, Standefer JC (1984) Cisplatin neuropathy, clinical, electrophysiologic, morphologic, and toxicologic studies. Cancer 54: 1269–1275
6. Mollman JE, Glover DJ, Hogan WM, Furman RE (1988) Cisplatin neuropathy, risk factors, prognosis and protection by WR-2721. Cancer 61: 2192–2195
7. Mollman JE (1990) Cisplatin neurotoxicity N Engl J Med 322: 126–127
8. Gerritsen van der Hoop R, Vecht CJ, Burg MEL van der et al (1990) Prevention of cisplatin neurotoxicity with an ACTH (4-9) analogue in patients with ovarian cancer. N Engl J Med 322: 89–94
9. Hamers FPT, Brakkee JH, Cavalletti E, et al. (1993) Reduced glutathione protects against cisplatin-induced neurotoxicity in rats. Cancer Res 53: 544–549
10. Gilsbach JM, Reulen HJ Ljunggren B, Brandt L, Holst H van, Mokry M, Essen C von, Conzen MA (1990) Early aneurysm surgery and preventive therapy with intravenously administered nimodipine: a multicenter, double-blind, dose-comparison study. Neurosurgery 26: 458
11. Cahn J (1985) Nimodipine – pharmacological and clinical properties. Proceedings I Nimotop Symposium Munich, Betze et al. (eds) Schattauer, Stuttgart, pp 137–140
12. Mickisch GH, Kossig J, Keilhauer G, Schlick E, Tschada RK, Alken PM (1990) Effects of calcium antagonists in mutlidrug resistance primary human renal carcinomas. Cancer Res 50: 3670–3674
13. Williams C (1992) Current issues in cancer: ovarian and cervical cancer. BMJ 304: 1501–1504
14. Smyth JF, Perren T, Wilkinson R, Prescott RJ, Quinn KJ, Tedeschi M (1994) Cisplatin and glutathione: a phase III, double-blind, randomised study in stage I–IV ovarian cancer. Ann Oncol 5 [Suppl 8]: 2
15. Cascinu S, Del Ferro E, Catalano G (1994) Neuroprotective effect of reduced glutathione on cisplatin based chemotherapy in advanced gastric cancer: a double-blind randomised trial. Ann Oncol 5 [Suppl 8]: 80
16. Dellaflor-Weiss E, Blommaert F, Gill I, Muggia FM (1994) Amifostine (WR 2721) protects from bone marrow toxicity of combinations of cisplatin and carboplatin without decreasing platinum-DNA adduct formation. Ann Oncol 5 [Suppl 5]: 125
17. Treskes M, Vijgh WJ van der (1993) WR2721 as a modulator of cisplatin and carboplatin induced side effects in comparison with other chemoprotective agents: a molecular approach. Can Chem Pharmacol 33: 93–106
18. Hamers FPT, Pette C, Bravenboer B, Vecht CJ, Neijt JP, (1993) Cisplatin induced neuropathy in mature rats: effects of the melanocortin-derived peptide ORG 2766. Cancer Chemotherapy Pharmacol 32: 162–166
19. Neijt J, Van der Burg M, Vecht C, Tijssen C, Nooy A, Vermorken J, Van Oosterom A, Van Houwelinger J, Gispen W (1994) A double-blind randomised study with ORG-2766, an ACTH (4-9)analog, to prevent cisplatin neuropathy. Proc Am Soc Clin Oncol 13: 261
20. McGuire WP, Hoskins WJ, Brady MF, et al. (1993) A phase III trial comparing cisplatin/cytoxan (PC) and cisplatin/taxol (PT) in advanced ovarian cancer (AOC) (abstract 808). Proc Am Soc Clin Oncol. 12: 255
21. Chaudry V, Rowinsky EK, Sartorius SE, Donehower RC, Cornblath DR (1994) Peripheral neuropathy from taxol and cisplatin combination chemotherapy: clinical and electrophysiological studies. Ann Neurol 35: 304–311