PREVENTION OF CISPLATIN NEUROTOXICITY WITH AN ACTH(4–9) ANALOGUE IN PATIENTS WITH OVARIAN CANCER

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Abstract In a randomized, double-blind, placebo-controlled study, we assessed the efficacy of an ACTH(4–9) analogue, Org 2766, in the prevention of cisplatin neuropathy in 55 women with ovarian cancer. The analogue was given subcutaneously in a dose of 0.25 mg (low dose) or 1 mg (high dose) per square meter of body-surface area before and after treatment with cisplatin and cyclophosphamide (75 and 750 mg per square meter every three weeks). The threshold of vibration perception was used as the principal measure of neurotoxicity.

After four cycles of chemotherapy, the mean (±SEM) threshold value for vibration perception in the placebo group increased from 0.67±0.12 to 1.61±0.43 μm of skin displacement ($P<0.0001$). In the high-dose treatment group, there was no increase in the threshold value after four cycles (from 0.54±0.12 to 0.50±0.06 μm). After six cycles of chemotherapy, the threshold value was 5.87±1.97 μm in the placebo group (more than an eightfold increase from base line), as compared with 0.88±0.17 μm (less than a twofold increase) in the high-dose treatment group ($P<0.005$). In the high-dose group, fewer neurologic signs and symptoms were recorded than in the placebo group. With the lower dose of the analogue, these protective effects were less prominent. No side effects were seen after treatment with Org 2766. The rates of clinical response to chemotherapy were similar in all groups.

These results suggest that Org 2766 can prevent or attenuate cisplatin neuropathy without adversely affecting the cytotoxic effect of the drug. (N Engl J Med 1990; 322:89-94.)

MELANOCORTINS (ACTH and α-melanocyte-stimulating hormone–like peptides) are known to affect the function of the nervous system in animals and humans.[1] Evidence obtained from studies in animals suggests that these peptides exert a beneficial effect on mechanisms of peripheral-nerve repair.[2] After peripheral-nerve crush injury, ACTH and a number of derived fragments (Fig. 1) have been reported to accelerate recovery and enhance nerve regeneration in rats at the histologic, electrophysiologic, and functional levels.[4-7] Recovery was also enhanced after transection of the nerve.[8] The mechanism of action is not known, but evidence suggests the presence of an α-melanocyte-stimulating hormone–like substance in degenerating[9] or regenerating[2] nerve tissue. This led to the hypothesis that the exogenously administered peptide mimics an endogenous repair signal.[10] If melanocortins are part of the natural cellular repertoire that counteracts noxious influences on the nerve, the peptides may be beneficial in a variety of nerve afflictions besides mechanical injury. Subsequent studies showed that these neuropeptides are also effective in preventing and treating peripheral neuropathies caused by neurotoxic drugs.[3]

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Cisplatin is an effective cytotoxic agent in the treatment of ovarian and testicular cancer. At present, polyneuropathy is considered to be a dose-limiting side effect.[11] Earlier studies indicated that in 45 to 100 percent of patients a sensory neuropathy developed, depending on the type of therapy applied.[12-16] Paresthesias and numbness appeared first, but in later stages a sensory ataxia severely impeded walking in a substantial number of patients. Neurologic signs included the loss of tendon reflexes and a decrease in sensory qualities (mainly thick-fiber mediated), such as vibration perception, fine touch perception, and kinesthesia.[12,15-17] After therapy ends, symptoms continue in up to 50 percent of the patients, even 6 to 30 months after the last treatment course.[16]

Recently, a model was developed to study cisplatin-induced neuropathy in rats. After repeated injections of cisplatin, a dose-dependent decrease in sensory-nerve conduction velocity occurred.[18] With this model, it was demonstrated that the neurotrophic peptide Org 2766 (L-methionyl sulfone–L-glutamyl–L-histidyl–L-phenylalanyl–D-lysyl–L-phenylalanine; Fig. 1), an ACTH(4–9) analogue without corticotropic or melanotropic activity, protected against cisplatin neurotoxicity when given concomitantly.[19,20]

In the present study the efficacy of Org 2766 in preventing or delaying cisplatin-induced neuropathy was assessed in patients. A double-blind, placebo-controlled, randomized trial was performed in women with ovarian cancer, all treated with the same cisplatin-based chemotherapy, who were given either Org 2766 (in one of two doses) or placebo. We used a sensory neurophysiologic variable (the threshold of vibration perception) to assess the degree of damage

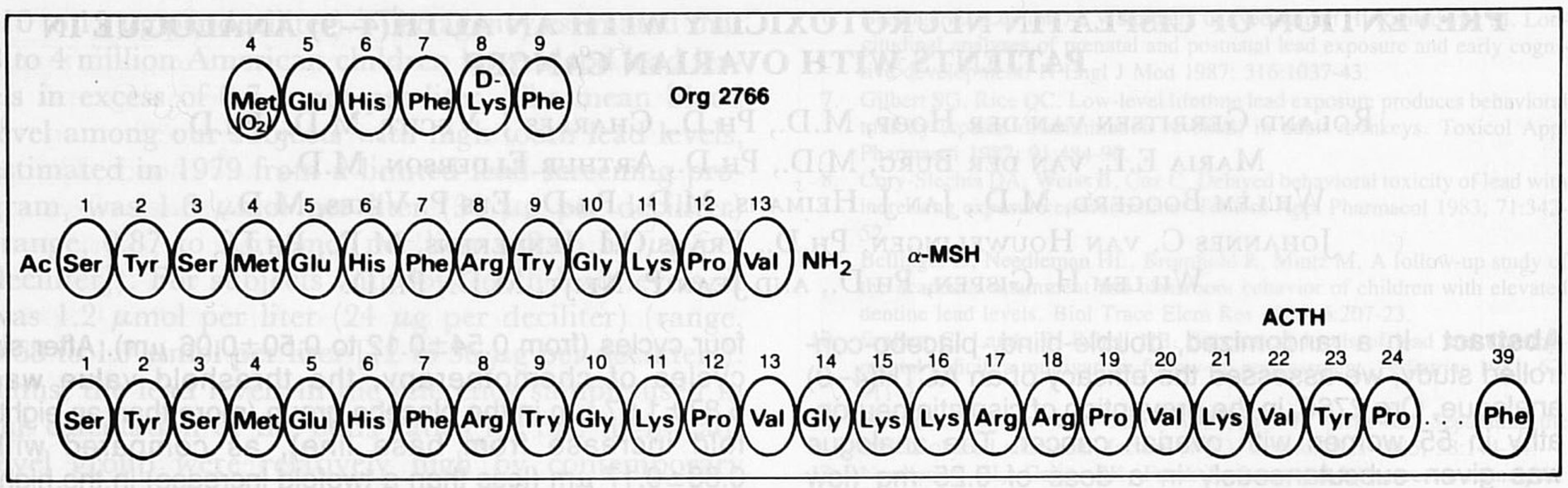

Figure 1. Amino Acid Sequences of ACTH, α-Melanocyte-Stimulating Hormone (α-MSH), and Org 2766.

Extensive structure–activity studies with fragments of ACTH and α-melanocyte-stimulating hormone have shown that the neurotrophic action of these melanocortins resides in the amino acid sequence 4–10, shared by ACTH and α-melanocyte-stimulating hormone.[1-4] Org 2766 is a structurally modified analogue of ACTH(4–9) with improved protection against breakdown.

cisplatin inflicted, because earlier studies had indicated that changes in this variable precede clinical signs.[15,21]

Methods

Patients

Women with a histologically verified epithelial ovarian carcinoma were eligible for the study. All patients had FIGO (International Federation of Gynecology and Obstetrics[22]) Stage III or IV disease. Patients were excluded if they were over the age of 70, had had previous chemotherapy, or had established clinical or subclinical neuropathy (abnormal vibration-perception thresholds or the presence of any neurologic symptom or sign listed in Table 1), diabetes mellitus, alcoholic disease, brain involvement or leptomeningeal disease, or inadequate bone marrow, liver, or renal function. Patients receiving vitamin B_1, B_6, or B_{12} supplements or following other vitamin diets were also excluded. Only patients with a World Health Organization performance status[23] of 0 (normal activity), 1 (symptoms, but fully ambulatory), or 2 (less than 50 percent of normal daytime hours spent in bed) were included in the study.

Drug Administration

The chemotherapy consisted of cyclophosphamide (750 mg per square meter of body-surface area) and cisplatin (75 mg per square meter), both administered on day 1. The schedule was repeated after three weeks. The patients were prehydrated with 1 liter of normal saline administered intravenously over a period of four hours, after which cyclophosphamide was given as a bolus intravenously. Immediately thereafter, cisplatin dissolved in 1 liter of normal saline was administered over a four-hour period. This was followed by further hydration with 2 liters of normal saline over a period of 16 hours. If the subsequent diuresis was less than 600 ml in 6 hours or if fluid retention was more than 1500 ml in 24 hours, 5 to 10 mg of furosemide was administered intravenously. When myelosuppression occurred, the dose of cyclophosphamide was modified. At least six courses of treatment were planned, but if the disease had progressed before the sixth cycle, therapy was discontinued. The protocol was identical to one used in a previous study by this group.[24]

Org 2766 was injected subcutaneously on day 1 at the start of prehydration and 24 hours later. It was administered in a low (0.25 mg per milliliter) or high (1 mg per milliliter) dose dissolved in water. Equal amounts of mannitol dissolved in water served as placebo. Patients received 1 ml of this solution per square meter. The test drug and placebo were identical in appearance, acidity, and effects immediately after injection. Both were supplied by Organon International (Oss, the Netherlands). Toxicologic studies in healthy volunteers and elderly patients had shown Org 2766 to be safe and without side effects or influences on blood biochemical and hematologic features, hormone levels, or urine.[25] No signs of anaphylaxis or disturbances of liver or kidney function, hematopoiesis, or electrolyte balance have been reported with either oral or subcutaneous administration.[26]

Evaluation of Therapy

Before each course of chemotherapy the participating oncologist took a history, performed a complete physical examination, assessed performance using the World Health Organization scale, and had blood samples analyzed for the hematocrit and to measure hemoglobin, white-cell, platelet, creatinine, and electrolyte levels.

Patients were examined by a neurologist before treatment and after two, four, and six courses. Patients were considered fully eligible for evaluation if measurements had been performed after four courses. As part of the neurologic examination, the answers to a number of obligatory questions and the results of various tests were scored as normal or abnormal, and then sum scores were calculated for both symptoms and signs.

The protocol stipulated that the threshold of vibration perception be measured on the second metacarpal bone of both hands at each neurologic examination. Before the study began, the change in vibration-perception threshold had been accepted as the sole primary dependent variable to assess the efficacy of Org 2766. To measure the change, all participating centers used the same instrument, a Vibrameter Type III (Somedic, Stockholm, Sweden). With this apparatus the investigator can vary the amplitude of the vibratory stimulus (recorded as micrometers of skin displacement) with an accuracy of up to 0.01 μm. An advantage of the Vibrameter is that the application pressure can be monitored and kept constant by the investigator.[27] The method of limits, as proposed by Goldberg and Lindblom,[28] was used to obtain the mean vibration-perception threshold. As the strength of the stimulus increased, the patient was asked to indicate when the stimulus was felt, and as the strength was decreased thereafter, the patient was asked to indicate when the stimulus could no longer be felt. This procedure was repeated three times, and the mean of the six recorded values yielded the threshold of vibration perception. Interobserver variance is small with this method.[28] The mean normal range (2 SD above and below the mean value) for the age group of 50 to 55 years lies between 0.15 and 1.00 μm. A pilot study showed that this method is sensitive, accurate, and reproducible. Increased values were associated with early cisplatin neurotoxicity. After four cycles of chemotherapy, vibration-perception thresholds were abnormal in all patients.[21] On the basis of this finding, a total of four treatment cycles was chosen as the chief end point of this study. We

Table 1. Symptoms and Signs in Patients Assessed after Four and Six Courses of Treatment.*

	Four Courses			Six Courses		
	Placebo Group (N = 13)	Low-Dose Org 2766 Group (N = 13)	High-Dose Org 2766 Group (N = 13)	Placebo Group (N = 12)	Low-Dose Org 2766 Group (N = 9)	High-Dose Org 2766 Group (N = 7)
	no. of patients					
Symptoms						
Paresthesias	5	1	1	8	3	2
Numbness	1	1	0	7	2	1
Loss of strength	1	0	0	1	0	0
Loss of dexterity	0	1	0	3	1	0
Unsteadiness	1	1	0	1	0	0
Pain	2	0	0	3	2	0
Lhermitte's sign	0	1	0	2	2	0
Sum score	0.77†	0.38	0.08	2.08‡	1.22	0.43
SEM	0.28	0.31	0.07	0.61	0.45	0.23
Signs						
Sense of pain	4	1	0	5	3	0
Fine touch	4	0	0	5	0	1
Sense of vibration	3	4	1	5	3	2
Achilles tendon reflex	3	0	0	6	1	2
Sum score I	1.08§	0.38	0.08	1.75	0.78	0.71
SEM	0.31	0.35	0.07	0.55	0.24	0.21
Sum score II	4.85¶	3.69	3.23	7.42¶	4.33	3.57
SEM	0.86	0.23	0.17	1.30	0.33	0.27

*Symptoms were scored as present (1) or absent (0). Signs were scored both as present or absent (I) and on a gradual scale (II). For score II, sense of pain, fine touch perception, and sense of vibration were measured at seven sites (the toe, foot, ankle, tibia, knee, thigh, and trochanter). The most distal positive site determined the score. The sum scores for signs and symptoms were calculated by adding the scores for each patient and dividing the result by the number of patients.

†P = 0.044. ‡P = 0.07. §P = 0.034. ¶P = 0.03.

chose to measure the vibration-perception threshold rather than sensory-nerve conduction because it was considered a sensitive method that did not cause discomfort, which we wanted to avoid if possible in these patients.

Organization and Mechanics of the Study

The departments of oncology and neurology of three university and two cancer hospitals were responsible for the recruitment, examination, and treatment of the patients between March 1, 1987, and January 10, 1989. Inclusion criteria, methods for evaluating the patients, and medical treatment were specified in a protocol and approved by the ethics committees of the participating centers. The women were screened on the basis of the eligibility criteria and gave their informed consent. The study was blinded with reference to the patient, the treating physician, and the evaluator, and placebo-controlled. Participating hospitals received a number of blocks with randomized treatment boxes and allocated patients to treatment in order of admission. Randomization had been performed before the study began, in blocks of four (two placebo, one high dose, and one low dose) for the first 36 women and in blocks of three (one for each possible treatment) for the rest. This method led to a preponderance of placebo over both low and high doses of Org 2766. We took this approach to obtain a well-documented control group for the vibration-perception thresholds. An interim analysis was performed after 31 patients had received four cycles of chemotherapy, but the treatment codes were not revealed to the physicians involved.

The final analysis included the data of 55 patients who had been admitted to the study.

Statistical Analysis

The homogeneity of the groups was assessed with analyses of variance for age and initial vibration-perception thresholds. To determine whether changes in vibration-perception threshold were dependent on age differences, we used Kendall's rank-correlation test[29] and Pearson's correlation tests.[30] To evaluate the efficacy of the drug, we compared the vibration-perception thresholds of all the groups after two, four, and six courses of treatment using an analysis of covariance with repeated measures and supplementary t-tests, with both starting value and age as covariates on log-transformed data. Chi-square tests were used to compare clinical symptoms and signs individually and to evaluate response rates. Sum scores of symptoms and signs were calculated as follows: Six symptoms (paresthesias, numbness, loss of dexterity, unsteadiness of gait, pain, and Lhermitte's sign, a feeling like an electric shock radiating through the body when the cervical spine is flexed or extended) elicited during the interview were scored as present (0) or absent (1), and a sum score of all symptoms (minimum, 0; maximum, 6) was calculated for each patient. Similarly, four signs (sense of pinpricks, sense of vibration as measured with a tuning fork, fine touch perception, and Achilles tendon reflexes) tested in the legs were scored as normal (0) or abnormal (1), and the sum score of signs was then computed for each patient (minimum, 0; maximum, 4). Group means were compared with the use of t-tests. For all signs except tendon reflexes, sum scores were also calculated according to a gradual scale (Table 1). The results were then compared with the use of exact permutation tests. Results with a two-tailed P value of less than 0.05 were considered to be statistically significant. Unless stated otherwise, the level of significance we indicate is for the comparison between the placebo group and the high-dose treatment group. The statistical program used was SPSS/PC+, Advanced Statistics (SPSS, Chicago).

Results

Patients' Characteristics and Homogeneity of the Groups

Fifty-five patients were admitted to the study; 22 were assigned to placebo, 17 to low-dose Org 2766, and 16 to high-dose Org 2766. At the time of this analysis, 42 patients had received two courses of treatment, 39 had received four courses and were considered fully eligible for evaluation, and 28 had received six courses. Sixteen patients were not fully eligible for evaluation: 1 (in the placebo group) refused further chemotherapy, 3 (1 in each group) had rapid progression of their tumor, and the remaining 12 had not yet received four courses of treatment. None of the patients were excluded because of violations of the protocol. No modifications in dose were made. The patients' characteristics are summarized in Table 2.

The mean duration of follow-up was 6.6 cycles (cumulative dose, 494 mg per square meter) for the 39 patients fully eligible for evaluation and 5.6 cycles (cumulative dose, 416 mg per square meter) for all 55 patients at the time of this analysis. The mean number of cycles for all the women who completed the study was 5.5, 6.2, and 6.7 for the placebo, low-dose, and high-dose groups, respectively ($P<0.08$).

Table 2. Characteristics of the 55 Women Admitted to the Study.

Characteristic*	Placebo Group (N = 22)	Low-Dose Org 2766 Group (N = 17)	High-Dose Org 2766 Group (N = 16)
Age (yr)	53	52	53
Range	39–65	31–65	22–66
FIGO (no. of patients)			
Stage III	19	12	13
Stage IV	3	5	3
Ascites (no. of patients)			
Absent	13	8	9
Present	9	9	7
WHO (no. of patients)			
Performance status 0	14	8	10
Performance status 1	6	9	6
Serum creatinine (μmol/liter)	81	86	81
Serum magnesium (μmol/liter)	83	82	86
Chemotherapy cycles			
Total no.	117	95	93
Mean no./patient	5.3	5.6	5.8

*FIGO denotes the International Federation of Gynecology and Obstetrics system of disease classification,[22] and WHO the World Health Organization system.[23]

The response to antitumor treatment could be assessed clinically in 34 patients by ultrasound examination or computerized tomography. Clinically complete remissions (defined as the complete regression of all clinically detectable tumor) occurred in 9 of 15 patients (60 percent) in the placebo group, 5 of 11 (45 percent) in the low-dose group, and 5 of 8 (63 percent) in the high-dose group. For partial remissions (defined as a decrease in measurable lesions of more than 50 percent) the corresponding results were 1 of 15 (7 percent), 4 of 11 (36 percent), and 1 of 8 (13 percent). The overall response rates (clinically complete and partial remissions) were 67, 82, and 75 percent, respectively ($P>0.2$).

Measurements of Vibration Perception

Means of the vibration-perception thresholds obtained before treatment began and after two, four, and six courses for the patients fully eligible for evaluation are given in Table 3. There were no significant differences between groups at the start of the study. Moderate changes were found in the placebo group after two courses of treatment. Mean vibration-perception thresholds increased significantly in the placebo group after four and six courses of treatment (by 0.94 and 5.20 μm, respectively; $P<0.0001$). There was also an increase in the low-dose treatment group (by 0.04 and 1.79 μm after four and six cycles, respectively). In the high-dose treatment group, there was no increase after two and four courses of treatment, but an increase of 0.34 μm after six cycles (t-tests performed after analysis of covariance on log-transformed data with age and initial value as covariates: $t = -2.54$, $P<0.02$; $t = -3.01$, $P<0.005$; and $t = -3.11$, $P<0.005$, respectively). Kendall's test for a correlation between age and increase in vibration-perception threshold demonstrated no significance ($W = 0.47$; $P>0.5$), whereas age and initial threshold of vibration perception were closely correlated ($P<0.001$).

Table 3. Thresholds of Vibration Perception as Measured with the Vibrameter before Chemotherapy and after Two, Four, and Six Treatment Cycles.

Period	Placebo Group	Low-Dose Org 2766 Group	High-Dose Org 2766 Group
	micrometers, mean ±SEM		
Base line	0.67±0.12	0.52±0.11	0.54±0.12
2 Cycles	0.75±0.10	0.41±0.05	0.40±0.06
4 Cycles	1.61±0.43*	0.56±0.11	0.50±0.06†
6 Cycles	5.87±1.97*	2.31±0.75	0.88±0.17†

*$P<0.0001$, as compared with base-line values.

†$P<0.005$, as compared with placebo at four and six cycles.

Neurologic Signs and Symptoms

Results pertaining to symptoms and signs are given in Table 1. None of the patients had any of the signs or symptoms before treatment. Paresthesias were invariably reported as the first symptom and were present in 5 of 13 patients (38 percent) in the placebo group after four courses, as compared with 1 of 13 (8 percent) in the low-dose group and 1 of 13 (8 percent) in the high-dose group (chi-square after Yates' correction, 1.95; $P = 0.16$). After six courses the corresponding numbers were 8 of 12 (67 percent), 3 of 9 (33 percent), and 2 of 7 (29 percent). Numbness became apparent only after six cycles, in 5 of 9 patients (56 percent) in the placebo group as compared with 1 of 6 (17 percent) in the low-dose group and 1 of 7 (14 percent) in the high-dose group. Loss of dexterity (3 of 12), sensations of pain (3 of 12), unsteadiness of gait (2 of 12), and Lhermitte's sign (2 of 12) were also recorded only after six cycles in the placebo group, and they were absent in the high-dose treatment group. The sum scores, calculated per patient for symptoms, also differed between the high-dose group and the placebo group (after four courses, $P = 0.044$ by exact permutation test; after six courses, $P = 0.07$).

Three of the 13 patients in the placebo group lost Achilles tendon reflexes after four cycles, whereas none of the patients in the treatment groups did. Changes in fine touch perception and the perception of pinpricks occurred in the placebo group (4 of 12) and the low-dose group (1 of 13), but not in the high-dose group. Sense of vibration, as measured with a tuning fork, was altered in 3 of 12, 4 of 13, and 1 of 13 patients in the respective groups. There were no statistically significant differences for any single sign, but the sum scores showed a difference between the placebo and high-dose treatment groups ($P = 0.03$ by exact permutation test). After six cycles the changes were more prominent, not only in the placebo group (5 of 12 for tendon reflexes, 5 of 12 for perception of pinpricks, 6 of 12 for sense of vibration, and 5 of 12 for fine touch perception), but also in the low-dose group (3 of 9, 3 of 9, 1 of 9, and 0 of 9, respectively) and the high-dose group (2 of 7, 0 of 7, 2 of 7, and 1 of 7, re-

spectively). The sum score for the gradual scale remained significantly different between the high-dose and placebo groups ($P = 0.03$ by exact permutation test).

A number of possible correlations were also investigated. Although there was no significant correlation between the threshold of vibration perception and the sum score of symptoms after either four ($r = 0.32$) or six ($r = 0.35$) courses of treatment, significant correlations were found between the vibration-perception threshold and the sum score of signs after both four and six courses ($r = 0.63$, $P<0.001$; and $r = 0.54$, $P<0.01$, respectively). The sum score of signs after four and six courses correlated well with that of symptoms after four courses ($r = 0.58$ and 0.65, $P<0.001$ for both comparisons).

Toxicity

No adverse reactions other than those clearly related to chemotherapy (nausea, vomiting, diarrhea, and impairment of renal function) were reported in any of the three groups.

Discussion

The results indicate that Org 2766 can exert a beneficial effect on cisplatin-induced neurotoxicity in women with ovarian cancer. We have shown that when given concomitantly with cisplatin, Org 2766 in a dose of 1 mg per square meter can prevent or attenuate an increase in the threshold of vibration perception. It also reduced the occurrence of symptoms of neuropathy after four cycles of treatment and signs of neuropathy after four and six cycles. The drug did not cause any side effects or affect the antitumor activity of cisplatin, although a larger study would be required to be certain of the latter. The response rate for chemotherapy was comparable to that reported earlier[24] and to rates found by others.[31,32]

Earlier studies showed that the sense of vibration is affected in a subclinical phase of cisplatin neuropathy and can be measured quantitatively and accurately.[15,21] Measurements of thresholds of vibration perception have been thoroughly validated, have the necessary sensitivity, and do not cause the patient discomfort.[27,28] Although measurements of sensory-nerve conduction and evoked potentials may better reflect the nature of neurophysiologic changes, they do not necessarily relate to the patient's clinical status. The increase in vibratory-perception thresholds in the placebo group after four and six courses of treatment corresponds closely with the decrease in the duration of perception of tuning-fork vibration reported previously.[15]

The high incidence of paresthesias in the placebo group after four treatment courses (cumulative dose, 300 mg per square meter) is in agreement with the findings of other investigators.[12-16] Other symptoms were less frequently observed in this stage and only became manifest in a substantial number of patients after six treatment courses (cumulative dose, 450 mg per square meter). Comparison with earlier studies is difficult, because of the use of different drugs and doses and the pooling of patients who had various tumors.[33] Therefore, our results can be evaluated only with respect to the specific combination of drugs used.

Little is known about the mechanism underlying cisplatin-induced neuropathy. Since the neuropathy is predominantly sensory and the concentrations of cisplatin in both spinal cord and brain tissue are 5- to 20-fold lower than elsewhere in the body, it is assumed that cisplatin affects the sensory neurons or supportive cells in the dorsal root ganglia, which are less well protected by the blood–brain barrier.[17]

A number of hypotheses have been put forward with respect to the mechanism of action of melanocortins such as α-melanocyte-stimulating hormone and Org 2766 on the peripheral nervous system. Evidence suggests the presence of an α-melanocyte-stimulating hormone–like substance in degenerating and regenerating nerve tissue.[9] This substance may trigger or facilitate neural repair. Exogenously administered melanocortins may mimic this endogenous signal.[10] It has also been suggested that the expression of the precursor of ACTH and ACTH-like peptides is enhanced after an injury to nerve tissue.[10] Likewise, Org 2766 may mimic or supply the resulting signal. In view of the wide range of injuries in which melanocortins have been shown to be of benefit in rats (crush injury,[4-7] cut injury,[8] diabetic neuropathy,[34] acrylamide neuropathy,[35] and cisplatin neuropathy[19,20]), it is unlikely that a direct interaction between Org 2766 and cisplatin in neurons is responsible for the observed effects. A more probable hypothesis may be that Org 2766 enhances the ability of neurons to overcome the toxic effects of cisplatin and similar drugs by stimulating defensive or compensatory mechanisms inherent in the neuron.[3]

One other drug, ethiofos (WR-2721), a mercaptamine derivative, is of potential interest with respect to cisplatin neurotoxicity. Concomitant use of this drug permitted the administration of a higher mean dose of cisplatin in a recently published, open, uncontrolled study.[33]

It is also interesting that the patients treated with Org 2766 (1 mg per square meter) tended to receive more chemotherapy cycles than those given placebo. If treatment with Org 2766 delayed or prevented cisplatin neurotoxicity, it would probably allow the administration of more treatment cycles if needed. Furthermore, patients would be in a more advantageous position if a tumor recurred and additional therapy were necessary. At present, neurotoxicity is a major obstacle to treatment with cisplatin. Our results are promising and could mean a better quality of life for patients treated with this drug. Perhaps prolonged treatment with this antitumor drug will become possible, but our findings do not convincingly allow that conclusion.

In summary, this study has provided evidence indicating that Org 2766 is a promising new drug for the

prevention of cisplatin-induced neuropathy. Whether Org 2766 may be useful in the treatment of other forms of neuropathy is currently being investigated.

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