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Original Paper

Phase II Study of Weekly High-dose Cisplatin for Six Cycles in Patients with Locally Advanced Squamous Cell Carcinoma of the Head and Neck

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In a phase I study of weekly administered cisplatin, we observed a major response in 8 of 9 patients with locally far advanced head and neck cancer. Therefore, a phase II study was initiated to explore the activity and tolerance of this weekly cisplatin regimen. 59 patients with locally advanced head and neck cancer were entered into this phase II study. Cisplatin was administered at a dose of 80 mg/m^2 weekly for 6 cycles. Cisplatin was administered in hypertonic saline (3% NaCl) as a 3-h infusion with standard pre- and posthydration. 51 patients were evaluable for response and 55 for toxicity. Only 9 patients were able to complete the treatment with the planned dose intensity of 80 mg/m^2/week. Complete disappearance of the tumour was observed in 8 patients and a partial response in 22 (response rate 59%; 51% of all eligible patients 95% CI limits 37–63%). Stable disease was observed in 12 patients, and the tumour progressed in 9 patients. 47 patients subsequently received high-dose radiotherapy, 1 radiotherapy and surgery and 4 patients second-line chemotherapy. The median progression-free survival and median overall survival for all patients were 32 weeks and 56 weeks, respectively. Haematological toxicity consisted of anaemia, leucocytopenia (grade 3 + 4 in 17 patients) and thrombocytopenia (grade 3 + 4 in 17 patients). Because of leuco- and/or thrombocytopenia, treatment was delayed in 30 patients while 13 were taken off the study because of delayed bone marrow recovery. Non-haematological toxicities were: ototoxicity grade 1 in 3 patients, grade 2 in 7 and grade 3 in 3 patients; nephrotoxicity grade 1 in 13 patients, grade 2 in 2 and grade 3 in 1 patient. Neurotoxicity grade 1 was observed in only 8 patients. Cisplatin, as a single agent, administered at high-dose intensity, has an antitumour activity comparable with that of combination regimens in locally advanced head and neck cancer. The pattern of toxicity is different: leuco- and thrombocytopenia jeopardise the dose intensity concept; for patients ototoxicity is the more relevant toxicity. Further studies with weekly cisplatin are of interest particularly with newer measures to reduce toxicity. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: head and neck cancer, cisplatin, phase II study, dose intensity

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INTRODUCTION

APPROXIMATELY 50–60% of patients with head and neck cancer present at diagnosis with a locally advanced tumour, stage 3 or 4. Depending on the site and the extension of the tumour, treatment with surgery followed by radiotherapy or with high-dose radiotherapy only, will yield an average cure rate of only 30–40%. Most patients will die from local recurrence, while 10–15% will die from distant metastases [1].

The contribution of neoadjuvant chemotherapy in locally far advanced head and neck cancer is still not clear in spite of the high response rates that can be achieved. Nevertheless, in many centres these patients are initially

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treated with chemotherapy followed by local therapy. The combination of cisplatin with continuous infusion of 5-fluorouracil over 4–5 days and the combination of cisplatin with bleomycin and methotrexate are considered the most active regimens [2–4], with response rates of 60–90% including 30–35% complete responses. Side-effects, such as nausea and vomiting, alopecia, phlebitis (with 5-fluorouracil regimens) and the need for lengthy hospital admission—or ambulatory pump facilities with central venous access—for continuous infusion schedules are frequent causes of patient non-compliance.

Cisplatin administered every 3–4 weeks as a single agent yields a response rate of only 20–30% in these patients [5, 6]. In a phase I study with weekly administered cisplatin, we observed a response in 8 of 9 patients with locally advanced head and neck cancer [7]. In this study, cisplatin at a dose of 80 mg/m^2/week was well tolerated by most chemotherapy-naive patients. This result suggested that single agent neoadjuvant cisplatin, given at a high dose-intensity, may yield a response rate comparable with that of combination chemotherapy regimens. In order to test this concept further, we performed a multicentre phase II study.

PATIENTS AND METHODS

All patients in the study had histological proof of squamous cell carcinoma of mucous membranes of the head and neck, tumour stage 3 or 4 according to the UICC classification and were considered unresectable by a team consisting of a head and neck surgeon, a radiotherapist and a medical oncologist. Further entry criteria were: age <75 years, ECOG performance status <2, life expectancy >3 months, no prior chemotherapy, no prior radiotherapy, clinically measurable disease or measurable lesion on CT-scan, WBC $>3.0 \times 10^9$/l, platelets $>100 \times 10^9$/l, serum creatinine <120 μmol/l and/or creatinine clearance >60 ml/min, serum bilirubin <25 μmol/l. Excluded were patients with undifferentiated nasopharyngeal cancer, tumours of the salivary glands and the lip, patients with distant metastases, patients with suspicion of CNS involvement due to ingrowth in the base of the skull, and patients with a Korsakoff's syndrome. All patients gave oral or written informed consent according to the rules of the Institute.

Before beginning treatment, patients had a full clinical examination with medical history, physical examination, measurement of the indicator lesions, full haematological counts and serum chemistries, creatinine clearance, ECG, chest X-ray and CT-scan of the head and neck.

During treatment, weekly haemoglobin, WBC, platelets, serum chemistry and creatinine clearance were obtained. Neurological examination and audiometry were conducted before start of the treatment, after 3 and 6 cisplatin administrations, and 3 months after cessation of treatment. The patients were hospitalised for 24 h once a week. Cisplatin at a dose of 80 mg/m^2 was dissolved in 250 ml 3% NaCl and administered as a 3-h infusion. Prehydration consisted of 1 litre dextrose/saline in 4 h + 20 mmol KCl + 2 g $MgSO_4$; posthydration consisted of 2 litres dextrose/saline in 8 h + 40 mmol KCl + 4 g $MgSO_4$. As an anti-emetic, 8 mg ondansetron or an equivalent dose of another $5HT_3$ antagonist was administered i.v. prior to the start of cisplatin.

Dose reductions were not allowed. If at the time of retreatment WBC were $<2.5 \times 10^9$/l and/or platelets were $<75 \times 10^9$/l treatment was postponed until recovery with a maximum delay of 3 weeks. In case of a longer delay, the patient was taken off study. In case of neuro- or nephrotoxicity ≥ grade 2, the patient was also taken off study.

Response to treatment was assessed by a medical oncologist, a head and neck surgeon and a radiotherapist 2 weeks after the last cisplatin administration, at which time further therapy was planned. The WHO guidelines for classification of response were used. Toxicity of the chemotherapy was also determined according to the WHO recommendations [8].

Table 1. Patient characteristics

Number of patients entered	59	
Male:female	44:15	
Median age (years, range)	54	(39–72)
Performance status		
0	13	
1	46	
Site of primary tumour		
Oropharynx	28	
Tongue base	11	
Hypopharynx	9	
Nasopharynx	6	
Larynx	3	
Oral cavity	2	
UICC-stage		
3	2	
4	57	
Differentiation grade		
Well	9	
Moderate	40	
Poor	10	

RESULTS

59 patients were entered in the study between May 1991 and August 1993. The patient characteristics are given in Table 1, the TNM-classification is given in detail in Figure 1.

Treatment

In total, 258 cycles of cisplatin were administered, with a median of 5 per patient (range 1–6). In Table 2 the number of cisplatin cycles administered per patient is specified. 22 patients (37%) received the planned six cycles, but only 9 reached the intended dose intensity of 80 mg/m^2/week; the dose intensity reached was 68 mg/m^2/week in 7 patients with 1 week delay and 60 mg/m^2/week in the 6 patients with 2 weeks delay.

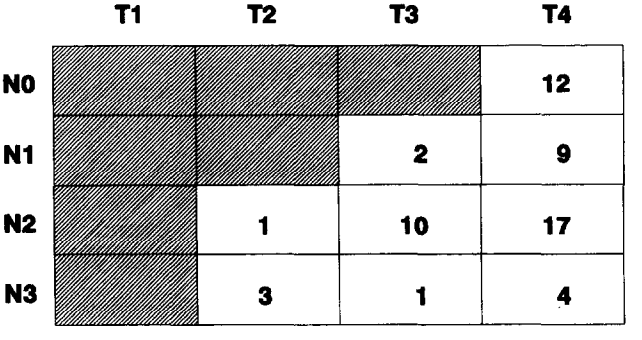

Figure 1. TNM-classifications.

Table 2. Number of cisplatin cycles administered per patient

Number of cisplatin cycles administered	Number of patients	Reason off study
1	8	PD 2 patients, CVA 1 patient, toxicity 5 patients*
2	2	PD 1 patient, refusal 1 patient
3	6	delay >3 wks 4 patients, PD 1 patient, ototoxicity 1 patient
4	10	delay >3 wks 6 patients, PD 2 patients, nephrotoxicity 1 patient, refusal 1 patient
5	11	delay >3 wks 3 patients, nephrotoxicity 3 patients, ototoxicity 1 patient, hypomagnesaemia
6	22	1 patient, angina pectoris 1 patient, pneumonia 1 patient, refusal 1 patient

*Reversible tubulus necrosis 1 patient, grade 2 nephrotoxicity 1 patient, grade 1 nephrotoxicity 1 patient, tinnitus 2 patients; PD, progressive disease; CVA, cerebrovascular accident.

Reasons not to complete the planned treatment were progressive disease in 6 patients, toxicity in 25 patients, intercurrent illness in 3 and refusal in 3 patients. Bone marrow toxicity was the reason 13 patients were taken off study mainly due to too slow recovery from thrombocytopenia. 3 patients were taken off study after the first cisplatin cycle because of nephrotoxicity and 2 patients because of ototoxicity. During later cycles, another 4 patients were taken off study because of nephrotoxicity, 1 patient because of hypomagnesaemia and 2 because of clinical hearing loss. These patients are included in the toxicity analysis.

Response

As nearly all patients had radiotherapy within 2–3 weeks after response evaluation, the 'responses' observed in this study do not all meet the WHO criterium of a confirmatory observation after at least 4 weeks.

51 patients were fully evaluable for response to chemotherapy. In 8 patients, response was not evaluated because they had received only 1 or 2 cisplatin administrations (Table 2) and 1 patient who refused the sixth cycle and refused evaluation. These 8 patients are considered as treatment failures in the overall evaluation. In 8 patients, the tumour disappeared completely clinically and/or radiologically (7 patients with oropharyngeal and 1 with hypopharyngeal cancer), and the tumour response met the criteria of a partial response in 22 patients for an overall response rate of 59% of the evaluable patients (95% confidence limits 47–72%) and 51% of all eligible patients (95% CI: 37–63%). In 17 of the responding patients, weekly clinical measurements were made, and in 15 patients the partial response status was reached after the third cisplatin administration. In 12 patients, the tumour remained stable; 6 patients were taken off study because of progressive disease while 3 additional patients had progressive disease at response evaluation. The median time to progressive disease in these patients was 4 weeks (range 1–8 weeks).

Comparison of clinical prognostic factors between the patients with a complete or partial response versus the non-responding patients showed no significant difference when tested for gender ($P = 0.75$), tumour site (oropharynx versus other localisations $P = 0.45$), histological differentiation (well versus moderate versus poorly differentiated: $P = 0.10$), T-stage ($P = 0.52$) or N-stage (N0 versus N_{1-3}) $P = 0.80$ (Fisher's exact test two-sided). Because of additional treatment after cisplatin (definitive radiotherapy in 47 patients, radiotherapy and surgery in 1 patient and second-line chemotherapy in 4 patients), no comments can be made about response duration of the chemotherapy regimen.

Relapse/survival

The overall progression-free survival was 32 weeks (range 1–252$^+$ weeks) and the median survival 56 weeks (range 3–252$^+$ weeks). 47 patients were treated with radiotherapy (60–70 Gy in fractions of 1.8–2 Gy) after chemotherapy and 1 patient had radiotherapy followed by a neck dissection for residual lymph nodes (which showed only necrosis at histological examination). 4 patients were treated with a second-line chemotherapy regimen and received radiotherapy later. 1 patient refused additional treatment and 3 patients were lost to follow-up and never started the proposed radiotherapy. The patient with the cerebrovascular accident, the patient with reversible tubulus necrosis and 1 patient with rapid progressive disease never started additional therapy. All 8 patients with a complete response on cisplatin had radiotherapy, of which 2 recurred locally after 57 and 62 weeks, respectively, and 1 died without evidence of the tumour at 62 weeks of a cardiac event. The other 5 patients are alive without evidence of disease at 130, 206, 208, 220 and 252 weeks.

Of 22 patients with a partial response on chemotherapy, 21 received radiotherapy. 1 patient refused radiotherapy. 14 patients had a complete response after radiotherapy, 5 patients had residual disease; in 2 patients follow-up data were insufficient to determine the disease status after radiotherapy. The median time to progressive disease in this group of patients was 40 weeks (range 8$^+$–182$^+$ weeks) and the median survival 62 weeks (range 16–182$^+$ weeks). With the exception of a patient relapsing with lung metastases, all first relapses were locoregionally.

Treatment outcome was dismal in the patients not responding to chemotherapy: of the 12 patients with stable disease, 11 had radiotherapy and only 1 patient achieved a complete response. All other patients had residual tumour, and the time to progressive disease in this group was median 28 weeks (range 10–60 weeks). 6 of the 9 patients with progressive disease with chemotherapy received radiotherapy, but all had residual tumour. The median survival was 36 weeks for the patients with stable disease and only 28 weeks for patients with progressive disease.

Toxicity

55 patients are included in the toxicity analysis. The results are reported in Table 3. Anaemia >grade 2 was observed in 7 patients; 22 patients required red cell trans-

Table 3. Worst toxicity observed per patient (WHO criteria)

	0	1	2	3	4
Anaemia	5	13	30	6	1
WBC	12	11	15	16	1
Platelets	11	13	14	9	8
Nausea and vomiting	9	12	14	20	0
Neurotoxicity	47	8	0	0	0
Ototoxicity	32	13	7	3	0
Nephrotoxicity	39	13	2	1	0

fusions for a total of 66 units of packed cells. Leuco- and thrombocytopenia >grade 2 were never observed before the third cisplatin administration. 1 patient developed leucocytopenia grade 4 and 8 patients thrombocytopenia grade 4. 4 patients required one platelet transfusion each. A delay in cisplatin administration due to leuco- or thrombocytopenia was necessary in 30 patients and 13 patients were taken off study because of a delay > 3 weeks.

Nausea and vomiting was reported by most patients in spite of the $5HT_3$ antagonists used, particularly after the third cisplatin administration. In 1 patient, a delay of one week was reported because of nausea and vomiting. Nausea and insufficient fluid intake was held responsible for nephrotoxicity in at least 4 patients.

Nephrotoxicity caused patients to be taken off study after the first administration in 3 patients. During further treatment, another 4 patients had an increase in serum creatinine leading to treatment discontinuation. 1 patient developed a symptomatic hypomagnesaemia (seizures). 10 other patients developed serum magnesium values <0.50 mmol/l.

The median serum creatinine of the eligible patients at the start of treatment was 74 μmol/l (range 51–120) and increased to a maximum median value during treatment of 110 μmol/l (range 59–629). According to the WHO criteria, 13 patients had a nephrotoxicity grade 1, 2 patients grade 2 and 1 patient a grade 3. In 7 patients nephrotoxicity improved 1 grade and in 1 patient 2 grades after cessation of cisplatin.

Ototoxicity was graded to the NCI-CTC criteria: grade 2 (tinnitus) was observed in 7 patients, and CTC-grade 3, clinical hearing loss, necessitating a hearing aid, in 3 patients. In one of these patients, hearing loss developed during radiotherapy. In 13 other patients, a decrease in high frequency hearing without clinical complaints was demonstrated (CTC-ototoxicity grade 1).

The median *weight loss* during treatment was 1.5 kg (range +3–12 kg). 9 patients had weight loss >5%, 1 patient >10% of starting body weight. In contrast, 14 patients gained weight during treatment.

Neurotoxicity grade 1 was observed in 8 patients, including 2 patients who developed paraesthesias after cessation of therapy. *Alopecia* was not observed.

DISCUSSION

The incidence of head and neck cancer, especially stage 3 and 4 tumours, is increasing in The Netherlands. Local treatment is curative in only a third of patients. Attempts to improve this disappointing result by initially treating patients with chemotherapy have not, thus far, resulted in a clear benefit [9–12]. Subgroups of patients may benefit from the combination because of improved local control rate or a delay in occurrence of distant metastases [3, 4]. In laryngeal cancer and oropharyngeal cancer, the combination of chemotherapy with radiotherapy can prevent mutilating surgery in a considerable group of patients [11, 15]. In most neoadjuvant chemotherapy combinations, a low-dose intensity is reached, especially for cisplatin. In a randomised phase II study of single agent cisplatin (60 mg/m^2 versus 120 mg/m^2 every 3 weeks), no advantage of the higher cisplatin dose was shown, but the study included only 24 previously untreated patients [6]. As a dose–response relationship for cisplatin is suggested in several tumour types, it is worthwhile testing schedules developed to reach a higher dose intensity in head and neck cancer. Forastiere and coworkers [16] obtained a response in 16 of 22 (73%) of patients with head and neck cancer with a regimen of cisplatin 40 mg/m^2 day 1–5 or 50 mg/m^2 day 1–4. In the present phase II study, we administered cisplatin weekly, also testing the dose intensity concept. An additional, theoretical, advantage of weekly chemotherapy administration is that cells repopulating after the previous chemotherapy dose have less time for regrowth than with conventional chemotherapy schedules [17]. The response rate of 59% in evaluable patients confirms our impression from the phase I study that cisplatin single agent administered at a relatively high-dose intensity has comparable activity with 'standard'-combination chemotherapy regimens, as was already suggested in Forastiere's study, which had a planned dose intensity of 50 mg/m^2/week. The results of our present study are also comparable with the results of the cisplatin–fluorouracil study performed by our group in a comparable patient group [18]. The patient compliance in our study was acceptable as only 3 patients refused treatment. The short duration of the treatment and the one-night hospital stay per week is perhaps more attractive to these patients than day 1–5 treatment schedules. The dismal prognosis in patients not responding to chemotherapy is striking. Only in 1 patient was radiotherapy able to convert a stable disease into a complete response and none of the patients with progressive disease on cisplatin responded to radiotherapy. This concurs with the report by Ensley and coworkers [19]. In contrast, 14 of 21 patients with a partial response on chemotherapy were rendered free of disease after radiotherapy. We could not identify a specific subgroup of patients with poor prognostic factors, such as extensive T-stage or N-status, which are correlated with poor treatment outcome [20, 21]. As in most responding patients, signs of objective or subjective improvement were present after three cisplatin administrations, the absence of signs of response after three administrations can be considered a reason to stop chemotherapy, sparing the patients further toxic treatment. Toxicity resulted in less than half the patients completing the planned treatment. Only 9 patients completed their treatment without any delay, reaching the planned dose intensity of 80 mg/m^2/week, while the other patients completing the planned treatment reached cisplatin dose intensities of 60–68 mg/m^2/week. In particular, leuco- and thrombocytopenia frequently precluded weekly administrations and was the main toxicity for which patients were taken off study. Schedule-related nephro- and ototoxicity caused the withdrawal of 7 patients, the patient with symptomatic hypomagnesaemia included. To diminish the risk of

neophrotoxicity cisplatin was administered in hypertonic saline, as used in other high-dose intensity schedules [16, 22, 23]. Graded according to the WHO-criteria, the risk of nephrotoxicity appears relatively low. Ototoxicity is, for the patients, a more troublesome side-effect of high-dose intensity schedules. Ototoxicity grade 2 (tinnitus) can be reversed, but grade 3 (clinical hearing loss), as observed in 3 of our patients, is not. In this study audiograms were not routinely performed in all patients so that ototoxicity grade 1 will have been missed in several patients. In other high-dose cisplatin sudies, ototoxicity grade 2 and 3 have been reported in up to 65% of patients [16, 22–25]. In Forastiere's study, 9 of 22 patients withdrew from study because of ototoxity. In that same study neurotoxicity grade 2 + 3 was reported in 6 patients. Neurotoxicity was not problematic in our schedule, probably because the cumulative dose of cisplatin was not high, but neurotoxic symptoms may develop up to 3 months after cessation off therapy, emphasising the need for prolonged follow-up [26, 27].

Whether a weekly chemotherapy schedule has any advantage over conventional combination chemotherapy regimens, and which cisplatin dose intensity will give optimal results, can only be shown by a randomised study. In view of the disappointing results of neoadjuvant chemotherapy in head and neck cancer and the more optimistic results of concomitant chemoradiotherapy schedules, testing this schedule with radiotherapy would be a more logical next step [28]. Studies to minimise toxicities should be a priority over randomised studies or combination with radiotherapy. Amifostine (WR 2721) is a drug with a broad protective effect on nephro-, neuro-, oto- and haematological toxicity [29]. The EORTC Head and Neck Cancer Cooperative Group recently started a randomised phase II study with weekly cisplatin at a dose of 70 mg/m^2/week for 6 weeks with or without amifostine to study the protective effect of this drug, especially on nephro- and ototoxicity. If these toxicities can be prevented, further studies with cisplatin at high-dose intensity schedules will be more feasible.

1. Million RR, Cassisi NJ, Clark JR. Cancer of the head and neck. In De Vita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*, 3rd edition. Philadelphia, PA, Lippincot 1989, 488–590.
2. Vogl SE, Schoenfeld DA, Kaplan BH, *et al.* A randomized prospective comparison of methotrexate with a combination of methotrexate, bleomycin and cisplatin in head and neck cancer. *Cancer* 1985, **56**, 432–442.
3. Ervin TJ, Clark JR, Weichselbaum RR, *et al.* An analysis of induction and adjuvant chemotherapy in the multidisciplinary treatment of squamous-cell carcinoma of the head and neck. *J Clin Oncol* 1987, **5**, 10–20.
4. Chang TM. Induction chemotherapy for advanced head and neck cancers: a literature review. *Head Neck Surg* 1988, **10**, 150–159.
5. Wittes RE, Heller K, Randolph V, *et al.* cis-Dichlorodiammineplatinum (II) based chemotherapy as initial treatment of advanced head and neck cancer. *Cancer Treat Rep* 1979, **63**, 1533–1538.
6. Veronesi A, Zagonel V, Tirelli U, *et al.* High-dose versus low-dose cisplatin in advanced head and neck squamous carcinoma: a randomized study. *J Clin Oncol* 1985, **3**, 1105–1108.
7. Planting AST, van der Burg MEL, de Boer-Dennert M, *et al.* Phase I/II study of a short course of weekly cisplatin in patients with advanced solid tumours. *Br J Cancer* 1993, **68**, 789–792.
8. *WHO Handbook for Reporting Results of Cancer Treatment.* WHO Offset Publication No. 48, World Health Organization, Geneva, 1979.
9. Tannock IF, Browman G. Lack of evidence for a role of chemotherapy in the routine management of locally advanced head and neck cancer. *J Clin Oncol* 1986, **4**, 1121–1126.
10. Toohill RJ, Anderson T, Byhardt RW, *et al.* Cisplatin and fluorouracil as neoadjuvant therapy in head and neck cancer. *Arch Otolaryngol Head Neck Surg* 1987, **113**, 758–761.
11. Head and Neck Contracts Program. Adjuvant chemotherapy for advanced head and neck squamous carcinoma: final report of the Head and Neck Contracts Program. *Cancer* 1987, **60**, 301–311.
12. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngel cancer. *N Engl J Med* 1991, **324**, 1685–1690.
13. Stell PM, Rawson NSB. Adjuvant chemotherapy in head and neck cancer. *Br J Cancer* 1990, **61**, 779–787.
14. Paccagnella A, Orlando A, Marchiori C, *et al.* Phase II trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della Teste e del Collo. *J Natl Cancer Inst* 1994, **86**, 265–272.
15. Pfister DG, Harrison LB, Strong EW, *et al.* Organ-function preservation in advanced oropharynx cancer: results with induction chemotherapy and radiation. *J Clin Oncol* 1995, **13**, 671–680.
16. Forastiere AA, Takasugi BJ, Baker SJ, *et al.* High-dose cisplatin in advanced head and neck cancer. *Cancer Chemother Pharmacol* 1987, **19**, 155–158.
17. Coldman AJ, Goldie JH. Impact of dose-intense chemotherapy on the development of permanent drug-resistance. *Semin Oncol* 1987, **14**(Suppl. 4), 29–33.
18. Verweij J, de Jong PC, de Mulder PHM, *et al.* Induction chemotherapy with cisplatin and continuous infusion 5-fluorouracil in locally far-advanced head and neck cancer. *Am J Clin Oncol* 1989, **12**, 420–424.
19. Ensley JF, Jacobs JR, Weaver A, *et al.* Correlation between response to cisplatinum-combination chemotherapy and subsequent radiotherapy in previously untreated patients with advanced squamous cell cancers of the head and neck. *Cancer* 1984, **54**, 811–814.
20. Clavel M, Maged Mansour AR. Head and neck cancer: prognostic factors for response to chemotherapy. *Eur J Cancer* 1991, **27A**, 356–361.
21. Janot F, Klijanienko J, Russo A, *et al.* Prognostic value of clinicopathological parameters in head and neck squamous cell carcinoma: a prospective analysis. *Br J Cancer* 1996, **73**, 531–538.
22. Ozols RF, Ostecha Y, Myers CE, *et al.* High-dose cisplatin in hypertonic saline in refractory ovarian cancer. *J Clin Oncol* 1985, **3**, 1246–1250.
23. Gandara DR, Wold H, Perez EA, *et al.* Cisplatin dose-intensity in non-small cell lung cancer: phase II results of a day 1 and 8 high-dose regimen. *J Natl Cancer* 1989, **81**, 790–794.
24. Reddel RR, Kefford RF, Grant JM, *et al.* Ototoxicity in patients receiving cisplatin: importance of dose and method of drug administration. *Cancer Treat Rep* 1982, **66**, 19–23.
25. Schaeffer SD, Post JD, Close LG, *et al.* Ototoxicity of low- and moderate-dose cisplatin. *Cancer* 1985, **56**, 1934–1939.
26. Siegal T, Haim N. Cisplatin-induced peripheral neuropathy. Frequent off-therapy deterioration, demyelinating syndromes, and muscle cramps. *Cancer* 1990, **66**, 1117–1123.
27. Hilkens PHE, Planting AST, van de Burg MEL, *et al.* Clinical course and risk factors of neurotoxicity following cisplatin in an intensive dosing schedule. *Eur J Neurol* 1994, **1**, 45–50.
28. Aisner J, Hiponia D, Conley B, *et al.* Combined modalities in the treatment of head and neck cancer. *Semin Oncol* 1995, **3**(Suppl. 6), 28–34.
29. Capizzi RL. Protection of normal tissues from the cytotoxic effects of chemotherapy by amifostine (ethyol): clinical experiences. *Semin Oncol* 1994, **21**(Suppl. 11), 8–15.

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