Weekly scheduling of cisplatin;

feasibility, efficacy and perspective

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Promotor:	Prof.dr. G. Stoter
Copromotor:	Dr. J. Verweij
Overige leden:	Prof.dr. P.H.M. de Mulder
	Prof.dr. G.M.M. Bartelink
	Prof.dr. A. Hagenbeek
	Prof.dr. J.W. Oosterhuis
	Prof.dr. P.C. de Jong

Aan mijn ouders

CONTENTS

CHAPTER 1

INTRODUCTION

1. Introduction

In this thesis studies of weekly administration of cisplatin are presented. Weekly administration of cisplatin is not new: already in the seventies weekly cisplatin regimens were explored but they were abandoned because of hematologic, renal and gastrointestinal toxicity (1-3). The administration of cisplatin in the outpatient setting and without adequate hydration certainly has contributed to the failure of these studies. A better understanding of the pathophysiology of renal toxicity led to hydration programs and the introduction of hypertonic saline; the development of a new generation of antiemetics ameliorated nausea and vomiting considerably and made it possible to administer cisplatin more frequently. Reexploration of weekly cisplatin thus became possible.

The theory behind weekly administration of cisplatin is based on the tumor biologic principle that frequent administration of chemotherapy in a high dose kills cancer cells more effectively and probably reduces the risk of the development of resistance (4-6). Treatment with weekly intervals also has the theoretical advantage that sensitive cells, in which DNA-repair is less effective than in resistant cells, have less time for regrowth compared to conventional 3-week schedules (7).
In this introduction the cytotoxic drugs used in our studies, cisplatin and etoposide, will be briefly discussed as well as the tumor types in which they were studied: head and neck cancer, non-small cell lung cancer and pleural mesothelioma. The indications for chemotherapy in these tumor types as well as the treatment results with cisplatin with or without etoposide will be presented to enable reference with the results presented in this thesis.

1.1. Cisplatin

Cisplatin is one of the most active and widely used cytotoxic drugs in solid tumors. Cisplatin acts at the DNA level by formation of adducts, or cross-links. The intrastrand guanine-guanine and guanine-adenosine adducts are predominant; less important are the monofunctional adducts. Interstrand cross links form only 1% of the adducts (8-10). Preclinical and clinical studies have tried to correlate the DNA-adduct formation with treatment outcome. For practical reasons DNA-adduct formation is studied in white blood cells or buccal cells. Several studies found that DNA-adduct levels were higher in responding patients compared to non-responders,

although there is a considerable interpatient variation in adduct formation (11-15). Further refining of estimation of DNA-adduct levels can in the future be of help to decide early in a treatment course to adjust the dose of cisplatin. This subject is discussed in more detail in chapter 9. Resistance to cisplatin is explained by reduced cellular uptake, increased intracellular activation of detoxification molecules such as gluthatione and metallothioneins, aberrant p53 expression, *c-myc* expression as well as increased removal of adducts by excision repair enzymes (15-23). Also increased cellular levels of topoisomerase 1 and topoisomerase 2 have been described to be related with increased DNA-repair after cisplatin (24,25). After intravenous administration cisplatin is rapidly and irreversibly bound to proteins; only the unbound platinum is biologically active. The plasma half life of cisplatinum, after a rapid distribution phase, varies from 14-23 minutes; the slow terminal half life varies from 67 hours to 120 hours. Approximately 25% of the platinum is excreted via the kidneys during the first 24 hours and up to 40% during the first 5 days. The renal clearance of unbound platinum is higher than the creatinine clearance indicating tubular secretion (27-31).

The side effects of cisplatin have been extensively described: nausea and vomiting, renal toxicity, ototoxicity, sensory neuropathy and hematologic toxicity. In recent years progress has been made in the prevention of acute nausea and vomiting by combined administration of 5-HT_3 antagonists and dexamethasone; delayed nausea and vomiting, however, is still a troublesome side effect (32). Renal toxicity, the dose limiting toxicity in the early cisplatin era, can now in part be prevented by adequate hydration and hypertonic saline or by concomitant administration of sodiumthiosulphate. The risk of renal toxicity increases per cycle and is related with the dose per cycle. Not only the decrease of the glomerular filtration rate but also tubular damage resulting in hyponatraemia, hypokalaemia and hypomagnesaemia can cause severe side effects (33-41). After reduction of these side effects it became possible to treat patients with higher doses of cisplatin and for longer duration resulting in the fact that neurotoxicity and ototoxicity are now dose limiting. Neurotoxicity is dependent on the cumulative cisplatin dose administered (42-48) while the damage to the Corti organ is related to the cisplatin plasma peak level and thus more related with dose per cycle and way of administration (49-52). Neurotoxicity will in general diminish after cessation of treatment, clinical hearing loss is irreversible.

Because of these toxicities cisplatin treatment can still be regarded as an intensive and for the patient potentially dangerous therapy.

Mechanisms to reduce toxicity further are very much needed. Several drugs have cytoprotective capacities. Sodiumthiosulfate, probenecid and acetylcysteine have been successfully used as protectors of renal toxicity but they have no influence on other toxicities. Diethyldithiocarbamate proved to be highly toxic in a randomized trial in lung cancer (53). Amifostine (WR 2721) has been extensively tested and has shown in preclinical and clinical studies a protective effect on renal, neurologic and hematologic toxicity (54-55). This drug is discussed in more detail in chapter 4. Recently, reduced glutathione showed a comparable protective effect on neurotoxicity and trombocytopenia related treatment delays in a placebo controlled randomized study (56).

1.2 The importance of dose and dose intensity of cisplatin

Since the nineteen-seventies much work has been done in experimental tumor systems on the relation of chemotherapy dose and treatment outcome (4-6).
The Goldie-Coltman hypothesis stresses that anticancer drugs need to be administered at the highest possible dose to increase the fractional cell kill to the highest level. This will lead to eradication of drug sensitive cancer cells. As resistance may develop early during treatment especially the dose in the first treatments should be as high as possible. In cell line and animal studies a steep dose-response relation exists for alkylating agents (4,5). From a theoretical point of view it is attractive to administer cytostatics at the highest possible dose with short intervals. In man this concept led to successful treatment in leukemia and malignant lymphomas. In solid tumors, up till now only in ovarian cancer it has been shown that a dose response relation exists (57-61). For other solid tumor types this has not (yet) been proven (62-66).

One way to study whether a relationship exists between dose and response, is by analysing dose intensity *i.e.*: the total dose of drug delivered per unit of time, generally expressed as mg/m^2/week. In this way dose intensities between treatments can be compared. Retrospective analysis of dose intensities in solid tumors suggested a dose intensity-response relationship for cisplatin in ovarian cancer, for combination chemotherapy in breast cancer, for fluorouracil in colon cancer and etoposide in small cell lung cancer (67).

However, comparison of dose-intensities is difficult because in general only the planned and not the actual dose intensity can be calculated from publications.

In high dose schedules toxicity may cause treatment delays and necessitate dose reductions so that the dose intensity delivered can be well below the dose-intensity aimed for. The only way to study the value of dose intensity is by prospective randomized studies.

In the randomized studies performed (62-66) the cisplatin dose intensity in the high dose arm did never exceed 41 mg/m^2/week, which is only a factor 2 higher than in standard regimens which may explain the negative outcome. Due to the toxicity profile of cisplatin higher dose intensities were not possible. Attempts to reach a higher "platination" by combining cisplatin with its analogue carboplatin failed in most studies as the hematologic toxicity of carboplatin was the cause of frequent treatment delays and dose reductions (68-73). The highest platinum dose intensity with a cisplatin-carboplatin combination was achieved by Waterhouse et al. (74): 83 mg/m^2/week. Kim et al. (75) with a cisplatin schedule of 180 mg/m^2 every 2 weeks, with sodiumthiosulfate, achieved a cisplatin dose intensity of 79 mg/m^2/week. In both schedules the toxicity was considerable and only a minority of patients could tolerate the regimens for 2 or more cycles. These results and the results from our own studies (chapter 3-5), suggest that at this moment a cisplatin dose intensity higher than 70-80 mg/m^2/week is not reachable. New measures to prevent side effects are needed before more intense dose escalation programs can begin.

1.3 Etoposide

Etoposide (VP 16-213) is a podophyllotoxin derivative. It exerts its action by inhibition of the enzyme topoisomerase II. Its mechanism of action, activity and side effects have been well described (76). In brief, the enzyme topoisomerase II is involved in the process of unwinding and cleaving of DNA during replication. During this process DNA strands are cleaved to allow passage of other DNA strands after which the break is resealed. When topoisomerase II is bound to the DNA this is turned into the cleavable complex. Etoposide stabilises the cleavable complex, resulting in double strand DNA breaks finally resulting in cell death. Topoisomerase II expression increases during the S-phase of the cell cycle and is maximal in the G2-M phase. The action of etoposide is therefore cell cycle specific. Resistance to etoposide, and the analogue teniposide, is contributed to low cellular topoisomerase II levels, increased cellular efflux via the membrane bound

p-glycoprotein in MDR 1 gene expressing cells, the expression of the multidrug resistance-associated protein (MRP) gene and prevention of induction of apoptosis by *bcl-2* (77-83).

Etoposide administered over several days is considerably more active than a one day administration (84-86). The binding of etoposide to the cleavable complex is rapidly reversible so that long term administration is more attractive than short term administration. Prolonged intravenous administration is feasible but rather impractical. The maximum tolerated dose of etoposide with continuous infusion is 25 mg/m^2/day (87-90). Oral administration has already been explored since 1974 (91-93) and considerable activity of oral etoposide has been shown in small cell lung cancer, refractory germ cell tumors, malignant lymphomas and ovarian cancer (94-98). The maximal tolerated dose of daily oral administration is 50 mg/m^2 for 21 days. Pharmacokinetic studies showed that with oral administration a steady state plasma etoposide level of >1 μg/ml, which is needed for cytotoxic action, can be maintained in most patients. There is, however, a considerable interpatient variation in resorption. The bioavailability of etoposide is also dose dependent. A bioavailability of $\geq$ 70% is reported for doses $\leq$ 100 mg, while at higher doses the bioavailability is 50% or lower. This explains why the risk of neutropenia, which correlates with the duration of steady state etoposide plasma levels >0.32 μg/ml, is difficult to predict (99-105). Whether fractionated dosing is superior over a single fraction is still under investigation (106).

Based on preclinical studies etoposide and cisplatin are considered to be synergistic. Although synergism was later questioned (107-113), clinically both drugs are considered to have more than just additive activity, while the non-overlapping toxicities make the combination attractive.

1.4. The patient population studied

1.4.1. Head and neck cancer

In 1992 in The Netherlands 1828 new patients were registered with head and neck cancer (cancer of the lip and salivary glands excluded) a figure globally increasing 10% each year (114). In 1994, 365 patients with head and neck cancer were referred to the Rotterdam Cooperative Head and Neck Group, and in 116 of these patients an indication for chemotherapy existed.

Table 1. Cisplatin single agent studies in head and neck cancer

	schedule	no. pts	RR%	CR%	PDI
Wittes 1977	3 mg/kg iv q 3 wk	26	30	8	
Jacobs 1978	80 mg/m²/24h q 3 wk	18	39	6	26.7
Sako 1978	120 mg/m² q 3 wk	15	33	13	40
	20 mg/m² d 1-5	15	27	7	33.3
Davis 1979	3 mg/kg iv q 3 wk	30	13	1	
Wittes 1979	120 mg/m² q 3 wk	22	40	5	40
Pannetiere 1980	50 mg/m² d 1+8 q 4wk	89	25	5	25
Creagan 1983	90 mg/m²/24 h q 3wk	23	13	0	30
Jacobs 1983	80 mg/m²/24 h q 3wk	40	18	8	26.7
Hong 1983	50 mg/m² d 1+8 q 4 wk	22	29	5	25
Schaefer 1983	100 mg/m² q 3 wk	26	3	0	33.3
GadMawla 1984	50 mg/m² q 3 wk	30	40	0	16.7
Salem 1984	20 mg/m² d1-5 ci q 4 wk	15	10	0	25
Morton 1985	100 mg/m²/24 h q 4 wk	31	13	3	25
Grose 1985	50 mg/m² d 1+8 q 4 wk	50	8	0	25
Veronesi 1985	120 mg/m² q 3 wk	31	16	3	40
	60 mg/m² q 3 wk	28	18	0	20
Forastiere 1987	40 mg/m² d 1-5 q 4 wk	22	73	10	50
Liverpool 1990	100 mg/m² q 4 wk	36	38	3	25
Jacobs 1992	100 mg/m² q 3 wk	83	17	4	33.3
Clavel 1994	50 mg/m² d 1+8 q 4 wk	113	16	3	25

RR% = response rate
CR% = complete response rate
PDI = Projected cisplatin dose intensity

These figures illustrate the magnitude of the problems faced in head and neck cancer.

Approximately 50-60% of the patients with head and neck cancer present at diagnosis with locally advanced disease stage III or IV. The standard treatment consists of surgery followed by radiotherapy or of high-dose radiotherapy only, depending on the site and extension of the tumor. The outcome of these local treatments is, however, moderate at best: 30-40% of the patients will recur locally while 10-15% of the patients will develop distant metastases (115). In recurrent disease surgery and reirradiation are rarely possible, while results of chemotherapy -as in metastatic disease- are very poor, with response rates below 30%. The duration of response is in general short without demonstrable survival benefit (116). In contrast, locally advanced head and neck cancer is highly responsive to chemotherapy. After the introduction of cisplatin the interest in upfront chemotherapy (before local therapies) increased enormously since cisplatin combination chemotherapy was reported to yield response rates of 60-90% including up to 30% complete responders. Especially the observation that complete responders to chemotherapy had an excellent survival after local treatment led to the widespread use of "neoadjuvant chemotherapy" as standard treatment (117). The optimism turned into disappointment after randomized trials failed to show improved survival of the combined modality over radiotherapy alone; the incidence of distant metastases was reduced in several studies but the local recurrence rate remained high. Therefore neoadjuvant chemotherapy is no longer considered to be standard treatment and should be investigated in study protocols only (118-122). The value of adjuvant chemotherapy after local treatment has not been adequately explored as increased toxicity after surgery and radiotherapy and poor patient compliance hamper such studies (123,124). It is this patient group with locally far advanced tumors in which we studied the weekly cisplatin regimen presented in chapter 3. In table 1 the results of cisplatin single agent studies are presented as a frame of reference (125-143).

1.4.2. Non-small cell lung cancer

In 1994 533 patients with non-small cell lung cancer were referred to the Daniel den Hoed Kliniek and 56 patients were referred to the department of medical oncology for chemotherapy, a considerably lower rate than in head and neck cancer.

The value of chemotherapy in non-small cell lung cancer (NSCLC) has been discussed as long as chemotherapy exists. Traditionally chemotherapy was only considered indicated in metastatic or recurrent disease and as the response rates were low and the response durations short a "wait and see" policy was advocated. Several small randomized studies comparing chemotherapy versus best supportive care showed a modest survival benefit but others did not. Only recently meta-analyses showed that cisplatin containing chemotherapy offers a short term survival benefit in these patients (144-146). Locally advanced NSCLC, stages IIIa and IIIb, is traditionally treated with high dose radiotherapy. However, the results of radiotherapy in stage III are disappointing: a local control rate of 50% and a 5- year survival of 3-5%. As chemotherapy is more active in locally advanced disease than in metastatic disease the combination of chemotherapy and radiotherapy plus or minus surgery has been extensively studied. In spite of initial optimistic reports of phase II studies, only a few randomized studies of induction chemotherapy followed by radiotherapy showed improved survival (147,148). A second approach, the combination of radiotherapy with cisplatin as radiosensitizer, proved to be successful with a daily low dose of cisplatin (149). This result led to various concomitant chemo-radiotherapy trials, none of which have results mature enough to draw conclusions.

A meta-analysis, based on the literature, showed that high dose cisplatin schedules (>100 mg/m^2) were more active than low dose cisplatin schedules (<70 mg/m^2) suggesting a dose-response relationship for cisplatin in this tumor type (150). The combination of cisplatin with mitomycin C or ifosfamide appeared better than the etoposide-cisplatin combination in this analysis. Randomized studies, however, still have not discovered the best cisplatin combination (151,152).

Cisplatin single agent has only moderate activity in non-small cell lung cancer with response rates varying from 9-36% (3,64,153-162). An overview of the activity of single agent cisplatin is given in table 2. The wide variation in response rates reflects the heterogeneity of the population studied.

In Europe the combination of cisplatin with etoposide is widely used. Etoposide as a single agent, intravenous or orally administered, has only limited activity in non-small cell lung cancer (91,163-170). The results of phase II studies with etoposide are presented in table 3. Results of the various etoposide-cisplatin schedules are reported in table 4 for reference with the results of the weekly cisplatin regimen reported in chapter 8 (63,171-197).

Table 2. Cisplatin single agent activity in non-small cell lung cancer

	schedule	no.pts	RR%	PDI
Rossof (1976)	75 mg/m^2 q 3 wk	11	9	25
Brittel (1978)	15 mg/m^2 d 1-5 q 4 wk	22	9	18.7
Casper (1979)	120 mg/m^2 q 4-6 wk	18	6	20-30
DeJager (1980)	120 mg/m^2 q 3 wk	61	25	40
Vogl (1982)	75 mg/m^2 wk 1-3 and q 3 wks thereafter	28	32	75
Bhuchar (1982)	100-140 mg/m^2 q 4 wk	26	0	25-35
Pannetiere (1983)	50 mg/m^2 d 1+8 q 4 wk	145	13	25
Klastersky (1989)	120 mg/m^2 q 4 wk	81	19	30
Gandara (1989)	100 mg/m^2 d 1+8 q 4 wk	76	36	50
Ellis (1991)	100 mg/m^2 d 1+8 q 4 wk	36	8	50
Gandara (1993)	50 mg/m^2 d 1+8 100 mg/m^2 d 1+8 q 4 wk	105 108	12 14	25 50
Sculier (1994)	120 mg/m^2 q 3-4 wk	56	23	30

RR% = response rate
PDI = projected cisplatin dose intensity

Table 3. Etoposide single agent studies in non-small cell lung cancer

	schedule	no.pts	RR%	
Falkson (1975)	200-400 mg po d 1-5	9	11	
Eagan (1978)	140 mg/m² d 1,3,5 q 4 weeks	44	18	
Nissen (1980)	60 mg/m² 90 mg/m² iv 2x/wk 135 mg/m²	60	3	
Chapman (1982)	120 mg/m² d 1,3,5 200 mg/m²	49	2	
Anderson (1982)	100 mg po b.i.d. day 1-5 q 4 wks	65	23	
Itri (1982)	120-150 mg/m² d 1,3,5	49	2	
Niederle (1991)	200-370 mg/m² d 1-3	29	23	(dosedep)
Waits (1992)	50 mg/m² d 1-21 po	25	25	
Blumenreich (1994)	50 mg po cont	16	0	

RR% = response rate

Tabel 4. Cisplatin-etoposide combination therapy in NSCLC

	schedule		stage	no. pts	RR%	PDI
Goldhirsch 1981	C:	100 mg/m² d 1		18	39	33.3
	E:	80 mg/m² d 1-3				
Longeval 1982	C:	60 mg/m² d 1	III	34	56	20
	E:	120 mg/m² d 3,5,7	IV	54	28	
Veronesi 1983	C:	20 mg/m² d 1-5	III	8	37	33.3
	E:	75 mg/m² d 1-5	IV	29		
Canobbio 1984	C:	50 mg/m² d 1	III	9	22	16.6
	E:	100 mg/m² d 1,3,5	IV	16	0	
Joss 1984	C:	80 mg/m² d 1	III	16	31	26.7
	E:	80 mg/m² d 1-3	IV	24	17	
Dhingra 1984	C:	60 mg/m² d 1		37	19	20
	E:	120 mg/m² d 4,6,8				
Mitrou 1984	C:	90 mg/m² d 1		46	22	22.5
	E:	100 mg/m² d 1-3				
Scagliotti 1985	C:	100 mg/m² d 1	III	36	41	25
	E:	120 mg/m² d 4,6,8	IV	30	7	
Pallares 1986	C:	60 mg/m² d 1		16	0	15
	E:	120 mg/m² d 1,3,5				
Ruckdeschel 1986	C:	60 mg/m² d 1		124	20	20
	E:	120 mg/m² d 4,6,8				
Splinter 1986	C:	80 mg/m² d 1	III	22	69	20
	E:	100 mg/m² d 1,2iv	IV	29		
		200 mg/m² d 3 po				
Klastersky 1986	C:	120 mg/m² d 1	III	42	42	40
		of	IV	51	18	
	C:	60 mg/m² d 1	III	43	30	20
	E:	120 mg/m² d 3,5,7	IV	71	21	
Focan 1988	C:	100 mg/m² d 1		40	28	25
	E:	240 mg/m² d 1-3				
Veronesi 1988	C:	20 mg/m² d 1-5		71	38	33
	E:	75 mg/m² d 1-5				

- Table 4 to be continued -

- Table 4 continued -

Hainsworth	C:	60	mg/m² d 1	III	9	6	15
1989	E:	100	mg/m² d 1+8	IV	40		
Klastersky	C:	120	mg/m² d 1	III	27	43	30
1989	E:	100	mg/m² d 1-3	IV	54	18	
Krook	C:	90	mg/m² d 1		17	50	22.5
1989	E:	60-130	mg/m² CI d 1-4				
Klastersky	C:	120	mg/m² d 1	III	53	27	30
1990	E:	100	mg/m² d 1-3	IV	61	27	
Marechal	C:	20	mg/m² d 1-5CI		26	53	33.3
1990	E:	50	mg/m² d 1-5CI				
Paccagnella	C:	100	mg/m² d 1		39	26	33.3
1990	E:	120	mg/m² d 1,3,5				
Gatzemeier	C:	40	mg/m² d 1+4	III	15	25	20
1991	E:	125	mg/m² d 1-4	IV	45		
Kaasa	C:	70	mg/m² d 1		44	11	23.3
1991	E:	100	mg/m² iv d 1				
		200	mg/m² po d 2,3				
Weick	C:	100	mg/m² d 1	III	52	16	25
1991	E:	100	mg/m² d 1-3	IV	83		
Furuse	C:	80	mg/m² d 1		18	22	26.6
1992	E:	40	mg/m² d 1-21 po				
Miller	C:	100	mg/m² d 1	III	6	41	25
1993	E:	50	mg/m² d 1-21 po	IV	26		
Saito	C:	30	mg/m² d 1-3 CI	III	17	20	22.5
1993	E:	80	mg/m² d 1-3 CI	IV	29		
Bonomi	C:	60	mg/m² d 1		42	11	15
1994	E:	120	mg/m² d 1-3				
Darwish	C:	120	mg/m² d 1	III	46	82	40
1994	E:	100	mg/m² d 1-3				
Crinò	C:	120	mg/m² d 1	III	54	38	40
1995	E:	100	mg/m² d 1-3	IV	76	14	

C: cisplatin dose; E: etoposide dose
RR% = response rate
PDI = projected cisplatin dose intensity

1.4.3. Malignant pleural mesothelioma

Malignant pleural mesothelioma is a rare disease. In 1992, 382 new patients were registered in The Netherlands. The incidence continues to increase every year and only after the year 2010 the incidence may fall again when the effects of the asbest law of 1977 will become visible (198). Only in very early stages aggressive surgery may be curative. In most patients this is not an option and as treatment results with chemotherapy and radiotherapy are far from impressive a conservative approach of "wait and watch" is generally advocated and treatment is confined to pleurodesis. Only in case of severe pain or increasing dyspnea patients are treated. In 1994, 23 patients with mesothelioma were referred to our department.

The results of chemotherapy are poor. An indication for this is the overview of Hansen and Hansen in 1991. At that date no less than 87 single agent studies and 36 combination chemotherapy studies had been reported with more than 13 patients each (199). Only combination regimens containing adriamycin and/or cisplatin yielded response rates >20% as was shown in a recent review of Aisner (200). Only one study reported the activity of the combination of intravenous etoposide with cisplatin with a partial response rate of 12% (201). The activity of single agent oral etoposide in this disease was questioned in a Finnish study (202).

As an alternative intracavitary cisplatin may be an attractive option in a disease confined to the pleural cavity. The procedure is feasible and high cisplatin concentrations can be obtained intrapleurally (203-205). A recent report on intrapleurally administration of interleukin-2 suggests that other modalities than systemic chemotherapy may also have a role in this tumor type (206).

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CHAPTER 2

PHASE I/II STUDY OF A SHORT COURSE OF WEEKLY CISPLATIN IN PATIENTS WITH ADVANCED SOLID TUMOURS

A.S.T. Planting, M.E.L. van der Burg, M. de Boer-Dennert, G. Stoter and J. Verweij

Department of Medical Oncology, Rotterdam Cancer Institute/Daniel den Hoed Kliniek, PO Box 5201, 3008 AE Rotterdam, The Netherlands

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SUMMARY

Twenty-five patients with advanced solid tumours were entered in a phase I/II study of six, weekly cycles of cisplatin. Nineteen patients were chemonaive and 6 were previously treated. The starting dose was 50 mg/m^2/week. This dose could be escalated without major toxicity to 70 mg/m^2/week. At a dose of 80 mg/m^2 myelosuppression grade 3 occurred as well as grade 1 nephro- and neurotoxicity. The maximum tolerated dose was 85 mg/m^2 with dose limiting thrombocytopenia. Hypertonic saline was effective in preventing nephrotoxicity. Ondansetron was a very effective antiemetic in the first weeks of treatment but its efficacy waned later on. Responses were observed in head and neck cancer, melanoma and mesothelioma. At the dose level of 80 mg/m^2 the optimal dose intensity was reached. This schedule will be tested further in phase II studies.

INTRODUCTION

Cisplatin is one of the most active and most widely used cytostatics. In vitro studies in human cancer cell lines and clinical trials in several tumour types have suggested a dose-response relationship for cisplatin (1-5). The application of high doses or frequent administration of lower doses of cisplatin is however, hampered by side effects such as severe nausea and vomiting, neurotoxicity and nephrotoxicity.

Until recently, even with the use of the most active antiemetic combination regimen (metoclopramide with lorazepam and dexamethasone), a considerable proportion of patients suffered from nausea and vomiting whereas the new $5HT_3$-antagonists are now found to be more effective in preventing acute nausea and vomiting induced by cisplatin (7-10).

In addition the risk of cisplatin nephrotoxicity can be decreased by administering cisplatin in hypertonic saline 3% (3,5-6,11). These protective measures may theoretically allow a higher cisplatin dose intensity (D.I.). We therefore performed a phase I/II study with six, weekly cycles of cisplatin, administered in 3% hypertonic saline, combined with the $5HT_3$-antagonist ondansetron as antiemetic.

PATIENTS AND METHODS

Patients were required to have metastatic or locally advanced cancer for which no adequate local treatment was available, age 18-75 years, a WHO performance status of 2 or better, an adequate bone marrow function with WBC $\geq$ 3.10^9/l and platelets $\geq$ 100.10^9/l, a serum bilirubin $<$ 25 μmol/l and a creatinine clearance $\geq$

60 ml/min. All patients gave oral informed consent according to institutional regulations, had a complete clinical work up including medical history, physical examination, haematology and biochemistry tests, a creatinine clearance, chest X-ray, ECG and ultrasound and/or CT-scans to measure indicator lesions.

The infusion schedule consisted of: pre-hydration with 1000 ml of dextrose-saline over 4 hours with 20 mmol KCl + 2 gram $MgSO_4$; cisplatin powder diluted in 250 ml 3% NaCl and administered over 3 hours followed by post-hydration with 2000 ml dextrose-saline with 40 mmol KCl + 4 gram $MgSO_4$ over 8 hours. As antiemetic all patients received ondansetron at a dose of 8 mg i.v. bolus before the start of cisplatin, followed by 1 mg/hour continuous intravenous infusion for 12 hours.

This regimen was repeated weekly for 6 weeks. Treatment was postponed for one week if WBC were $< 2.5 \times 10^9$/l and/or platelets $< 75 \times 10^9$/l. In case of treatment delay of $\geq$ 3 weeks or the occurrence of nephro- or neurotoxicity $\geq$ grade 2 the patient was taken off study.

Dose reductions were not allowed. At each dose level at least 3 patients were treated and evaluated for toxicity before patients were entered at the next dose level. All patients had a weekly physical examination and determinations of haemoglobin, WBC and platelets, serum calcium, magnesium, creatinine, liver function tests and creatinine clearance. Response to treatment was evaluated 2 weeks after the last cisplatin administration. For response evaluation and toxicity grading, with exception of grading of gastrointestinal toxicity, the WHO criteria were used (12). Toxicity is reported as the worst grade observed during the whole treatment period. For grading of nausea and vomiting a modified grading system was used: grade 0 none, grade 1: mild to moderate nausea not interfering with adequate fluid and food intake, grade 2: nausea interfering with adequate fluid and/or food intake and/or vomiting < 5x in 24 hours, grade 3: any nausea or vomiting worse than grade 2 but not requiring i.v. support and grade 4 any nausea and/or vomiting for which hospital admission was necessary.

The dose intensity of cisplatin was calculated as the total amount of cisplatin administered divided by the total number of treatment weeks necessary to administer the total dose and is expressed in milligrams per square meter per week; in patients completing 6 treatment cycles in 6 weeks the total dose is divided by 6; in case of treatment delay the total dose administered is divided by 6 + the number of weeks delay.

In those patients who did not receive the last dosage(s) due to toxicity or progressive disease the total amount of cisplatin administered was calculated over six weeks.

RESULTS

Twenty-five patients were entered in the study. The patient characteristics are given in table 1. Six patients had been pretreated with a non-cisplatin chemotherapy regimen. The starting dose of cisplatin was 50 mg/m^2/week. The number of patients and the number of administrations per dose level are shown in table 2. At the dose levels of 50, 60 and 70 mg/m^2 toxicity was mild to moderate and uncomplicated with the exception of one patient at 70 mg/m^2 who did not receive the sixth cycle because of slow recovery of platelets. The other patients had no treatment delays.

Table 1. Patient characteristics

Total no. of patients entered	25
male : female	18 : 7
median (range) years	51 (23-69)
median performance status (WHO, range)	1 (0-1)
Tumour types	
Head/neck cancer locally advanced	9
Head/neck cancer metastatic	3
Mesothelioma pleura	7
Sarcoma	2
Melanoma	2
Adenocarcinoma unknown primary	1
Lung squamous cell carcinoma	1

At the dose level of 80 mg/m^2 2 patients developed grade 3 myelo-suppression, and in one heavily pretreated patient thrombocytopenia grade 4 occurred. Therefore 3 additional patients were entered at this dose level, all developing grade 3 myelosuppression, mainly occurring after the fourth cycle. Subsequently the dose was escalated to 85 mg/m^2.

At this dose thrombocytopenia grade 4 was seen in 4 out of 7 patients, while leucocytopenia grade 3 developed in 2. One of these patients, with obstructive lung cancer, died due to sepsis and pneumonia with haemoptysis, during leucocytopenia and thrombocytopenia. Thereafter 3 additional chemonaive patients were treated at 80 mg/m^2 without any grade 4 toxicity. At this dose level 2 patients received 6 cycles without any delay, 5 patients had one cycle delayed for one week and 2 patients did not receive the sixth cisplatin dose, one because of slow recovery of platelets and one because of progressive disease.

The median time to development for both leucocytopenia and thrombocytopenia was 35 days. The median duration of leucocytopenia was 7 and of thrombocytopenia 10 days. All 25 patients in the study developed grade 1 anaemia.

Nephrotoxicity WHO grade 1 was observed in 8 patients, solely at the dose levels of 80 and 85 mg/m^2. At the lower dose levels most patients had a slight increase in serum creatinine but none exceeded the upper level of WHO grade 0. In 5 of the 8 patients who developed grade 1 nephrotoxicity the serum creatinine improved to near normal pretreatment levels after cessation of treatment. An overview of the haematologic toxicity and nephrotoxicity in relation to the cisplatin dose level is given in table 3. Other toxicities are shown in table 4. Asymptomatic hypomagnesemia <0.65 mmol/l was observed in 3 patients, one each at dose levels of 50, 70 and 75 mg/m^2 in all occurring after the 4th cisplatin administration. Six patients at the 2 highest dose levels experienced neurotoxicity grade 1. In one patient the neurotoxicity deteriorated to grade 2 after completion of treatment but this patient also had a vitamin B12 deficiency. In the other patients no late deterioration of neurotoxicity or late development of neurotoxicity was observed. Ototoxicity grade 2 (tinnitus) was observed in one patient at 70 mg/m^2 and grade 3 (hearing loss requiring a hearing aid) in 2 patients at 85 mg/m^2.

Ondansetron was highly effective in preventing nausea and vomiting, especially in the first 3-4 weeks of treatment. However, at the dose level of 85 mg/m^2 3 out of 7 patients vomited during the first administrations. The effect of ondansetron waned with the last 2-3 doses of cisplatin and, at all dose levels, most patients suffered from nausea and occasional vomiting during the final weeks of treatment. Diarrhoea was not observed. Table 2 also shows the mean cumulative dose and achieved dose intensity of cisplatin in mg/m^2/week. At the dose level of 80 mg/m^2/week the same dose intensity was reached as with the dose level of 85 mg/m^2/week but with less toxicity.

Table 2.

DOSE LEVEL	CISPLATIN DOSE ($mg/m^2/wk$)	No. PATIENTS/ No. ADMINISTR.	MEAN CUMULATIVE DOSE OF CISPLATIN GIVEN (mg/m^2)	MEAN CISPLATIN DOSE INTENSITY ($mg/m^2/wk$)	% CISPLATIN DELIVERED OF PLANNED DOSE
1	50	3/18	300	50	100
2	60	3/18	360	60	100
3	70	3/17*	397	66	94
4	80	9/52**	462	70	87,5
5	85	7/40***	485	70	70

* 1 patient did not receive 6th cisplatin dose because of progressive disease

** 2 patients did not receive 6th cisplatin dose because of slow recovery of platelets or progressive disease

*** 1 patient received only 4 courses of cisplatin because of infectious complication

Twenty-four patients were evaluable for response. We observed a histologically confirmed complete response in one patient with malignant melanoma, a partial response in 8 out of 9 patients with locally advanced head and neck cancer and in 2 out of 3 patients with local recurrence and metastatic head and neck cancer. A partial response was observed in 4 out of 7 patients with mesothelioma. Most patients with head- and neck cancer were subsequently irradiated for which reason the duration of response can not be determined. In the mesothelioma patients responses lasted 2,4,4 and 8 months respectively, while the melanoma patient is still in complete remission after 30 months.

DISCUSSION

Cisplatin has a broad range of activity in solid tumours and is widely used in combination chemotherapy regimens. A relationship between treatment intensity and response has been shown in ovarian cancer (3,13-14) but is controversial in other tumour types. An improvement in treatment outcome with higher than standard cisplatin doses per course was reported for non small cell lung cancer (15,5), testicular cancer (16,17) and head and neck cancer (6), but randomized studies comparing standard with high cisplatin dosages (in general in day 1-5 or day 1+8 schedules) failed to show any benefit for the high dose arms in testicular cancer (18), non small cell lung cancer (19) and malignant melanoma (20). Another approach to increase the platinum dose intensity is to increase the frequency of cisplatin administration, or to combine cisplatin with its analogue carboplatin.

More frequent administration of cisplatin theoretically has the additional advantage that sublethally damaged tumour cells may be killed by the next dosage. Suggestive evidence to support this notion is provided by observations in poor risk germ cell tumours, where closely spaced cisplatin therapy has been investigated (17,21,22). Early studies with weekly administration of cisplatin were hampered by the side effects which can nowadays be partly prevented (23,24). We investigated the feasibility of weekly administration of cisplatin, with administration in 3% hypertonic saline and the concomitant use of ondansetron as preventive measures.

The starting dose was 50 mg/m^2/week for 6 weeks. At the dose level of 85 mg/m^2/week the dose limiting toxicity was thrombocytopenia and necessitated dosage delays in most patients jeopardizing the dose intensity aimed for. The dose level of 80 mg/m^2 appeared to be safe for previously untreated patients and allowed a treatment with a mean dose intensity of 70 mg/m^2/week.

Table 3. Haematologic and nephrotoxicity observed

DOSE LEVEL	CISPLATIN DOSE ($mg/m^2/wk$)	No. PATIENTS/ No. ADMINISTR.	MEDIAN NADIR X $10^9/l$		MEDIAN SERUM CREATININE AT START OF TREATMENT (+ range; $\mu mol/l$)	HIGHEST SERUM CREATININE OBSERVED DURING TREATMENT (+ range; $\mu mol/l$)
			Platelets (range)	WBC (range)		
1	50	3/18	95 (46-221)	2.4 (1.8-5.5)	83 (80-93)	104 (93-106)
2	60	3/18	158 (64-223)	3.2 (2.1-5.2)	78 (70-128)	91 (77-132)
3	70	3/17*	87 (42-92)	3.6 (2.3-3.9)	92 (91-103)	104 (102-114)
4	80	9/52	58 # (25-181)	2.5 (1.6-4.7)	99 (67-121)	114 (76-180)
5	85	7/40	27 ## (14-186)	3.0 (1.2-3.6)	82 (69-95)	156 (76-183)

* 1 patient did not receive 6th cisplatin dose because of progressive disease
\# 1 patient grade 4
\## 4 patients grade 4; toxic death

Table 4. Other toxicities observed (WHO; worst grade observed)

CDDP DOSE IN mg/m²/wk	No. PATIENTS	GI*	NEURO	OTO
			WHO GRADE	
		0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
50	3	0 2 1 0 0	3 0 0 0 0	3 0 0 0 0
60	3	1 0 2 0 0	3 0 0 0 0	3 0 0 0 0
70	3	0 0 2 1 0	3 0 0 0 0	2 0 1 0 0
80	9	1 1 5 2 0	4 4 1 0 0	9 0 0 0 0
85	7	1 0 3 3 0	6 1 0 0 0	5 0 0 2 0

* modified criteria; see patients and methods

The severity of leucocytopenia did not differ between the two highest dose levels and grade 4 leucocytopenia was not observed (table 3). The risk of nephrotoxicity with this schedule is low as is the risk of neurotoxicity. The risk of ototoxicity, however, is higher than with standard cisplatin schedules and is in this study comparable to other dose intense cisplatin regimens. Nausea and vomiting could be effectively prevented by ondansetron in the first 3-4 weeks of treatment especially at dosages lower than 80 mg/m². However, with continuation of treatment the efficacy of ondansetron gradually waned. Nevertheless we conclude that weekly administration of cisplatin for a period of 6 weeks is feasible and when administered in hypertonic saline and combined with a 5-HT_3 antagonist a higher dose intensity can be reached than with previously reported weekly schedules or with schedules combining cisplatin and carboplatin. Higano et al. (25) also administered cisplatin on a weekly schedule in non small cell lung cancer but failed to reach a high response rate; in this study weekly cisplatin was combined with mitomycin C, vinblastin and fluorouracil which hampered the cisplatin dose intensity reached which was approximately 40-44 mg/m²/week.

Studies with the combination of cisplatin and carboplatin also appear to have resulted in dose intensities lower than we achieved with single agent cisplatin (26). Assuming a "normal" surface area of 1.7 m^2 and a GFR of 100 ml/min Calvert (26) calculated an AUC of 1 unit of carboplatin per week to be equivalent in dose intensity to 18.4 mg/m^2 of cisplatin per week. Using this formula the cisplatin equivalent dose intensities varied in the cisplatin plus carboplatin studies from 36-63 mg/m^2/week (27-30), with the highest dose intensity only achieved during the first treatment cycle (32). These dose intensities compare unfavourable with the dose intensity that we achieved for the whole treatment period of 6 cycles. The highest dose intensity reached in 5- day regimens every 4 weeks is 50 mg/m^2/week (4) again lower than we achieved. The encouraging results we observed in head and neck cancer and mesothelioma warrant further exploration in phase II studies. The dosage for these studies is 80 mg/m^2/week for 6 weeks in previously untreated patients. However, it is obvious that randomized studies comparing these new schedules with standard schedules of cisplatin administration are required to establish the clinical benefit.

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CHAPTER 3

PHASE II STUDY OF WEEKLY HIGH-DOSE CISPLATIN FOR SIX CYCLES IN PATIENTS WITH LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

A.S.T. Planting[1], P.H.M. de Mulder[2], A. de Graeff[3] and J. Verweij[1]

[1]Department of Medical Oncology, Rotterdam Cancer Institute/ Daniel den Hoed Kliniek, Rotterdam;[2] Department of Medical Oncology University Hospital Nijmegen, the Netherlands and[3] Department of Internal Medicine University Hospital Utrecht, The Netherlands.

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SUMMARY

Background: In a phase I study of weekly administered cisplatin we observed a major response in 8 out of 9 patients with locally far advanced head and neck cancer. All patients, previously considered for palliative treatment only, had radiation therapy with curative intent thereafter. Therefore a phase II study was initiated to explore the activity and tolerance of this weekly cisplatin regimen further in this patient group.

Patients and methods: Fifty-nine patients with locally advanced head and neck cancer were entered in this phase II study. Cisplatin was administered at a dose of 80 mg/m^2 weekly for six cycles. Cisplatin was administered in hypertonic saline (3% NaCl) as a 3-hour infusion with standard pre- and post hydration.

Results: Fifty patients were evaluable for response and fifty-five for toxicity. Nine patients only were able to complete the treatment with the planned dose intensity of 80 mg/m^2/week. A complete response was observed in 8 and a partial response in 22 of the evaluable patients (60%; 51% of all eligible patients; 95% CI limits 37-63%). Stable disease was observed in 12 patients while the tumor progressed in 9 patients. Forty-seven patients had subsequent high dose radiotherapy, one radiotherapy and surgery and 4 patients were treated with second line chemotherapy. The median progression-free survival and median overall survival for all patients were 32 weeks and 56 weeks respectively.

Haematologic toxicity consisted of anemia, 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 patients were taken off study because of delayed bone marrow recovery. Non haematologic toxicities were : ototoxicity grade 1 in 13 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.

Conclusion: Cisplatin as a single agent administered at a high dose-intensity has an anti-tumor activity comparable to that of combination regimens in locally advanced head and neck cancer. The pattern of toxicity is however different: leuco- and thrombocytopenia jeopardize the dose intensity concept; for patients ototoxicity is the more relevant toxicity. Further studies with weekly cisplatin are of interest especially with newer measures to reduce toxicity.

INTRODUCTION

Approximately 50-60% of patients with head and neck cancer present at diagnosis with a locally advanced tumor stage 3 or 4. Depending on the site and the extension of the tumor, treatment with surgery followed by radiotherapy or with high-dose radiotherapy only, will yield a cure rate which averages only 30-40%. Most patients will die from a 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 centers these patients are treated upfront with chemotherapy followed by local therapy. The combination of cisplatin with continuous infusion of 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 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 noncompliance.

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 out 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 to that of combination chemotherapy regimens. In order to test this concept further we performed a multicenter phase II study.

PATIENTS AND METHODS

All patients in the study had histologic proof of squamous cell carcinoma of mucous membranes of the head and neck, tumor stage 3 or 4 according to the UICC classification and 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 x 10^9/l, platelets $>$ 100 x 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, tumors 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 as well as patients with a Korsakoff's syndrome. All patients gave oral or written informed consent according to the rules of the institute.

Before start of the treatment patients had a full clinical work up 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.

Neurologic examination and audiometry were done before start of treatment, after 3 and 6 cisplatin administrations and 3 months after cessation of treatment.

The patients were hospitalized for 24 hours once a week. Cisplatin at a dose of 80 mg/m^2 was dissolved in 250 ml 3% NaCl and administered as a 3- hour infusion. Prehydration consisted of 1 liter dextrose/saline in 4 hours + 20 mmol KCl + 2 gram $MgSO_4$; posthydration consisted of 2 liters dextrose/saline in 8 hours + 40 mmol KCl + 4 gram $MgSO_4$. As antiemetic 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 x 10^9/l and/or platelets were < 75 x 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 the team of medical oncologist, head and neck surgeon and 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).

RESULTS

Fifty-nine 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.

Table 1. Patient Characteristics

No. of patients entered	59	
male : female	44 : 15	
median age (years, range)	54	(39-72)
performance status 0	13	
1	46	
site of primary tumor		
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	

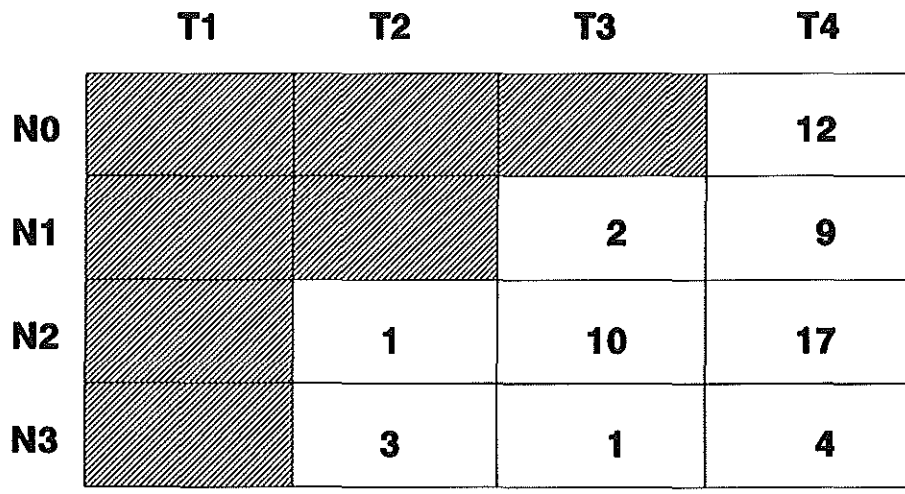

Figure 1. TNM classification

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. Twenty-two patients (37%) received the planned 6 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 one week delay and 60 mg/m^2/week in the 6 patients with 2 weeks delay.

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 to take 13 patients off study mainly due to too slow recovery of thrombocytopenia. Three patients were taken off study already 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, one patient because of hypomagnesaemia and two 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.

Fifty patients are fully evaluable for response to chemotherapy. In nine patients response was not evaluated; these were the patients receiving only one or two cisplatin administrations- see table 2- and one patient who refused the sixth cycle and refused evaluation. These nine patients are considered as treatment failures in the over-all evaluation. In 8 patients the tumor disappeared completely clinically and/ or radiologically (7 patients with oropharyngeal and one with hypopharyngeal cancer) and the tumor response met the criteria of a partial response in 22 patients for an overall response in 60% 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 done, in 15 patients the partial response status was already reached after the 3rd cisplatin administration. In 12 patients the tumor 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).

Table 2. No. of CDDP cycles administered per patient

		Reason off study
1 cycle	8 pts	PD 2 pts, CVA 1 pt, toxicity 5 pts[1]
2 cycles	2 pts	PD 1 pt, refusal 1 pt
3 cycles	6 pts	delay > 3 wks 4 pts, PD 1 pt, ototoxicity 1 pt
4 cycles	10 pts	delay > 3 wks 6 pts, PD 2 pts, nephrotox 1 pt, refusal 1 pt
5 cycles	11 pts	delay > 3 wks 3 pts, nephrotox 3 pts, ototox 1 pt, hypomagnesaemia 1 pt, angina pectoris 1 pt, pneumonia 1 pt, refusal 1 pt
6 cycles	22 pts	

[1] reversible tubulus necrosis 1 pt, nephrotox grade 2 1 pt, nephrotox grade 1 1 pt, tinnitus 2 pts

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 ($p=0.75$), localisation (oropharynx versus other localisations $p=0.45$), histological differentiation grade (well *vs* moderate *vs* poorly differentiated: $p=0.10$), T-stage ($p=0.52$) or N-stage ($N0 vs N_{1-3}$) $p=0.80$ (Fishers exact test 2-sided). Because of additional treatment after cisplatin (definitive radiotherapy in 47 patients, radiotherapy and surgery in one 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). Forty-seven patients were treated with radiotherapy (60-70Gy in fractions of 1.8-2 Gy) after chemotherapy and one patient had radiotherapy followed by a neck dissection for residual lymphnodes (which showed only necrosis at histologic examination). Four patients were treated with a second line chemotherapy regimen and received radiotherapy at a later moment. One 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 one patient with rapid progressive disease never started additional therapy. All 8 patients with a complete response on cisplatin had radiotherapy and two patients

recurred locally after 57 and 62 weeks respectively, one patient died without evidence of disease (NED) 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. One patient refused radiotherapy. Fourteen 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 eleven had radiotherapy and only one patient achieved a complete response. All other patients kept tumor residue; the time to progressive disease in this group was median 28 weeks (range 10-60 weeks). Six out of the 9 patients with progressive disease on chemotherapy had radiotherapy and in none the NED status could be reached. The median survival was 36 weeks for the patients with stable disease and only 28 weeks for patients with progressive disease.

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
N/V	9	12	14	20	0
neurotoxicity	47	8	0	0	0
ototoxicity	32	13	7	3	0
nephrotoxicity	39	13	2	1	0

Toxicity

Fifty-five 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 transfusions for a total of 66 units of packed cells. Leuco- and thrombocytope-

nia > grade 2 were never observed before the 3rd cisplatin administration. One patient developed leucocytopenia grade 4 and 8 patients thrombocytopenia grade 4. Four 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 retreatment 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 one patient a delay of 1 week was reported because of nausea and vomiting. Nausea and insufficient fluid intake was held responsible for nephrotoxicity in at least 4 patients.

Nephrotoxicity was the reason to take patients off study after the very first administration in 3 patients. During further treatment another 4 patients had an increase in serum creatinine leading to treatment discontinuation. One patient developed a symptomatic hypomagnesaemia (seizures). Ten other patients developed serum magnesium values <0.50 mmol/l.

The median serum creatinine of the eligible patients at 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, two patients grade 2 and one patient a grade 3. In 7 patients nephrotoxicity improved one grade and in one 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 kg - -12 kg). Nine patients had weight loss >5%, one patient >10% of starting body weight. On the contrary 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 in head and neck cancer, especially of stage 3 and 4 tumors, is increasing in The Netherlands.

Local treatment is curative in only one third of the patients. Attempts to improve this disappointing result by treating patients upfront with chemotherapy have not resulted thus far in a clear benefit (9-12). Subgroups of patients may however still benefit from the combination because of improved local control rate or a delay in occurrence of distant metastases (14-15). In laryngeal cancer and oropharyngeal cancer, the combination of chemotherapy with radiotherapy can prevent mutilating surgery in a considerable group of patients (11-13). In most neoadjuvant chemotherapy combinations a low dose intensity was reached especially for cisplatin. In a randomized 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 tumor types, it is worthwhile to test schedules developed to reach a higher dose-intensity also in head and neck cancer. Forastiere et al.(16) obtained a response in 16 out 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 60% 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 to "standard"-combination chemotherapy regimens as was already suggested in Forastieres study, which had a planned dose intensity of 50 mg/m^2/week. The results of our present study are also comparable to 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. Striking is the dismal prognosis in patients not responding to chemotherapy. Only in one patient the radiotherapy was able to convert a stable disease into a complete response and none of the patients with progressive disease on cisplatin responded on radiotherapy. This corresponds with the report by Ensley et al.(19). In contrast, 14 of the 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, prognostic factors which are correlated with poor

treatment outcome (20,21). As in most responding patients signs of objective or subjective improvement were already present after 3 cisplatin administrations, the absence of signs of response after 3 administrations can be considered a reason to stop chemotherapy sparing the patients further toxic treatment. The toxicity of the treatment schedule was the cause that less than half of the patients were capable of completing the planned treatment. Only nine 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. Especially leuco- and thrombocytopenia precluded the weekly administrations frequently and was the main toxicity for which patients were taken off study. When the patients taken off study due to toxicity after the first cisplatin dose are left out of consideration, as they would have failed any cisplatin containing regimen, schedule related nephro- and ototoxicity was the cause of withdrawal of seven patients, the patient with symptomatic hypomagnesaemia included. We tried to diminish the risk of nephrotoxicity by administering cisplatin in hypertonic saline, as is done in other high-dose intensity schedules (16,22-23). Graded according to the WHO-criteria the risk of nephrotoxicity appears rather low. Ototoxicity is for the patients a more troublesome side effect of high-dose intensity schedules. Ototoxicity grade 2 (tinnitus) can be reversible 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 studies ototoxicity grade 2 and 3 are reported in even up to 65%.(16,22-25). In Forastieres study e.g. 9 out of 22 patients left the study because of ototoxicity. 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 is not high, but neurotoxic symptoms may develop up to 3 months after cessation off therapy underscoring the need for long 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 randomized study. In view of the disappointing results of neoadjuvant chemotherapy in head and neck cancer and the more optimistic results of concomitant chemo-radiotherapy schedules, testing this schedule with radiotherapy would be a more logical next step (28). Studies to minimize toxicities have to our opinion, however, first priority over randomized studies or combination with radiotherapy. Ethyol (WR 2721) is a drug with a broad

protective effect on nephro-, neuro-, oto- and haematologic toxicity (29). The EORTC Head and Neck Cancer Cooperative Group recently started a randomized phase II study with weekly cisplatin at a dose of 70 mg/m^2/week for six weeks with or without Ethyol to study the protective effect of the latter drug, especially on nephro- and ototoxicity. If these toxicities can be prevented, further studies with cisplatin in high dose-intensity schedules will be more feasible.

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CHAPTER 4

RANDOMIZED STUDY OF A SHORT COURSE OF WEEKLY CISPLATIN WITH OR WITHOUT AMIFOSTINE IN ADVANCED HEAD AND NECK CANCER

A.S.T. Planting[1], G. Catimel[2], P.H.M. de Mulder[3], A. de Graeff[4], F. Höppener[5], J. Verweij[1], W. Oster[6] and J.B. Vermorken[7]

for the Chemotherapy Subcommittee of the EORTC Head and Neck Cooperative Group

[1] Rotterdam Cancer Institute/University Hospital Rotterdam, The Netherlands,

[2] Centre Leon Berard, Lyon,France

[3] University Hospital Nijmegen, The Netherlands

[4] University Hospital Utrecht, The Netherlands

[5] EORTC New Drug Development Office, Amsterdam, The Netherlands

[6] USB Pharma Ltd, Watford, UK

[7] University Hospital Vrije Universiteit, Amsterdam, The Netherlands

SUMMARY

Background: Cisplatin is one of the most active cytotoxic agents available for the treatment of patients with head and neck cancer. In a previous phase II study with weekly administration of cisplatin, a response rate of 51% was achieved. However, only in a minority of the patients the planned high dose intensity of 80 mg/m^2/week could be reached because of toxicity, mainly thrombocytopenia and ototoxicity. Amifostine is a cytoprotective drug that can diminish the toxicity of alkylating agents and platinum compounds. Therefore the effect of amifostine on toxicity and activity of weekly cisplatin was investigated in a randomized study.

Patients and methods: Patients with locally advanced, recurrent or metastatic head and neck cancer were eligible. After a feasibility study to test the optimal dose of amifostine and the optimal anti-emetic schedule, patients were randomized to weekly cisplatin 70 mg/m^2 for six cycles preceded by amifostine 740 mg/m^2, or cisplatin only. Cisplatin was administered in hypertonic saline (3% NaCl) as a 1-hour infusion; amifostine was administered as a 15-minute infusion directly before the administration of cisplatin.

Results: Fourteen patients were entered in the feasibility study and 74 in the randomized study. The median number of cisplatin administrations in the randomized study was six (range 2-6), equal in both arms. In both treatment arms the median dose intensity of cisplatin achieved was the planned 70 mg/m^2/week. Patients completing the 6 cycles had less delays due to myelosuppression in the amifostine arm ($p=0.02$). Hypomagnesaemia grade 2+3 was significantly less observed in the amifostine arm ($p=0.02$), as well as hyponatremia grade 3+4 ($p=0.04$). Neurotoxicity analysed by serial vibration perception thresholds (VPT) showed a diminished incidence of subclinical neurotoxicity in the amifostine arm ($p=0.03$). Hypotension was the main side effect of amifostine but only of relevance in one patient. The antitumor activity of cisplatin was preserved as 63% of the evaluable patients in the amifostine arm responded compared to 50% of the evaluable patients in the cisplatin alone arm.

Conclusion: Our study indicates that amifostine reduces the risk of hypomagnesaemia and neurotoxicity and to a lesser degree of trombocytopenia without compromising the antitumor effect of cisplatin in a weekly schedule.

INTRODUCTION

Approximately 50-60% of the patients with head and neck cancer present at diagnosis with a locally advanced tumor stage III or IV. Treatment usually consists

of surgery followed by radiotherapy or of high dose radiotherapy. However, these treatments yield a cure rate of only 30-40%. Most patients will recur locoregionally, while 10-15% will die from distant metastases (1). Locally advanced head and neck cancer is highly responsive to chemotherapy. The combinations of cisplatin with either bleomycin and methotrexate or with a 96-hour continuous infusion of fluorouracil are considered to be the most active regimens with response rates of 60-90%, of which 30-35% complete (2-3). The contribution of induction chemotherapy on survival in locally advanced head and neck cancer is however, not clear (4,5). In locally recurrent or metastatic disease the results of chemotherapy are very disappointing with response rates of only 20-30%, of short duration and without demonstrable effect on survival (5).

For cisplatin, the corner-stone of chemotherapy in locally advanced head and neck cancer, a dose-response relation is suggested in several tumor types (6). Therefore clinical studies with high-dose and high-dose intensity regimens are attractive. As with modern antiemetics nausea and vomiting can be treated more efficiently and as with vigorous hydration and the administration of cisplatin in hypertonic saline the risk of nephrotoxicity can be reduced (7-9), neuro- and ototoxicity are now the most cumbersome cisplatin toxicities. In a phase II study of weekly single agent cisplatin at a dose of 80 mg/m^2/week for six cycles in locally far advanced head and neck cancer a response was obtained in 51% of the patients, suggesting that cisplatin administered at a higher dose intensity is more active than at standard doses. With this weekly schedule hematologic toxicity, especially thrombocytopenia, was the main reason for treatment delays or the reason to take patients off study. Other major toxicities were hypomagnesaemia grade 2+3 in 20%, ototoxicity grade 2+3 in 18% and nephrotoxicity grade 2+3 in 5% of the patients (10). Because of these side effects, only 9 out of 59 patients completed the treatment without interruption and reached the planned dose intensity of 80 mg/m^2/week.

Amifostine (WR-2721; Ethyol) is an organic thiophosphate. In preclinical and clinical studies amifostine showed selective protection of normal tissues against radiation-induced toxicities and toxicities induced by alkylating agents and platinum compounds without influencing the anti-tumor effects of these treatments (11-21). Amifostine is a prodrug which has to be converted into the active metabolite, the free thiol WR-1065. Selective protection of normal tissues is explained by the more rapid uptake of WR-1065 in normal cells as compared to tumor cells, which is due to the difference in membrane- and capillary bound alkaline phosphatase and diffe-

rences in pH between normal and tumor cells (22). As amifostine has a very short plasma half-life (< 10 minutes), the drug has to be administered directly before the administration of chemotherapy (22,23). Specific side effects reported of amifostine are hypotension, nausea, vomiting, sneezing, a warm flushed feeling, mild somnolence, hypocalcaemia (mostly asymptomatic) and very rarely allergic reactions (24,25).
The EORTC Head and Neck Cancer Cooperative Group decided to explore the weekly cisplatin regimen further in a randomized study comparing weekly cisplatin to weekly cisplatin with amifostine.
This paper reports both on the feasibility part of the study and the results of the randomized study.

PATIENTS AND METHODS

Patients in this study were required to have a histologic proof of squamous cell carcinoma of the mucous membranes of the head and neck, locally advanced disease stage III or IV, locally recurrent disease after previous radiotherapy and/or surgery or with distant metastases, measurable disease, no prior chemotherapy with the exception of neoadjuvant chemotherapy > 12 months before entering this study, age between 18-70 years, WHO performance status ≤2, WBC count ≥4.0 x 10^9/l, platelet count ≥100 x 10^9/l, serum creatinine ≤120 μmol/l or creatinine clearance >60 ml/min, liver function tests and bilirubin <2.0 x the upper limit of the normal range, no suspicion of active infection. Excluded from the study were patients with undifferentiated carcinoma of the nasopharynx, patients with hypertension requiring more intensive medication than diuretics only, patients with concomitant neurological, psychological or medical disorders making them unsuitable for treatment or follow up per protocol and patients with CNS involvement. All patients gave written informed consent.

Before the start of treatment patients had a full clinical work up with medical history, physical examination, measurement of indicator lesions, full hematological counts and serum chemistries, creatinine clearance, ECG, chest X-ray, baseline audiometry and neurologic examination, including estimation of the vibration perception threshold (VPT). The VPT was measured at the dorsum of the second metacarpal bone of both hands. All centers made use of a Vibrameter type IV (Somatic AB, Stockholm, Sweden).

During treatment the patients had weekly a medical history and physical examination taken, weekly determination of full blood counts, serum chemistries and creatinine clearance. Neurologic examination and audiometry were repeated after the 3rd and 6th cisplatin administration and, if possible, 3 and 6 months later.

Patients were registered and randomized at the EORTC New Drug Development Office in Amsterdam. Patients were stratified by institution and by disease extent (locally advanced versus locally recurrent or metastatic disease).
Response to treatment was assessed 2 weeks after the last cisplatin dose. The WHO criteria for evaluation of response were used (26); toxicity, with exception of amifostine-induced hypotension, was graded according to the NCI-CTC criteria (27).
For grading of amifostine related hypotension a modified grading system was used:

Grade 0	No hypotension
Grade 1	Hypotension not requiring amifostine interruption
Grade 2	Hypotension requiring interruption once
Grade 3	Hypotension requiring interruption more than once
Grade 4	Prolonged hypotension requiring dose reduction
Grade 5	Hypotension accompanied by complications or requiring therapy other than rapid saline infusion.

Study design

The study was planned to consist of a feasibility study, a randomized study and, depending on the results of the randomized study, a dose escalation study. The feasibility study was considered necessary because firstly, experience with weekly administration of amifostine with cisplatin was lacking and secondly, patients with head and neck cancer were reported to have an increased susceptibility to hypotension (28). The second part of the study consisted of a randomized study, to compare toxicity and efficacy of both schedules. Based on the results of other studies, which showed considerable reduction of nephro-and neurotoxicity (16,19), it was postulated that 30 fully evaluable patients per treatment arm would be sufficient to detect a significant reduction in nephro- and neurotoxicity (29). The third part of the study was planned as a cisplatin-dose escalation study in case a significant protective effect of amifostine was shown.

Treatment schedule

Patients were hospitalized weekly for 24 hours.

Antiemetic regimen

In the feasibility part of the study the first 10 patients received an antiemetic regimen consisting of lorazepam 2 mg orally 6 hours prior to administration of the chemotherapy, 1 mg iv directly after chemotherapy followed by 1 mg iv every 6 hours if indicated plus ondansetron 8 mg iv 30 minutes prior to and 4 and 8 hours after cisplatin combined with dexamethasone 10 mg 30 minutes prior to chemotherapy, and 10 mg iv after 4 and 8 hours.

After experience in 10 patients this antiemetic regimen was changed into: tiëthylperazine 6.5 mg po 4 hours and 30 minutes before chemotherapy combined with ondansetron 8 mg 30 minutes before and 8 mg 8 hours after chemotherapy plus dexamethasone 20 mg 30 min before and 8 hours after chemotherapy. Four patients in the feasibility study and all patients in the randomized study were treated with this antiemetic regimen.

Cisplatin

Standard prehydration consisted of 1 liter of normal saline or dextrose/saline with suppletion of 20 mmol KCl and 2 grams of $MgSO_4$ and was given over 2 hours. Cisplatin powder was dissolved in 250 ml of hypertonic saline (3%) and administered at a dose of 70 mg/m^2 over 1 hour followed by posthydration with 4 liters of normal saline or dextrose/saline (with 80 mmol KCl and 8 grams of $MgSO_4$) over 24 hours. In case of urine output <100 ml/hour 100 ml of mannitol 20% and/or 10 mg furosemide was administered depending on the local practice of the institute.

Amifostine

Amifostine was dissolved in normal saline to a concentration of 50 mg/ml and was administered as a rapid infusion over 15 minutes immediately before the cisplatin was given. During the amifostine administration patients were kept in the supine position and blood pressure was measured at least every 5 minutes.

Before starting amifostine a threshold blood pressure was determined under which value amifostine had to be interrupted. The threshold mean systolic blood pressure was calculated by taking the average of 3 blood pressures taken within 2 hours before the amifostine administration.

The guideline for interruption of amifostine was:

	Mean baseline blood pressure in mm Hg				
	< 100	100-119	120-139	140-180	>180
Decrease in systolic BP (mm Hg)	20	25	30	40	50

In case of a drop in blood pressure below the calculated threshold the amifostine infusion was interrupted and infusion of normal saline started. In case of return of blood pressure above the threshold within 5 minutes the amifostine infusion was restarted. In case the hypotension lasted >5 minutes amifostine was further withheld for that cycle and for the next cycle the amifostine dose was reduced by 25%.

Dose reductions of cisplatin were not allowed in this study. If at planned retreatment WBC were $<2.5 \times 10^9/l$ and/or platelets were $<75 \times 10^9/l$ the treatment was postponed until recovery above these values. In case of a treatment delay of > 2 weeks patients were taken off study. The development of nephro- or neurotoxicity grade 2 and the development of clinical hearing loss were also reasons to take a patient off study.

Statistics

Percentages were compared using the chi-square test (without correction for continuity). Variables with an approximately continuous distribution were compared between treatment groups with the signed-rank Mann-Whitney U test. For comparisons over time within treatment groups the signed rank test of Wilcoxon was used.

RESULTS

Fourteen patients were entered in the feasibility study and 74 patients in the randomized study.

Feasibility study

The characteristics of the patients are given in table 1. The starting dose of amifostine was 910 mg/m^2 in combination with the lorazepam containing antiemetic

regimen. The first 5 patients received 27 cisplatin administrations (in 1 cycle the cisplatin dose was reduced to 56 mg/m^2). In these first 5 patients 2 experienced hypotension grade 1, one grade 2 and 2 patients grade 4; vomiting grade 3 or 4 occurred in 2 patients. In the next cohort of 5 patients (25 cisplatin administrations) the amifostine dose was reduced to 740 mg/m^2. Still hypotension grade 3+4 was observed in 2 patients but grade 3 and 4 vomiting was no more observed. As it was assumed that lorazepam contributed to the hypotensions, in the third part of the feasibility study 4 patients were treated with the new antiemetic regimen containing tiëthylperzine. Only in one out of 22 cycles hypotension grade 3 was observed and no more grade 4 hypotension nor grade 3 or 4 vomiting. For this reason the second antiemetic regimen was selected as standard for the randomized study. Other toxicities observed which were considered related to amifostine were: sneezing (5 patients), flushing (8 patients), myalgias (1 pt). The other toxicities are presented in table 2. Thirteen patients were evaluable for response: one patient had a complete and 5 patients a partial response, 4 patients had stable disease and 3 patients progressive disease. One patient was not evaluated because he was taken off study before the fourth cisplatin administration because of ototoxicity.

Table 1. Patient characteristics feasibility study

No. patients entered		14
male : female		10 : 4
median age (range)		52 y (27-66 y)
Performance status	0	3
	1	10
	2	1
Tumor stage		
Locally advanced		12
Distant metastases		2
Localization primary tumor		
Oropharynx		7
Supraglottic larynx		2
Maxillary sinus		2
Nasopharynx		1
External ear canal		1
Tongue base		1

Table 2. Toxicities observed in the feasibility study: worst by patient (n=14)

CTC Grade	0	1	2	3	4
Anaemia	3	7	3	1	0
Leucopenia	4	6	2	2	0
Neutropenia	6	2	3	2	1
Thrombocytopenia	7	6	0	1	0
Nephrotoxicity *	13	1	0	0	0
Ototoxicity	8	3	2	1	0
Neurotoxicity	12	2	0	0	0
Alopecia	12	1	1	0	0
Hyponatremia	9	2	3	0	0
Hypomagnesemia	12	1	1	0	0
Hypocalcemia	13	1	0	0	0

* serum creatinine

Table 3. Patient characteristics randomized study.

	Cisplatin + amifostine	Cisplatin only
No. of patients entered	37	37
No. of patients treated	36	37
Gender: male	27	28
female	10	9
Age : median (years)	54	54
(range)	(35-69)	(36-67)
Performance Status median	1	1
(range)	0 - 2	0 - 1
Disease status:		
Locally advanced	29	29
Locally recurrent	5	7
Metastatic	3	1
Prior radiotherapy	9	7
Prior neoadjuvant chemother.	3	0

Randomized study

Seventy-four patients were randomized in the second part of the study. The patient characteristics are shown in table 3. Both groups were well balanced according to gender, age and disease extent. Three patients randomized to the cisplatin-amifostine arm had a performance status of 2, while 3 patients pretreated with neoadjuvant chemotherapy >1 year before, were also randomized to the

cisplatin-amifostine arm. One patient randomized to the cisplatin-amifostine arm never started treatment and is excluded from the analysis.
In the amifostine arm in total 184 cycles of cisplatin were administered compared to 202 cycles in the cisplatin only arm (p=0.06). In both treatment arms the median number of cisplatin administrations was 6 (range 2-6). The median cisplatin dose intensity achieved was equal in both treatment arms: 70 mg/m^2/week. The results are given in table 4.

Table 4. Treatment results randomized study

	Cisplatin + amifostine	Cisplatin	
No. of patients treated	36	37	
Total no. of cycles	184	202	p=0.06
Median no. of cycles per pat.	6	6	
(range)	(2-6)	(2-6)	
Patients completing 6 cycles	20	28	p=0.07
Without delay	15	20	p=0.29
No. of patients with delays	5	9	
for myelosuppression	2	8	p=0.08
Total no. of weeks delayed for myelosuppression	15	25	p=0.17
No.of weeks delayed for myelo-suppression in pts completing 6 cycles	3	13	p=0.02
Median cisplatin dose intensity achieved (mg/m^2/week)	70	70	
Reasons for < 6 cycles:			
-Progressive disease	3	2	
-Early death	3	0	
-Haematol.toxicity	4	3	
-Ototoxicity	3	3	
-Infection	1	1	
-Protocol violation	1	0	
-Physician preference	1		

In the cisplatin-amifostine arm 20 patients completed 6 cycles (56%) versus 28 patients in the cisplatin only arm (76%) (p=0.07). The main reason for this difference between both arms is the early death of 3 patients in the amifostine arm (2 patients with known cardiovascular disease died at home, one patient died of asphyxia). Other reasons not to complete the 6 cycles in the combination arm were:

progressive disease in 3 patients, delay due to leukopenia >2 weeks in 4 patients, ototoxicity in 3 patients, pneumonia in 1 patient, a protocol violation in 1 patient and in 1 patient the reason was "physicians preference" because of planning of additional radiotherapy. The reasons not to complete 6 cycles in the cisplatin only arm were progressive disease in 1 patient, delay > 2 weeks due to hematologic toxicity in 4 patients (neutropenia in 2 and combination of neutro-and trombocytopenia in 2), ototoxicity in 3 patients and a pneumonia in 1 patient. The patients completing 6 cycles had less treatment delays in the amifostine arm versus the cisplatin only arm mainly because of less hematologic toxicity. (vide infra).

Toxicity analysis

Table 5. Toxicity analysis; CTC-grading; worst toxicity per patient.

	Cisplatin + amifostine				cisplatin only			
Grade	1	2	3	4	1	2	3	4
Anemia	11	19	2	0	14	15	3	0
Leucopenia	8	11	2	2	4	10	5	0
Neutropenia	5	9	8	2	5	6	10	1
Thrombocytopenia	20	7	0	1	10	4	2	4
Nephrotoxicity	6	2	0	0	5	0	0	0
Ototoxicity	6	7	3	0	3	10	4	0
Neurotoxicity	4	0	0	0	5	0	0	0
Nausea	12	13	3	0	18	6	2	0
Vomiting	9	13	3	2	6	9	3	0
Diarrhoea	3	0	1	0	5	2	0	1
Stomatitis	2	1	0	0	2	0	0	0
Hypocalcemia	6	2	2	0	7	2	1	0
Hypokalemia	7	1	0	1	7	6	0	0
Hypomagnesemia	8	5	0	0	7	7	7	0
Hyponatremia	13	4	0	0	17	4	3	1
Hypophosphatemia	5	1	1	0	6	0	0	0
Alopecia	1	0	0	0	2	0	0	0

Hematologic toxicity

The hematologic toxicity is presented in table 5. There was no difference in the occurrence of leucopenia (p=0.76) and neutropenia (p=0.98) between the two

arms. However, more patients in the cisplatin only arm experienced trombocytopenia grade 3+4 compared to the combination arm : 6 versus 1 patients (p=0.08). In the combination arm 4 patients were taken off study because of treatment delay >2 weeks due too slow bone marrow recovery (3 patients with leucopenia and one patient with both leuco-and trombocytopenia) and 3 patients in the cisplatin alone arm (2 patients because of trombocytopenia and 1 patient because of neutropenia). The total number of weeks delayed because of haematologic toxicity was not different between both arms: 15 weeks in the combination arm and 25 weeks in the cisplatin only arm (p=0.17) The patients completing the 6 chemotherapy cycles, however, had significantly less weeks delay due to bone marrow toxicity in the combination arm compared to the cisplatin only arm: 3 weeks delay versus 13 weeks delay (p=0.025).

Nephrotoxicity

Nephrotoxicity grade 2, based on serum creatinine levels, was reported in 2 patients in the amifostine arm; one of the patients was taken off study after the fourth cisplatin administration during neutropenic fever and in the second patient grade 2 nephrotoxicity was reported after completion of treatment. In both patients the serum creatinine returned to baseline level during follow up. Nephrotoxicity grade 1 was reported in 5 patients in the cisplatin only and in 6 patients in the combination arm. Comparison of creatinine clearances cycle by cycle (calculated with the Cockroft-Gault formula) showed no differences between both treatment arms, as is shown in table 6.

Table 6. Renal toxicity

	No. of patients		Median creatinine clearance* ml/min		
Cycle	Cis + ami	Cis only	Cis + ami	Cis only	p-value
1	36	37	82	97	0,09
2	36	37	82	91	0,38
3	34	35	87	90	0,44
4	31	34	86	85	0,82
5	27	31	87	85	0,46
6	20	28	84	82	0,83
post 6	20	28	89	81	0,32

* calculated creatinine clearance by Cockroft-Gault formula

Although the median creatinine clearance decreased in the cisplatin only arm from 97 ml/min to 81 ml/min after 6 cisplatin cycles while the median clearance remained at least stable in the cisplatin-amifostine arm this difference was not statistically different($p = 0.12$; Mann Whitney U-test).

Hypomagnesemia/Hyponatremia

Hypomagnesemia grade 2+3 was observed in 5 patients in the combination arm versus 14 in the cisplatin only arm ($p=0.02$); there were 8 cycles in the combination arm complicated by hypomagnesaemia >grade 1 versus 27 cycles in the cisplatin only arm ($p=0.006$). Clinical side effects related to hypomagnesaemia were not reported. In the cisplatin only arm 4 patients had hyponatremia grade 3+4 versus none in the amifostine-arm ($p=0.04$).
There were no significant differences between both treatment arms in the occurrence in hypokalaemia, hypocalcaemia or hypophosphatemia.

Neurotoxicity

Clinical neurotoxicity was limited to grade 1 only and was reported in 4 patients in the combination arm and 5 patients in the cisplatin only arm. As neurotoxicity can develop after cessation of treatment the clinical neurotoxicity grading was based on worst symptoms up to 3 months after treatment. For the same reason the VPT analysis was done in patients in whom 3-month VPT values were available. The mean cumulative cisplatin dose in the analysed patients was 394 mg/m^2 in the combination arm versus 401 mg/m^2 in the cisplatin only arm. Details are shown in table 7. Per VPT-examination 3 measurements were done at the left and at the right hand. The mean of these 3 values was taken as value for the VPT and in the table the median of these VPT-means are reported. The VPT's of the left hand show less increase in the amifostine arm compared to the cisplatin alone arm ($p=0.03$). Due to an imbalance at baseline for the cisplatin-amifostine arm for VPT values of the right hand (due to the limited number of data) the increase of the VPT's for the right hand is not significant different ($p=0.07$). This imbalance is probably caused by the low number of patients analyzed at 3 months as the median VPT for the right hand at baseline, when all patients in the amifostine arm are considered, was 0.73, identical to the VPT-values of the left hand, so that with more data on longer follow up this difference may disappear.

Table 7. Neurotoxicity: VPT analysis (median values)

	Cisplatin+amifostine	cisplatin
Left hand baseline(all patients)	0.77	0.77
Right hand baseline(all patients)	0.73	0.74
Left hand baseline#	0.70	0.65
Left hand 3 months#	0.85	1.13*
Right hand baseline#	0.58	0.75
Right hand 3 months#	0.86	1.15 **

#=patients with VPT values at baseline and after 3 months follow up: 14 patients in the cisplatin + amifostine arm; 20 patients in the cisplatin only arm.
* p=0.03 and **p=0.07 for difference in increase of VPT after treatment.

Ototoxicity

Although tinnitus was reported less frequent in the amifostine arm there was no difference in the occurrence of clinical ototoxicity grade 2+3 between both treatment arms (p=0.24). Ototoxicity grade 3, clinical hearing loss, was reported in 3 patients in the combination arm and 4 patients in the cisplatin alone arm. Analysis of the serial audiometries in both arms of the study showed that hearing loss was most frequently seen at the high-frequency levels (4000 and 8000 Hz). Details are shown in table 8.

Table 8. Ototoxicity; analysis of audiometry*

Cisplatin + amifostine (n = 31 patients)				Cisplatin only (n = 33 patients)		
left ear		right ear		left ear	right ear	
250 Hz	5 dB	0 dB	(+20--25)	0 dB	0 dB	(0-30)
500 Hz	5 dB	0 dB	(+15--35)	0 dB	0 dB	(+10--10)
1000 Hz	5 dB	0 dB	(+10--40)	5 dB	0 dB	(+30--15)
2000 Hz	5 dB	5 dB	(+30--40)	10 dB	5 dB	(+10--50)
4000 Hz	15 dB	15 dB	(+5--55)	20 dB	15 dB	(+10--45)
8000 Hz	30 dB	30 dB	(+10--70)	35 dB	25 dB	(+10--90)

* median loss of decibels (+ range)

The median hearing loss at 4000 Hz was 15 decibels (db), identical in the right and left ears and identical in both treatment arms. At 8000 Hz the median hearing loss was 30 db in both ears in the amifostine arm, while in the cisplatin alone arm it was 25 db and 35 db in the right and left ear, respectively.
As many patients had already impaired hearing function at baseline, patients with "normal" ears at baseline (<30 decibel hearing loss at 4000 and 8000 Herz) were analyzed separately. Also in this small subgroup (only six patients in the amifostine arm and 9 in the cisplatin only arm) no difference in the audiologic parameters could be shown.

Gastrointestinal toxicity

Nausea and vomiting were reported slightly more frequent in the combination arm, not unexpected, as amifostine itself can cause these side effects. Vomiting grade 4 was reported in 2 patients in the amifostine arm. Other gastrointestinal side effects were equal in both treatment arms.

Amifostine toxicities

Hypotension (for grading system see section" Patients and Methods") during the infusion of amifostine was reported in 17 patients (47%) and in 45 out of 184 cycles (24%). Hypotension grade 3 was reported in 2 patients (3 cycles) and grade 4 hypotension in 3 patients (4 cycles), and occurred only during the first or second amifostine administration. In 2 patients hypotension did not recur after a 25% dose reduction according to the protocol. In one patient, grade 4 hypotension recurred despite dose reduction and amifostine was further withheld in this patient.

One patient died shortly after the second amifostine administration. This patient, with an obstructive local recurrence of oropharyngeal cancer, suffered from a hypotension (RR 70/50) 9 minutes after the start of amifostine and the administration was interrupted. Shortly thereafter the patient became dyspnoeic because of airway obstruction by tough sputum, became unconsciousness and died shortly thereafter. As the patient had a written "Do Not Resuscitate" request in case of cardio-pulmonary emergencies he was not resuscitated. The postmortem revealed asphyxia due to mechanical obstruction and pulmonary oedema.

Other, minor, side effects of amifostine reported were dizziness (7 patients), flushing (6 patients), feelings of anxiety (2 patients), palpitations (3 patients) and collaps (one patient) due to episodes of hypotension. A typical amifostine side effect is sneezing. This side effect was reported by 6 patients.

Dizziness was also reported by 5 patients in the cisplatin only arm.

Response analysis

Although the main goal of the randomized study was comparison of toxicity all X-rays, CT-scans and MRI's of all responding patients as well as an at random selection of non-responding patients were independently reviewed by a radiologist experienced in head and neck oncology. This radiologist worked in a hospital not participating in the trial and was unaware of the treatment patients received. In case of discrepancies between the response classification of the reviewer and the treating clinician the CT-scans or MRI's were reviewed by a team of the author's but in doubt the response was always rounded down to the least favourable response category. Ten patients were not evaluated because initial measurements were done with other techniques than at follow up (5 patients), missing CT-scans 1 patient, early death 3 patients or the patient was lost to follow up. In the amifostine group 2 patients obtained a complete response and 17 a partial response out of 30 evaluable patients (63%; 53% of eligible patients); in the cisplatin only arm 34 patients were evaluable for response and 17 had a partial response (50%; 46% of eligible patients). In patients with locally advanced disease there were 23 evaluable patients in the amifostine arm (1 CR and 15 PR : response rate 70%) and 26 in the cisplatin only arm (partial response in 13 patients : 50%). The low number of complete responders can be attributed to the early time of response evaluation and the very strict criteria with which CT-scans and MRI's were judged. As all patients with locally advanced disease had radiotherapy starting two weeks after the last cisplatin administration and the treatment was left free for the other patient categories no information can be given on response duration. Analysis of survival will be a subject of a later report.

DISCUSSION

The incidence of head and neck cancer in the western world is still rising and most patients present at diagnosis with stage III or IV tumors. In locally advanced disease cisplatin containing neoadjuvant chemotherapy is frequently given although the real value of neoadjuvant chemotherapy still has to be proven (4,5). The combination of cisplatin with continuous infusion of fluorouracil is generally considered to be the standard regimen. However, side effects of this regimen (nausea, vomiting, lengthy hospital stays, phlebitis- or the need for central venous access) are a frequent cause of patient noncompliance. Regimens with shorter

hospital stays might be more attractive to this particular patient group.
We previously explored a regimen with weekly administration of cisplatin, aiming at a treatment with a high dose intensity, and the patient compliance in that study was good (10). Toxicity, mainly thrombocytopenia, ototoxicity and renal toxicity, precluded completion of the 6 planned cycles in 40% of the patients and the median cisplatin dose intensity achieved was 60 mg/m^2/week in stead of the planned 80 mg/m^2/week. Nevertheless 51% of the eligible patients and 60% of evaluable patients responded. Measures to reduce the toxicity of this schedule were thus considered worthwhile to explore.

Amifostine (WR-2721) is one of several cytoprotective drugs that entered clinical trials the last decade. WR-2721 is a prodrug; the active metabolite, the free thiol WR-1065 accumulates rapidly in normal cells but slowly in tumor cells (30). WR-1065 is a potent scavanger of oxygen-free radicals and binds to active platinum species thereby preventing platinum-DNA adduct formation (31,32). Because of the short half life of the compound the drug has to be administered directly before cisplatin and for the same reason cisplatin was administered in this study over one hour. As the phase 1 studies of amifostine suggested that patients with head and neck cancer are more prone to hypotension than patients with other tumor types (13) we started the study with a feasibility study to test the combination of amifostine and cisplatin in a weekly regimen. With an amifostine dose of 740 mg/m^2 the risk of serious hypotension was low, nevertheless, patient monitoring during amifostine administration is necessary. In the randomized study hypotension grade 3+4 occurred in 5 patients and always during the first or second cycle. Other side effects reported, palpitations, feelings of anxiety and drowsiness, were mainly related to the hypotensive episodes and were of minor importance. A typical side effect is sneezing. Hypocalcaemia is a rarely reported side effect; in our study calcium was not routinely determined after 24 or 48 hours so this side effect was not observed. In the randomized study the comparison of cisplatin toxicities was the main interest.

Protection of bone marrow toxicity by amifostine was limited to protection of thrombocytopenia although the difference did not reach the appropriate level of significance. However, in the subgroup of patients completing treatment there were less treatment delays due to hematologic toxicity in the combination arm. This observation is in agreement with observations in animal studies with carboplatin and fluorouracil where amifostine selectively protected the animals from developing thrombocytopenia (17). It is also in agreement with results obtained in randomized

trials in patients treated with various cytotoxic agents (alkylating agents, platinum compounds, mitomycin C) with or without amifostine (15, 18, 20, 21). We did not observe any protection of the other hematopoietic cell lineages.

For renal toxicity no difference was shown when analysed by serum creatinine. The incidence of renal toxicity, measured as such, was low in both arms of the study. Therefore, any additional effect of amifostine would have been difficult to show. This low incidence can be explained by the use of hypertonic saline and the vigorous hydration program in this study. Nevertheless, in the cisplatin only arm the creatinine clearance decreased during treatment from 97 ml/min to 81 ml/min while it remained stable in the combination arm. The difference was however not statistically significant.

With respect to the development of hypomagnesaemia (an indication of tubular damage in this case induced by cisplatin [33-36]), grade 2 or more hypomagnesaemia was significantly less in the combination arm. Although major symptoms such as epileptic seizures, ventricular tachycardias and cortical blindness fortunately occur only in a minority of patients, minor complaints such as muscle weakness, anorexia and nausea are frequently reported. Several randomized studies showed the importance but also the limited success of intravenous or oral magnesium supplementation (37,38), making the protective effect of amifostine on hypomagnesaemia of particular value. Also the occurrence of hyponatremia grade 3+4 was limited to the cisplatin only arm, indicating a protective effect of amifostine at the level of the renal tubule.

The third cisplatin toxicity on which amifostine showed a protective effect in a previous study is neurotoxicity (16). In our study measurement of the VPT was selected as VPT's are a more objective and sensitive indicator of neurotoxicity than the CTC criteria. As cisplatin neurotoxicity can become manifest up to 3 months after the last cisplatin dose (39,40) VPT's were separately analyzed in the patients with 3 month follow up. The limited number of patients with long term follow up hampers a complete analysis but the increase in VPT was less in the amifostine arm and VPT values stayed well below the values we obtained in previous studies with cisplatin only, indicating a protective effect of amifostine (40). The discrepancy between the left and right hand can be explained by the limited size of the patient group and make additional studies with more complete data worthwhile.

The fourth major cisplatin toxicity in which we were interested, and which is reported frequently in high dose schedules, is ototoxicity. In contrast to neurotoxicity, the risk of ototoxicity is more dependent on the cisplatin dose per

cycle than the cumulative dose. Also the cisplatin peak plasma levels, which are high with a 1-hour infusion, are of influence (41-43).
In this study a protective effect was not shown. A recently published study on protection of cisplatin induced ototoxicity in hamsters showed that amifostine had no effect while sodium thiosulfate was more active (44). This preclinical study fits well with our observation and further studies on prevention of ototoxicity are of utmost importance. However, nearly all patients in our study had at start of treatment already a considerable hearing loss. Studies in other tumor types are therefore necessary.

Amifostine thus showed a protective effect in this study on three organ systems but, nevertheless in the combination arm the cisplatin-dose intensity was not higher than in the cisplatin only arm. For this reason, and due to the lack of protection on ototoxicity, it was decided not to continue with the planned dose-escalation study.
Amifostine itself had manageable side effects. The drug compares in this way favorable with other cytoprotective agents. Diethyldithiocarbamate (DDTC), a heavy metal chelating agent, is an effective protector in animals studies. However, its side effects in patients limits its use. A study by Gandara et al. comparing DDTC with placebo in high dose cisplatin regimens in lung and ovarian cancer not only showed no protection on cisplatin toxicities but also more patients in the DDTC arm had to stop treatment because of side effects (45). Sodiumthiosulfate, successfully used as nephroprotector in ovarian cancer treated with high-dose cisplatin intraperitoneally, as well as probenecid (44,45) have the disadvantage that they only protect the kidneys while for sodiumthiosulphate inhibition of cisplatin activity is suggested (45). A recently published randomized phase II trial in advanced gastric cancer, treated with a weekly chemotherapy regimen containing cisplatin 40 mg/m^2 weekly plus or minus reduced gluthation (GSH), showed significantly less neurotoxicity and less treatment delays due to thrombocytopenia in the GSH arm (46). In that study no clinical ototoxicity was observed, probably related to the low cisplatin dose per cycle. Analysis of nephrotoxicity or mineral disorders were not reported.

The response rate in locally advanced disease of 70% in the combination arm and 50% in the cisplatin only arm is somewhat lower than reported for most combination regimens (2-5), however, the patients in our study all had extensive irresectable disease. The fear that amifostine would not only protect normal tissues but also tumor tissue is not confirmed as the response rate in the amifostine arm was even slightly higher than in the cisplatin only arm. Therefore we conclude that

the addition of amifostine to the weekly cisplatin regimen was of benefit. As amifostine also protects normal tissues from late radiation damage (11) further studies with amifostine and cisplatin or carboplatin plus radiotherapy in head and neck cancer are warranted.

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CHAPTER 5

WEEKLY HIGH-DOSE CISPLATIN IN MALIGNANT PLEURAL MESOTHELIOMA

A.S.Th. Planting, J.H.M. Schellens, S.H. Goey, M.E.L. van der Burg, M. de Boer-Dennert, G. Stoter, J. Verweij

Department of Medical Oncology, Rotterdam Cancer Institute/Dr. Daniel den Hoed Kliniek, Rotterdam, The Netherlands

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ABSTRACT

Background: Cisplatin at conventional doses has marginal activity in mesothelioma. A dose response relation for cisplatin has been suggested in other tumor types. In a phase I study on weekly cisplatin administration, 3 out of 5 patients with mesothelioma responded. Therefore a phase II study with weekly cisplatin was started with the recommended dose of 80 mg/m^2/week for six weeks.

Patients and methods: Fourteen patients with mesothelioma stage II, with measurable lesions, were treated with cisplatin at a dose of 80 mg/m^2 weekly for six weeks. Cisplatin was administered in NaCl 3% and combined with ondansetron as antiemetic.

Results: Five patients had a partial response (response rate 36%; 95% confidence interval 12-65%) lasting 2-8 months. Seven patients had stable disease. Ototoxicity was the most troublesome side effect: grade 2 in 3 and grade 3 in 2 patients.

Conclusions: cisplatin given at a higher dose intensity than in conventional schedules is active in mesothelioma. The response duration is however short possibly due to lack of effective maintenance therapy.

INTRODUCTION

The outlook for patients with pleural mesothelioma is still grim. Curative surgery is seldom possible and the results of radiotherapy are poor except for palliation of pain. The results of chemotherapy are far from encouraging: of those drugs tested in adequate numbers of patients only doxorubicin and cisplatin yield some activity with partial remission rates of 10-15% (1-3).

In vitro studies and studies in several tumor types in man have suggested a dose-response relationship for cisplatin (4,5). Attempts to increase cisplatin dose intensity were until recently hampered by its toxicity. Recently it was shown that administration of cisplatin in 3% hypertonic saline in part prevents nephrotoxicity (4) while 5 HT_3-receptor antagonists more effectively prevent nausea and vomiting than the older antiemetics. In a phase I/II study with a weekly cisplatin schedule, with the above mentioned supportive measures, we found that a dose of 80 mg/m^2 weekly for six weeks was feasible in chemonaive patients with solid tumors (6). In that study five patients with pleural mesothelioma were treated at different dose levels and 3 of them obtained a partial response. For this reason we started a study in mesothelioma at the recommended dose.

PATIENTS AND METHODS

All patients entered in the study had histological proof of pleural mesothelioma, Butchard stage IIa, a WHO performance status of 2 or better, measurable solid mass on CT-scan, WBC $>4.0 \times 10^9$/l and platelets $>100 \times 10^9$/l, serum creatinine <120 μmol/l and/or a creatinine clearance of >60 ml/min and serum bilirubin <25 μmol/l.

During treatment all patients had a weekly full history and physical examination as well as full blood counts, biochemical screen and creatinine clearance. Cisplatin was administered in 250 ml of 3% hypertonic saline at a dose of 80 mg/m^2 in 3 hours, repeated weekly for 6 weeks; prehydration consisted of 1 liter dextrose saline with 20 mmol KCl and 1 gram $MgSO_4$ in 3 hours, posthydration consisted of 2 liters dextrose-saline plus 40 mmol KCl and 2 gram $MgSO_4$ in 8 hours. As antiemetic therapy an 8 mg ondansetron i.v. bolus was given at the start of the cisplatin infusion. Dose reductions were not made. If at scheduled treatment WBC count was $<2.5 \times 10^9$/l and/or a platelet count was $<75 \times 10^9$/l the scheduled cisplatin dosage was postponed until recovery. In case of a delay >3 weeks or the occurrence of grade 2 nephro- or neurotoxicity the patient was taken off study. After 6 cisplatin administrations no further anti-tumour treatment was given until progression.

Toxicity was graded weekly; response to treatment was assessed 2 weeks after the last cisplatin dosage by CT-scan. The WHO response and toxicity criteria were used.

TREATMENT RESULTS

Fourteen patients entered the study. The patient characteristics are given in table 1. All patients were male. No patient received prior chemotherapy. All patients were evaluable for response and toxicity. Five patients obtained a partial response with response durations of 2, 4, 6, 6 and 8 months; seven patients had stable disease for a median duration of 12 weeks (range 8-24 weeks); in three of them pleural fluid decreased and a decrease in use of analgesics was reported in four patients. Two patients progressed. The 14 patients received a total of 79 doses of cisplatin. In 4 patients the fourth administration had to be delayed for two weeks and in one patient cycle 5 was delayed for three weeks due to thrombocytopenia. Two patients received 4 doses of cisplatin because of early progressive disease and in one patient the sixth dosage was cancelled because of slow recovery of platelets.

Six patients completed the treatment in 6 weeks. The mean cisplatin dose intensity achieved for the whole study period was 69 mg/m^2/week (range 53-80 mg/m^2/week).

Table 1.

Total no. of patients entered		14	
Median age in years (range)		63	(41-70)
Median performance status WHO (range)		1	(0-1)
Previous therapy:	- intrapleural IL-2	5	
	- bleomycin pleurodesis	2	
	- radiotherapy	1	
Median no. of cisplatin administrations		6	(4-6)
Mean cisplatin dose intensity reached (mg/m^2/wk) + range		69	(53-80)

Toxicity: anaemia grade 1 or 2 developed in all patients, a leucocytopenia grade 3 in 2 patients (median lowest nadir WBC 2.5 x 10 ^{9}/l; range 1.2-4.2) and thrombocytopenia grade 3 in 4 and grade 4 in 1 of the patients (median lowest nadir platelets 122 x 10^9/l; range 17-187). None of the patients required a platelet transfusion. Nausea and vomiting was effectively controlled by ondansetron only during the first 3-4 administrations. Nephrotoxicity grade 1 was observed in only 3 patients, ototoxicity grade 2 in 3 and grade 3 in 2, neurotoxicity grade 1 in 2 patients and grade 2 in one patient. The patient with neurotoxicity grade 2 also had a vitamin B12 deficiency. Asymptomatic hypomagnesaemia <0.70 mmol/l was observed in 6 patients.

DISCUSSION

Mesothelioma is a tumor resistant to any type of conventional chemotherapy. More effective supportive measures allow cisplatin treatment at higher dose intensities than before(4-6). In this study we reached a mean dose intensity of 69 mg/m^2/week, while per patient the dose intensity ranged from 53-80 mg/m^2/week.

Nephrotoxicity and gastrointestinal toxicity were no major problem while the incidence of neurotoxicity is comparable to cisplatin regimens with lower dose intensities. Ototoxicity is a matter of concern because clinical hearing loss usually is irreversible. Nevertheless we conclude that treatment with weekly cisplatin is worthwhile to be studied further in this disease because five patients obtained a partial response (response rate 36%; 95% confidence interval 12-65%) which compares favourably with other cisplatin studies (7,8). Responses unfortunately were of limited duration, possibly because of the lack of treatment continuation. Continuation of cisplatin however, was considered impossible in view of the expected cumulative toxicities. As a recently completed EORTC study showed that low dose continuous oral etoposide can also induce responses in this disease with acceptable toxicity (Postmus, personal communication), we decided to stop this study and start a phase II study with the combination of cisplatin at a slightly lower weekly dose in combination with oral etoposide.

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CHAPTER 6

PHASE I STUDY OF WEEKLY HIGH DOSE CISPLATIN COMBINED WITH LONG TERM ORAL ETOPOSIDE IN ADVANCED SOLID TUMORS

A.S.T. Planting, M.E.L. van der Burg, M. de Boer-Dennert, G. Stoter and J. Verweij

Department of Medical Oncology, Division of Experimental Chemotherapy, Rotterdam Cancer Institute/Daniel den Hoed Kliniek, Rotterdam, The Netherlands

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SUMMARY

Background: In a previous phase I study we showed that cisplatin single agent can be given weekly for six weeks at a dose of 80 mg/m^2/wk. Etoposide has suggested synergistic activity with cisplatin and the drug can orally be given continuously. We therefore performed a phase I study with weekly cisplatin combined with oral etoposide.

Patients and methods: Nineteen patients with metastases of a solid tumor were entered in the study. Cisplatin was administered in hypertonic saline (NaCl 3%). Etoposide was administered as 50 mg capsules.

Results: The starting dose was cisplatin weekly at a dose of 70 mg/m^2 for six weeks combined with daily oral etoposide at a dose of 50 mg. At the maximum tolerated dose of cisplatin 75 mg/m^2/wk and etoposide 50 mg/m^2 daily, leucocytopenia and thrombocytopenia were dose limiting toxicities and resulted in frequent treatment delays. Other toxicities were mild. Finally a dose of cisplatin 70 mg/m^2/wk weeks 1-2-3 and weeks 5-6-7 in combination with etoposide 50 mg orally day 1-15 and day 29-43 combined a high median cisplatin dose intensity of 52.5 mg/m^2/wk with a good patient tolerance.

Conclusion: It is feasible to administer frequently dosed cisplatin in combination with oral etoposide. Leucocytopenia and thrombocytopenia are dose limiting toxicities. The schedule will be explored further in phase II studies.

INTRODUCTION

Cisplatin containing combination chemotherapy regimens have been studied extensively in all sorts of tumors. In most regimens cisplatin is given in dosages of 80-100 mg/m^2 once every 3 or 4 weeks, because side effects preclude higher dose intensities. In vitro studies in human cancer cell lines and studies in ovarian- lung- and head and neck cancer have suggested that higher doses of cisplatin may overcome resistance and may lead to higher response rates (1-3). We have performed a phase I study with weekly administration of single agent cisplatin administered in hypertonic saline. A dose of 80 mg/m^2/week for six weeks in chemonaive patients was feasible (4).

Etoposide has a clear schedule dependent activity, and long term plasma etoposide levels >1 μg/ml are needed for activity. This can be easily achieved with the oral formulation of etoposide. At lower dosages, e.g. 50 mg/day, the bioavailabilty is almost 100% (5). Clinical efficacy of chronic oral etoposide in various tumor types has been reported (6).

A dose of 50 mg/m^2 daily for 21 days every 28 days is tolerable with granulocytopenia being the dose limiting toxicity. Based on our results of the phase I study with weekly cisplatin, we performed a phase I study with weekly cisplatin combined with oral etoposide. The primary aim was to develop a regimen with a high cisplatin dose intensity, with manageable toxicity, which could be used in neoadjuvant regimens in locally advanced solid tumours.

PATIENTS AND METHODS

Entry criteria

Patients in this study had histologic or cytologic proof of metastases of a solid tumour considered not amenable to surgery or radiotherapy, and with no better chemotherapeutic options. All patients had measurable or evaluable lesions on X-ray, ultrasound and/or CT-scan, age $\leq$ 75 years, a WHO performance score of $\leq$2, serum creatinine $\leq$ 120 μmol/l or creatinine clearance $\geq$70 ml/min, serum bilirubine $\leq$ 25 μmol/l and adequate bone marrow reserve. Patients with brain or leptomeningeal metastases were excluded. All patients gave oral informed consent.

Before start of the treatment all patients had a complete medical history and physical examination, ECG, determination and measurements of study parameters by chest X-ray, CT-scan and/or ultrasound. During treatment patients had twice weekly full hematologic blood counts and weekly determination of liver functions, renal function, Na, K, Ca, albumin and magnesium as well as a weekly creatinine clearance. Clinical neurologic examination was done at the start of treatment and 3-weekly thereafter; if indicated audiometry was done.

Response to treatment was assessed at week 4 and 2 weeks after the last cisplatin administration. The standard WHO criteria were used for evaluation of response and estimation of toxicity (7).

Treatment schedule

The treatment regimen consisted of prehydration with 1000 ml dextrose-saline + 20 mmol KCl + 1 gram $MgSO_4$ in 4 hours; cisplatin was dissolved in 250 ml 3% NaCl and administered over 3 hours followed by posthydration with 2 liters of dextrose- saline + 40 mmol KCl + 2 gram $MgSO_4$ in 8 hours. All patients received 8 mg of ondansetron as antiemetic at start of the cisplatin infusion. A total of 6 cisplatin administrations were planned for each patient. Etoposide was administered as 50 mg gelatin capsules once daily on an empty stomach and

dosages were if necessary adjusted to the 50 mg capsules such that the total etoposide dose administered during the planned treatment period deviated <5% from the calculated total dose. Patients with a response or stable disease were offered continuation of treatment with etoposide orally at a dose of 50 mg/m^2/day day 1-21 every 4 weeks until progression or for maximally 4 courses.

Dose reductions were not allowed. If at the day of planned cisplatin administration WBC were <2.5 x 10^9/l and/or platelets were <75 x 10^9/l treatment was postponed for one week, with a maximum delay of 3 weeks. In case of a delay >3 weeks or in case of neuro-or nephrotoxicity grade 2 patients were taken off study.

RESULTS

Nineteen patients were entered in the study. The patient characteristics are given in table 1. Three patients were pretreated with 5-fluorouracil, two patients with oral hexadecylphosphocholine and three patients with a combination of 5 fluorouracil and IL-2.

The dose levels and schedules studied were: *level 1* cisplatin 70 mg/m^2 weekly for 6 weeks combined with etoposide orally daily day 1-42 at a dose of 50 mg. Six patients were entered at this dose level; thrombocytopenia was the most frequently observed side effect although a grade 4 thrombocytopenia was observed in only 1 patient. In 4 out of the 6 patients a delay in planned treatment was necessary because of bonemarrow toxicity. The median cisplatin dose intensity reached at this dose level was 52.5 mg/m^2/wk.

In level 2 4 patients were treated with cisplatin 75 mg/m^2 weekly x 6 with etoposide 50 mg day 1-42. At this dose level two patients had a thrombocytopenia grade 4 and all patients had a grade 3 leucocytopenia causing a delay of the fourth planned cisplatin administration for two or three weeks in all 4 patients, reducing the cisplatin dose intensity to 56.2 mg/m^2/wk instead of the planned 75 mg/m^2. *At level 3* cisplatin was fixed at 75 mg/m^2 weekly and the dose of etoposide was escalated to 50 mg/m^2 daily day 1-42. At this dose level 3 patients were entered; one patient had a grade 4 granulocytopenia and 2 patients thrombocytopenia grade 4 necessitating a total delay of 8 weeks in the planned 18 administrations of cisplatin.

As in dose levels 1-3 bone marrow toxicity caused frequent treatment delays at week 4, we lowered for *dose level 4* the cisplatin dose to 70 mg/m^2 with introduction of a one-week interval after week 3 and limited the administration of etoposide to 15 days per 4 weeks.

Table 1. Patient characteristics phase I study

No of patients entered	19	
male: female	14:5	
median age (years; range)	55	(28-69)
Median PS WHO	1	(0-1)
Tumour types		
colon cancer	11	
carc unkn.primary	4	
melanoma	3	
lung adenocarcinoma	1	
Previous therapy		
surgery	16	
chemotherapy	5	
chemo/immunotherapy	3	
radiotherapy	2	
none	3	

With this schedule a cisplatin dose intensity was reached of 52.5 mg/m^2/wk comparable to dose levels 1 and 2 due to less treatment delays combined with a more acceptable haematologic toxicity as is shown in table 2. The non hematologic toxicities observed were: renal toxicity grade 1, neurotoxicity grade 1 and clinical hearing loss in 1 patient all at dose level 3. All patients had alopecia. Nausea and vomiting was frequently observed at all dose levels.

Response evaluation

A partial response was observed in 4 patients with colorectal cancer (three with liver metastases- duration 7, 10 and 10 months- and one with lymphnode metastases for a duration of 4 months), in the patient with a CUP in the mediastinum (8 months) and in the patient with non-small cell lung cancer (6 months). As responding patients continued treatment with oral etoposide the duration of response is estimated for the whole treatment period. Responses were observed at any dose level.

Table 2.

Dose level	No. of pts.	No. of CDDP admin.	CDDP admin. delayed	Total no. of weeks delay	Dose intensity CDDP reached ($mg/m^2/wk$)	Median nadir WHO (+ range)		
						WBC	PLAT	Hb
1	6	32	4	8	52.5 (52.5-70)	1.8 (1.6-3.7)	43 (13-187)	5.9 (4.3-6.2)
2	4	23	4	9	56.2 (50-56.2)	1.3 (1.2-1.6)	22 (9-89)	5.2 (4.3-6.1)
3	3	13	3	8	50 (41.6-50)	1.1 (0.4-2.3)	18 (5-35)	5.2 (5.1-5.3)
4	6	33	4	6	52.5 (46.7-60)	2.7 (1.4-5.7)	100 (57-200)	5.9 (4.8-8.4)

DISCUSSION

The combination of cisplatin and etoposide is frequently used although evidence of true synergism is still controversial in vitro (8). Weekly administration of conventional dosages of cisplatin results in a treatment with a high dose intensity combined with encouraging activity and good patient compliance (4). Based on the results of our previous weekly cisplatin schedule (4) we started with a cisplatin dosage of 70 mg/m^2 weekly combined with oral etoposide at an absolute dose of 50 mg. As expected from toxicity data of another phase I study with this combination (9) bone marrow toxicity was also the dose limiting toxicity in this study and leuco- and thrombocytopenia were the main cause of treatment delays. As treatment delays jeopardize the concept of cisplatin dose intensity we selected dose level 4, with a median cisplatin dose intensity of 52.5 mg/m^2/wk and acceptable toxicity as optimal for further studies. As responses were observed in colorectal cancer, as well as in non-small cell lung cancer and CUP phase II studies were started in these tumour types.

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CHAPTER 7

PHASE II STUDY OF A SHORT COURSE OF WEEKLY HIGH-DOSE CISPLATIN COMBINED WITH LONG TERM ORAL ETOPOSIDE IN PLEURAL MESOTHELIOMA

A.S.T. Planting[1], M.E.L. van der Burg[1], S.H. Goey[1], J.H.M. Schellens[1], M.J. van den Bent[2], M. de Boer-Dennert[1], G. Stoter[1] and J. Verweij[1]

[1]Department of Medical Oncology (Division of Experimental Chemotherapy and Pharmacology) and [2]Department of Neurology, Rotterdam Cancer Institute/Daniel den Hoed Kliniek, Rotterdam, The Netherlands

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SUMMARY

Background: In a previous phase II study with a dose-intensive weekly cisplatin schedule for six cycles we observed a partial response in 5 out of 14 patients with pleural mesothelioma. However, response duration was short (median 6 months). As oral etoposide may theoretically be synergistic to cisplatin we performed a phase II study with the combination of both drugs.

Patients and methods: Twenty-five chemonaive patients with pleural mesothelioma were treated with cisplatin 70 mg/m^2 days 1-8-15 and days 29-36-43 in combination with oral etoposide 50 mg days 1-15 and days 29-43. Patients with stable disease or better continued treatment with oral etoposide 50 mg/m^2/day days 1-21 every 28 days.

Results: All patients were evaluable for response and toxicity. A complete response was observed in one patient and a partial response in 5 patients (RR% 24%; 95% CI:10-45%) for a median duration of 30 weeks. Twelve patients had stable disease. The response status did never improve during maintenance treatment with oral etoposide.

Most patients tolerated the regimen very well. Toxicity was mainly haematologic with leucocytopenia causing treatment delays in 8 patients. Ototoxicity grade 1 or 2 was observed in 8 patients, neurotoxicity grade 1 in 9 patients and nephrotoxicity grade 1 in 1 patient.

Conclusion: Frequently administered cisplatin in combination with oral etoposide has a moderate but definite activity in pleural mesothelioma.

INTRODUCTION

Malignant pleural mesothelioma is frequently diagnosed in geographic regions with shipyards and is predominant in middle aged men. The prognosis for patients with this type of cancer remains poor. Curative surgery is possible only in a minority of patients (1) and radiotherapy only has a role for treatment of pain. This lack of effective treatment forms a challenge to explore new ways in this disease.

Up to now the value of chemotherapy is very limited: response rates are low and the impact on survival is difficult to interpret because occasionally patients can survive for a long period of time even without treatment (2). Doxorubicin and cisplatin are considered active drugs even though they yield a response rate of only $\pm$ 15% and responses are of short duration (3-5). Because of this, in most patients treatment is limited to symptomatic care or pleurodesis. In a previous phase II study with weekly administration of cisplatin for six cycles we observed a response

in 5 out of 14 patients with pleural mesothelioma. However, response duration was short, median 6 months (range 2-8 months). This could have been related to the lack of maintenance chemotherapy in that study (6).

Etoposide is frequently combined with cisplatin for the treatment of many tumor types, although true synergism has not been proven yet. In an EORTC phase II study with i.v. etoposide a partial response was observed in only 2 out of 43 evaluable patients (J. van Meerbeeck, personal communication). Recent studies have shown that long term inhibition of the enzyme topoisomerase-II can be achieved by chronic oral administration of etoposide. At low dosages, up to 100 mg, the bioavailability is almost 100% (7). In a phase I study we have shown that frequent administration of high-dose cisplatin combined with oral etoposide is feasible (8). We performed a phase II study with this regimen in patients with pleural mesothelioma.

PATIENTS AND METHODS

Patients were required to have measurable malignant mesothelioma of the pleura, modified Butchard stage 2 a (tumor involving chest wall and/ or mediastinum and/or pericardium) or stage 2 b (tumor involving contralateral pleura), histology being confirmed as mesothelioma by the Dutch mesothelioma panel of pathologists. Eligibility criteria further included a WHO performance status of 2 or better, white blood cell count $>3.0 \times 10^9$/l, platelet count $>100 \times 10^9$/l, creatinine clearance >60 ml/min and a serum bilirubin <25 μmol/l. All patients had full medical history and physical examination before start of treatment, an ECG, a chest X-ray and CT-of the chest and abdomen with and without i.v. contrast and if appropriate clinical measurement of pathological lymphnodes or skin metastases.

All patients had a neurologic examination including estimation of vibration perception threshold before the start, after completion of cisplatin treatment and 3 months thereafter.

During treatment patients had weekly physical examination and assessment of toxicity, weekly full blood counts and estimation of serum electrolytes, -calcium, magnesium, -creatinine and liver function tests as well as creatinine clearance.
Response to treatment was assessed two weeks after the last cisplatin administration. The standard WHO criteria were used for evaluation of response and toxicity (9).

Treatment schedule

Cisplatin was administered at a dose of 70 mg/m^2 days 1-8-15 and days 29-36-43; oral etoposide was administered at a dose of 50 mg daily days 1-15 and days 29-43. During the cisplatin administration patients were hospitalized for 24 hours. The treatment regimen consisted of prehydration with 1000 ml dextrose-saline + 20 mmol KCl + 1 gram $MgSO_4$ in 4 hours; cisplatin powder was dissolved in 250 ml 3% NaCl and administered over 3 hours followed by posthydration with 2 liters of dextrose-saline + 40 mmol KCl + 2 gram $MgSO_4$ in 8 hours. As antiemetic 8 mg ondansetron was given as a slow i.v. bolus directly before start of the cisplatin administration and was repeated if necessary after 12 hours. In case of delayed nausea and vomiting metoclopramide 20 mg t.i.d. orally or per suppository was given.

Dose reductions were not allowed. If at the day of planned cisplatin administration WBC were $<2.5 \times 10^9$/l and/ or platelets were $<75 \times 10^9$/l treatment was postponed until recovery above these values with a maximum delay of two weeks. In case of a delay >2 weeks or in case of neuro- or nephrotoxicity grade 2 patients were to be taken off study.

Patients responding to treatment or with stable disease at response evaluation continued treatment with oral etoposide at a dose of 50 mg/m^2 days 1-21 every 28 days for a maximum of 4 cycles.

Etoposide was administered as 50 mg gelatin capsules and the dosage was adjusted such that the administered dose deviated $<5\%$ from the total planned dose of etoposide. During the treatment with oral etoposide patients had full blood counts every 2 weeks and serum electrolytes, liver- and renal function tests were taken every 4 weeks. Tumor response was evaluated every 8 weeks.

RESULTS

Twenty-five consecutive patients who met the eligibility criteria were entered into the study. The first patient was entered october 1991, the last patient may 1994. The patient characteristics are given in table 1.

All patients were chemonaive; 3 patients were pretreated with TNF-α intrapleurally and 4 patients were previously treated with intrapleural IL-2. One patient treated with IL-2 i.p. had a partial response lasting 6 months, all other patients had progressive disease on intrapleural therapy. All patients were evaluable for response and toxicity. One patient had a complete disappearance of pleural tumormass and pleural fluid, this complete response is ongoing for 52^+ weeks.

Table 1. Patient characteristics

No. of patients entered	25	
male : female	23 : 2	
median age (range)	56	(42-69)
median PS (range)	1	(0-1)
stage Butchard IIa	10	
Butchard IIb	15	
Previous treatment:		
TNF intrapleural	3	
IL-2 intrapleural	4	

Five patients had a partial response for a median duration of 30 weeks (range 20-90 weeks); 12 patients had stable disease with a median duration of 28 weeks (range 14-52 weeks). Seven patients had progressive disease. In all responding patients and in 6 of the 12 SD patients a decreased need for analgesics was noted. The overall response rate is 24% (95% CI: 10-45%). The median survival of the responding patients was 16 months (range 6-30^{+} months) compared to 8 months (range 4-12 months) in patients with stable disease and 5 months (range 3-9 months) in patients with progressive disease.

Side effects (table 2) observed were mainly haematologic: all patients developed anaemia, grade 3 in 2 patients and grade 4 in 1. The latter patient had a recurrent haematothorax explaining this excessive transfusion need. In total 17 patients required packed cell transfusions for a total of 87 units. Leucocytopenia grade 3 and 4 was observed in 6 patients (24%) and 1 patient had a grade 4 thrombocytopenia (4%).

There were no instances of neutropenic fever and only 1 patient required platelet transfusion. The non-haematologic toxicities observed were: alopecia in all patients, clinical neurotoxicity grade 1 in 9 patients (36%) usually observed at the end of the treatment period, and a reversible grade 1 nephrotoxicity in 1 (4%). Ototoxicity grade 1 (CTC grading: changes in audiogram) was observed in 4 patients but as most patients were industrial- or shipyard workers most patients had

an abnormal pretreatment audiogram. Four patients complained of tinnitus but none had clinical hearing loss.

The median weight loss during treatment was 4 kg (range 11 kg weight loss to 4 kg weight gain).

Most patients tolerated treatment remarkably well and 17 completed treatment without any delay. In these patients the planned cisplatin dose intensity of 60 mg/m^2/week could be reached. In five patients a delay of one week and in 3 a delay of 2 weeks was necessary because of leucocytopenia, which invariably developed in cycle 4 or 5. In these patients dose intensities were reached of 52,5 mg/m^2/week and 46.6 mg/m^2/week respectively. Eighteen patients continued oral etoposide after response evaluation for a median of 4 cycles per patient (range 2-4). Seven patients were taken off treatment before the fourth etoposide cycle because of disease progression in 6 and a refusal in one. Of note, the response status after the 6 cisplatin cycles never improved further during the period of maintenance treatment with oral etoposide.

Table 2. Worst toxicity per patient

	0	1	2	3	4
Haemoglobin	0	7	15	2	1
Leucocytes	1	4	13	6	1
Platelets	13	8	3	0	1
Nausea/ vomiting	0	12	5	7	1
Neurotoxicity	16	9	0	0	0
Ototoxicity	17	4	4	0	0
Nephrotoxicity	24	1	0	0	0

DISCUSSION

In the industrial area of Rotterdam with it's shipyards, the incidence of pleural mesothelioma is high : 6.2 per 100.000 men per year (10). Because of the lack of effective treatments a wait and see policy is considered standard in this disease and usually patients are only referred for treatment in case of symptomatic disease. In a previous study we have shown that weekly administration of cisplatin induced an objective response in 5 out of 14 patients. In the present study we tried to confirm these results with a slightly less dose-intense cisplatin regimen combined with oral etoposide with the aim to make the responses more durable. With objective

responses in 6 patients, including 1 complete response, our present results are comparable with our previous result with weekly cisplatin single agent but present responses seem more durable. Obviously the latter can only be proven in a randomized study. Nevertheless one could speculate that also in mesothelioma some synergism may exist between cisplatin and etoposide, particularly because a recent Finnish study (11) indicated that single agent oral etoposide is not active. This can explain why no further improvement in response status was observed during the continuous treatment with oral etoposide in our study. Our results and those of a recent study on a dose -intensified doxorubicin/ifosfamide schedule with a 32% response rate (12) suggest that with more dose intensive schedules mesothelioma is not necessarily truly chemotherapy-resistant.

Further studies in mesothelioma of dose intensive chemotherapy schedules appear justifiable.

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CHAPTER 8

A PHASE II STUDY OF WEEKLY HIGH-DOSE CISPLATIN COMBINED WITH ORAL ETOPOSIDE IN ADVANCED NON-SMALL CELL LUNG CANCER

A.S.T. Planting[1], G.S. Kho[2], M.E.L. van der Burg[1], S.H. Goey[1], J.H.M. Schellens[1], M.J. van den Bent[3], A. van der Gaast [1], M. de Boer-Dennert[1], G. Stoter[1] and J. Verweij[1]

[1]Department of Medical Oncology, [3]Department of Neurology, Rotterdam Cancer Institute/University Hospital Rotterdam, Groene Hilledijk 301, 3075 EA Rotterdam

[2]Department of Pulmonology, University Hospital Rotterdam, dr. Molewaterplein 40, 3015 GD Rotterdam

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SUMMARY

Background: As a dose response relationship is suggested for cisplatin it appears attractive to explore high dose-intensity regimens in non-small cell lung cancer. In a phase 1 study of weekly administered cisplatin combined with oral etoposide we were able to achieve a cisplatin dose intensity of 52.5-60 mg/m^2/week in most patients. We subsequently explored this regimen in advanced non-small cell lung cancer.

Patients and methods: Patients were treated with cisplatin 70 mg/m^2 days 1-8-15 and 29-36-43 combined with oral etoposide 50 mg on days 1-15 and days 29-43. Patients with stable disease or better continued treatment with oral etoposide 50 mg/m^2/day days 1-21 every 28 days for a maximum of 4 cycles.

Results: Twenty-two stage III and 31 stage IV patients entered the study. The median number of cisplatin administrations was 6 per patient; 17 patients reached the planned cisplatin dose intensity of 60 mg/m^2/week, 11 patients achieved 52.5 mg/m^2/week and 7 patients 47 mg/m^2/week.

Eleven out of 21 stage III patients had a partial response (response rate 51% 95%-C.I. 36-81%) and 9 out of 28 patients with stage IV disease (32%; 95%-CI 15-49%).

Toxicity was mainly haematologic with granulocytopenia being the most frequent cause of treatment delays. Nephrotoxicity grade 1 was observed in 7 patients. Two patients had clinical hearing loss.

Conclusion: With this schedule a high median cisplatin dose intensity of 52.5-60 mg/m^2/week was reached. The response rate of 51% in stage III disease makes this schedule attractive to explore further, however, this schedule is not recommended for routine use in stage IV disease.

INTRODUCTION

The prognosis for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) remains poor in spite of the continuous exploration of new cytotoxic drugs and the introduction of combined modality regimens. The impact of cisplatin containing chemotherapy on survival is modest [1-3]. The meta-analysis of Donnadieu et al. [4] showed that the response rate obtained with combinations of cisplatin with either podophyllotoxins, vinca alkaloids or with ifosfamide and mitomycin C averages 34% in stage III disease but only 22% in metastatic disease.

The combination of cisplatin and etoposide is widely used in NSCLC. Both drugs have only limited single agent activity with response rates varying from

8-30% [5-15]. The combination is suggested to be synergistic in cell lines as well as clinically [16,17]. Activity and side effects of commonly applied schedules of this combination have been extensively described [18].

In several tumor types a relation has been suggested between cisplatin dose intensity and response rate or response duration [19-22]. However, prospective randomized studies addressing the issue of cisplatin dose intensity in NSCLC have not been conclusive [19,23,24]. The highest cisplatin dose intensity reached in these studies was 41 mg/m^2/week [24].

In a phase I study exploring weekly administration of cisplatin combined with oral etoposide, we were able to reach a higher median cisplatin dose intensity of 52.5 mg/m^2/week [25]. In this schedule we made use of oral etoposide since it's long term administration is feasible and activity has been shown in various tumors including NSCLC [26,27]. The results of the phase II study with this dose intense regimen in advanced NSCLC are reported here.

PATIENTS AND METHODS

Patients with histologically proven NSCLC with locally advanced disease stage IIIa or IIIb [28] or with distant metastases were entered in this study. Eligibility criteria consisted further of: measurable lesion, a WHO performance status of 2 or better; white blood cell count $>3.0 \times 10^9$/l, platelet count $>100 \times 10^9$/l, creatinine clearance >60 ml/min and serum bilirubin <25 μmol/l. All patients had a full medical history and physical examination before start of the treatment, an ECG, a chest X-ray and CT-of the chest and upper abdomen with and without i.v. contrast and, if appropriate, clinical measurement of pathological lymph-nodes or skin metastases.

All patients had neurological examination before the start and after completion of the cisplatin treatment and every 3 months thereafter.

During treatment patients had a weekly physical examination, assessment of toxicity, full blood counts and determination of serum electrolytes, calcium, magnesium, creatinine and liver function tests and creatinine clearance.

Response to treatment was assessed two weeks after the last cisplatin administration. Standard WHO criteria were used for evaluation of response and toxicity [29] .

TREATMENT SCHEDULE

Cisplatin was administered at a dose of 70 mg/m^2 days 1-8-15 and days 29-36-

43. Oral etoposide was administered at a dose of 50 mg daily on days 1-15 and days 29-43. During the cisplatin administration patients were hospitalized for 24 hours. The treatment regimen consisted of prehydration with 1000 ml dextrose-saline + 20 mmol KCl + 1 gram $MgSO_4$ in 4 hours; cisplatin powder was dissolved in 250 ml 3% NaCl and administered over 3 hours followed by posthydration with 2 liters of dextrose-saline + 40 mmol KCl + 2 gram $MgSO_4$ in 8 hours. As antiemetic regimen 8 mg ondansetron + 10 mg dexamethasone were given as a slow i.v. bolus directly before starting the cisplatin administration and was repeated if necessary after 12 hours. For delayed nausea and vomiting metoclopramide 20 mg t.i.d. was given orally or per suppository.

Dose reductions were not allowed. If at the day of planned cisplatin administration WBC were $<2.5 \times 10^9$/l and/ or platelets were $<75 \times 10^9$/l, treatment was postponed until recovery above these values with a maximum delay of two weeks. In case of a delay >2 weeks or in case of neuro- or nephrotoxicity grade 2, patients had to be taken off study.

Patients responding to treatment, or with stable disease at first response evaluation, continued treatment with oral etoposide at a dose of 50 mg/m^2 days 1-21 every 28 days for a maximum of 4 cycles. Etoposide was administered as 50 mg soft gelatin capsules and the dosage was adjusted such that the administered dose per treatment cycle deviated <5% from the planned dose. During the treatment with oral etoposide patients had full blood counts every 2 weeks and determination of serum electrolytes, liver- and renal function tests every 4 weeks. Tumor response was evaluated every 8 weeks.

RESULTS

Fifty-four patients were registered in the study. One patient was considered ineligible because of small cell histology. Three patients were considered not evaluable for response: one patient never started treatment, one patient had a protocol violation (too low cisplatin dose) and one patient had concomitant radiotherapy on the indicator lesion. Fifteen patients did not complete the planned treatment : 6 patients because of progressive disease, 2 patients because of treatment delay >2 weeks because of leucocytopenia, 2 patients refused further treatment (one after the first and one after the 4th cisplatin administration), one patient died from a myocardial infarction, one patient was taken off study because of tinnitus after the second cisplatin cycle and one patient because of neutropenic fever, one because of erysipelas and one because of reversible cortical blindness after the

fifth cisplatin cycle. These patients are considered as treatment failures in the response analysis. Fifty patients are thus evaluated for response and 47 for toxicity analysis. The patient demographics are shown in Table 1.

Table 1. Patient characteristics

No. of eligible patients		53	
male : female		40 : 13	
median age, years (range)		56	(32-70)
performance status (ECOG)		1	(0-2)
Stage	IIIa	5	
	IIIb	17	
	IV	31	
previous therapy			
	radiotherapy	10	
	surgery	3	
	radiother + surgery	3	
histology			
	squamous cell carcinoma	23	
	adenocarcinoma	22	
	large cell undiff carcinoma	8	

In total the 53 eligible patients received 264 administrations of cisplatin, with a median of 6 per patient (range 0-6). Reasons not to complete the 6 planned cisplatin administrations are shown in table 2. A treatment delay of one week was necessary in 14 patients and of 2 weeks in 7 patients because of slow recovery of leucocytes and/or platelets. With the exception of the patient with neutropenic fever leuco- and thrombocytopenia were not observed before the third cisplatin administration. Of the 35 patients who completed the planned treatment 17 reached the planned cisplatin dose intensity of 60 mg/m^2/week, eleven patients with a one week- delay reached a dose intensity of 52.5 mg/m^2/week and seven patients with 2 weeks delay 47 mg/m^2/week.

Thirty-one patients continued oral etoposide after the first response evaluation : two patients for one course, 10 patients 2 courses, 4 patients 3 and 15 the full 4 courses. In 14 patients etoposide cycles were delayed once or twice for 1 week because of leucocytopenia.

Table 2. Reasons for patients not to complete the planned treatment

No. of CDDP administrations:		reason off study
0	1 pt	never started
1	3 pts	refusal 1, irradiation on indicator lesion 1, early PD 1
2	2 pts	neutropenic fever 1, ototoxicity 1
3	6 pts	PD 3, cardiac death 1, ototoxicity 1, > 2 wk delay 1
4	1 pt	refusal
5	5 pts	PD 2, cerebral tox. 1, delay > 2 wk 1, erysipelas 1
6	35 pt	

Response

Twenty-one out of 22 patients with stage III disease were evaluated for response; one patient was not evaluable because of concomitant radiotherapy. All 5 patients with a stage IIIa tumor responded and 2 patients underwent a pneumonectomy. Both patients had viable tumor in the surgical specimen. One patient died of ARDS postoperatively, the other patient is alive without disease at 220^{+} weeks. Two patients had radiotherapy but relapsed at 21 and 36 weeks respectively, one patient refused further treatment. Of the 17 stage IIIb patients 13 completed treatment and 6 had a partial response. Including the 4 patients who refused or did not complete treatment due to toxicity as treatment failures, the over-all response rate in stage III disease was 52% (95% confidence interval: 32-77%). Four stage IIIb patients did not continue oral etoposide because of radiotherapy. The other pa-

tients continued with oral etoposide. The over-all median survival time for all stage III patients was 48 weeks (range 7-220^{+} weeks).

Of the 31 patients with stage IV disease 29 were evaluated for response. Two patients were not evaluable: one patient never started treatment and one patient received a wrong cisplatin dose. Nine patients had a partial response (31%; 95% confidence interval: 15-49%) with a median duration of 28 weeks (range 16-44 weeks). Twelve patients had stable disease with a median duration of 18 weeks (range 12-32 weeks). The median overall survival time in stage IV patients was 45 weeks (range 26-106 weeks). Patients with primary progressive disease survived median 16 weeks only (range 3-45 weeks). The chance of achieving a response was equal for the histologic subtypes : of 21 evaluable patients with squamous cell carcinoma 12 had a response versus 6/18 in adenocarcinoma and 2/7 in large cell undifferentiated carcinoma ($p=0.29$; Fishers exact test).

Toxicity

The toxicity data are summarized in table 3. The worst toxicity per patient observed over the whole treatment period is shown according to the WHO grading. For ototoxicity the CTC- grading was used [31]. Anaemia was universal with 38 patients developing >grade 1 anaemia. Thirty patients required packed red cell transfusions for a total of 127 units. Grade 3+4 leucocytopenia was observed in 17 patients. Leucocytopenia was the main cause of treatment delays, mainly occurring on day 29 when the fourth cisplatin administration was planned. Only one patient developed a neutropenic fever. There were no toxic deaths. Thrombocytopenia grade 3 was observed in 6 patients and grade 4 in 2. One patient required a platelet transfusion once. No haemorragic complications were observed.

All patients developed alopecia; nausea and vomiting was seldom observed during the first 3 weeks of the treatment but occurred frequent during continuation of treatment, and was also frequent reported during the oral etoposide maintenance phase. Nephrotoxicity was limited to grade 1 in 7 patients. With the exception of the patient with reversible cortical blindness neurotoxicity was limited to grade 1 in 13 patients.

Two patients reported clinical hearing loss (CTC-grade 3) and 12 patients tinnitus (ototoxicity grade 2). Hypomagnesaemia <0.55 mmol/l was observed in 10 patients.

One patient developed seizures after the sixth cisplatin administration with a magnesium level of 0.23 mmol/l.

Table 3. Toxicity (WHO-grading; worst toxicity per patient)

WHO GRADE	0	1	2	3	4
Anaemia	0	9	31	7	0
WBC	4	12	14	13	4
Platelets	13	19	7	6	2
Nephrotoxicity	40	7	0	0	0
Neurotoxicity	33	13	0	0	1*
Ototoxicity (CTC)	25	8	12	2	0

* : patient with reversible cortical blindness

DISCUSSION

Numerous phase II and III studies have been performed in NSCLC over the last two decades and still the discussion on " the best" regimen is ongoing. The combination of cisplatin and etoposide is frequently used and the response rate averages 30% [18]. Studies analyzing the results in locally advanced disease separately report higher response rates of even up to 69% in this subset of patients [31].

Retrospective analyses in several tumor types have suggested that dose intensity of chemotherapy may be important [32,33]. However, prospective randomized studies addressing cisplatin dose intensity in non-small cell lung cancer are inconclusive. The first study was reported in 1981 by Gralla et al. In this study cisplatin 120 mg/m^2 was compared to cisplatin 60 mg/m^2, given every 4 weeks in combination with vindesine. The response rate was equal in both arms [43%] but the response duration was superior in the high dose arm as compared to the low dose arm (12 versus 5.5 months) and the median survival of responders in the high dose arm was more than double the survival of responders in the low dose arm [19]. Klastersky et al. compared cisplatin 120 mg/m^2 or cisplatin 60 mg/m^2 in combination with etoposide every 3-4 weeks and observed no difference in response rate or survival between both treatment arms [23]. In the 3-arm study of

Gandara et al. cisplatin single agent 50 mg/m^2 day 1+8 every 4 weeks was compared with cisplatin single agent high dose 100 mg/m^2 day 1+8 versus cisplatin 100 mg/m^2 day 1+8 plus mitomycin C 8 mg/m^2 day 1 every 4 weeks. Only stage IV patients were included in this study. A response was observed in 12% in the standard dose arm and 14% in the high dose single agent cisplatin arm. In the high dose arm with mitomycin C the response rate was 27%. Complete responders were only observed in the high dose arms. Survival was, however, not different between the treatment arms. The highest cisplatin dose intensity reached in these studies was 41 mg/m^2/week [24].

In a phase 1 study we have shown that with weekly administration of cisplatin a higher cisplatin dose intensity can be reached [25]. Weekly administration of chemotherapy also has the theoretical advantage that regrowth of sublethally damaged tumor cells will be hindered more effectively than in schedules with longer intervals. Studies performed in the seventies with weekly administration of cisplatin showed activity in NSCLC and head and neck cancer but were not explored further because of toxicity [9,34,35]. With improved supportive measures weekly administration of cisplatin has become feasible and our present study again confirms this: most patients reached a cisplatin dose intensity of 52.5-60 mg/m^2/-week and we observed a response in 32% of patients with stage IV and in 52% of the patients with stage III disease. This response rate is comparable to that of other "high ranking" regimens [31,36].

Also compared to other studies using frequent dosing of cisplatin in NSCLC the dose intensity we achieved is high. Higano et al. administered weekly cisplatin at a dose of 50 mg/m^2/week in combination with mitomycin C, vinblastine and fluorouracil and reported a response in 23% of their patients but they only included patients with distant metastases. The median dose intensity of cisplatin reached in their study was 40-44 mg/m^2/week [37]. O'Dwyer et al. reported a phase II study of weekly cisplatin at a dose of 30 mg/m^2 combined with weekly 24-hour infusions of fluorouracil and vinblastine. Forty-four percent of their patients responded, the median duration of response was, however, only 4 months [38].

In general the toxicity of our regimen was acceptable. Only one patient had neutropenic fever; there were no toxic deaths. Granulocytopenia and to a lesser degree thrombocytopenia were the most frequent causes of treatment delay partly jeopardizing the dose intensity concept. Only 7 patients developed renal toxicity grade 1; this low number may be related to the administration of cisplatin in hypertonic saline and the vigorous hydration program. In Higano's study, also

applying cisplatin administration in hypertonic saline, renal toxicity grade 2 and higher was observed in only 6 out of 77 patients [37]. These results contrast with those of Vogl [9] et al. who reported renal toxicity in 40% of 30 patients treated with cisplatin 75 mg/m^2 days 1-8-15 and every 3 weeks thereafter with cisplatin administered in dextrose-saline.

Thirteen patients in our study developed neurotoxicity grade 1; no patient developed grade 2 despite the fact that most patients received a cumulative cisplatin dose of 420 mg/m^2. All these patients were followed for 6 months if possible as is known that neurotoxic signs may even worsen after cessation of treatment [39]. Cortical blindness is a very seldom reported manifestation of cisplatin neurotoxicity; a relation with hypomagnesaemia is suggested [40]. Hypomagnesaemia can lead to focal or generalized seizures, as we observed in another patient. Our patient, however, had on the day of visual loss a normal serum magnesium level; he recovered completely. Ototoxicity grade 2+ 3 was observed in 28% of the patients which is common in high-dose cisplatin regimens. Kim et al. administering cisplatin 180 mg/m^2 every 2 weeks in combination with sodium thiosulfate, therewith achieving a median cisplatin dose intensity of 79 mg/m^2/week, reported hearing loss in 9 out of 19 patients [41]. Gandara reported 17% ototoxicity in the high dose cisplatin arm of his study [24]. As clinical hearing loss is irreversible it now replaces the classical cisplatin toxicities as nephro- and gastrointestinal toxicity, as dose limiting. The response rate of 52% in stage III disease warrants in our opinion further exploration in locally advanced NSCLC and combination with radiotherapy might be attractive provided that toxicity can be limited. Recently the RTOG reported a study with cisplatin 50 mg/m^2 day 1+8 combined with oral etoposide 75 or 100 mg/day day 1-14 with concomitant hyperfractionated radiotherapy. The response rate of 70% was encouraging but the toxicity, especially hematologic toxicity and oesophagitis, was high [42]. Combination with chemoprotective agents (such as WR-2721 or sodium thiosulphate) could be of interest for these high dose schedules. If they indeed have a protective effect on toxicity, randomized studies comparing high-dose intense regimens with standard dose regimens in larger patient populations or combination with radiotherapy would become possible. In stage IV disease, however, to our opinion equal treatment results can be achieved with less intense regimens.

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CHAPTER 9

RELATIONSHIP BETWEEN THE EXPOSURE TO CISPLATIN, DNA-ADDUCT FORMATION IN LEUCOCYTES AND TUMOUR RESPONSE IN PATIENTS WITH SOLID TUMOURS

J.H.M. Schellens, J. Ma, A.S.Th. Planting, M.E.L. van der Burg, E. van Meerten, M. de Boer-Dennert, P.I.M. Schmitz[1], G. Stoter, J. Verweij

Dept. Medical Oncology and Dept. of Biostatistics[1], Rotterdam Cancer Institute (Daniel den Hoed Kliniek), P.O. Box 5201, 3008 AE Rotterdam, The Netherlands

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SUMMARY

The study was designed to investigate possible relationships between tumour response and exposure to cisplatin (area under the curve of unbound cisplatin in plasma: AUC) and DNA-adduct formation in leucocytes (WBC) in patients with solid tumours. Patients were treated with 6 weekly courses of cisplatin at a dose of 70 or 80 mg/m^2. The AUC was determined during the first course and DNA-adduct levels in WBC during all courses at base-line, 1 hour (Amax) and 15 hours after a 3-hour infusion of cisplatin. The area under the DNA-adduct-time curve (AUA) was calculated. The tumour response was determined after 6 courses. Forty-five evaluable patients received 237 courses of cisplatin. Sixteen patients with head and neck cancer received a dose of 80 mg/m^2 and 29 with various other tumour types 70 mg/m^2 plus daily 50 mg oral etoposide. There were 20 responders (partial and complete) and 25 nonresponders (stable and progressive disease). The AUC was highly variable (mean $\pm$ SD = 2.48 $\pm$ 0.51 μg.hr/ml; range 1.10 - 3.82) and was closely correlated with the AUA ($R=0.78$, $p<0.0001$) and Amax ($R=0.73$, $p<0.0001$). The AUC, AUA and Amax were significantly higher in responders than in nonresponders in the total population ($p<0.0001$) and in the 2 subgroups treated at 70 or 80 mg/m^2. In logistic regression analysis AUC, AUA and Amax were important predictors of response.
The magnitude of exposure to cisplatin is, through DNA-adduct formation the major determinant of the response rate in this population. Hence, individualized dosing of cisplatin using AUC or DNA-adducts should lead to increased response rates.

INTRODUCTION

Cisplatin is considered the most active drug in testicular and ovarian cancer (Loehrer, 1984, Motzer, et al., 1988, Ozols, et al, 1988, Kaye, et al, 1992, Bajorin, et al, 1993, Levin, et al, 1993, Stoter, et al, 1995) and it has considerable activity against several other solid tumours (Alberts, et al, 1991, Glover, et al, 1987, Stoter, et al, 1987, Hansen, 1992, Slotman, et al, 1992, Hainsworth, 1993, Krarup, 1991, Planting, et al, 1993a, Paccagnella, et al, 1994, Roth, et al, 1994, Planting, et al, 1994). The clinical application of cisplatin is limited however by the existence or development of resistance and the induction of severe side effects (Loehrer, 1984, Eastman, 1988, Daugaard, 1989, Ozols, 1989, Cavaletti, et al, 1992, Siegal, 1990).

It is common practice to dose cisplatin per m^2 body surface area. However, this strategy results in wide interpatient differences in the magnitude of exposure to cisplatin, i.e. the area under the concentration-time curve (AUC) in plasma or tissues (Himmelstein, et al, 1981, Reece, et al, 1987, Reece, et al, 1989). Importantly, several clinical studies in ovarian and testicular cancer clearly established significant relationships between dose, dose-intensity and total delivered dose on the one hand and tumour response rate and side effects on the other (Ozols, et al, 1988, Kaye, et al, 1992, Levin, et al, 1993, Ozols, 1989, Bruckner, et al, 1981, Samson, et al, 1984, Levin, 1987, Markman, 1993). Interpatient differences in the dose-response and dose-toxicity relationship can be explained by interpatient differences in the dose-AUC relationship, by pharmacodynamic variability, or by both.

For the cisplatin analogue carboplatin, retrospective analyses in ovarian and testicular cancer revealed significant relationships between the AUC and the likelihood of a tumour response (Jodrell, et al, 1992, Childs, et al, 1992). Earlier studies revealed that the AUC was predictive of the dose-limiting thrombocytopenia (Calvert, et al, 1982, Egorin, et al, 1984). This, combined with the close correlation between renal function and the AUC of carboplatin has lead to the clinical application of practical methods to individualize carboplatin treatment (Childs, et al, 1992, Egorin, et al, 1985, Calvert, et al, 1989).

The cytotoxicity of cisplatin is most closely correlated with its covalent binding to nuclear DNA, so called crosslinks or adducts (Eastman, 1986, Reed, et al, 1986, Reed, et al, 1987, Fichtinger-Schepman, et al, 1987). For practical reasons DNA-adducts have been frequently quantitated in WBC (Reed, et al, 1986, Reed, et al, 1987, Fichtinger-Schepman, et al, 1987, Reed, et al, 1993, Parker, et al, 1991, Hengstler, et al, 1992, Motzer, et al, 1994). Clinical studies with cisplatin and carboplatin in various types of solid tumours revealed significantly higher DNA-adduct levels in WBC and buccal cells in responders than in nonresponders (Reed, et al, 1986, Reed, et al, 1993, Parker, et al, 1991, Hengstler, et al, 1992, Reed, et al, 1988, Reed, et al, 1990, Gill, et al, 1991, Blommaert, et al, 1993). DNA-adduct levels in tumour tissue were correlated with the levels in healthy tissues (Poirier, et al, 1992). Of note, no significant relationships have been established between the AUC of cisplatin and the DNA-adduct formation (Reed, et al, 1988).

We hypothesized that the likelihood of a tumour response in potentially sensitive tumours and interindividual variation in the formation of DNA-adducts in WBC are dominated by interpatient differences in the magnitude of exposure to active, i.e. nonprotein bound, cisplatin. We tested this hypothesis prospectively in a patient population with various types of solid tumours with potential sensitivity for cisplatin.

METHODS

Selection of patients and treatment schedule

All patients gave informed consent according to local regulatory requirements. Eligibility for the study required a pathologically confirmed cancer not curable by surgery, radiotherapy or chemotherapy and with potential sensitivity for cisplatin, such as head and neck cancer (H/N), mesothelioma, non-small cell lung cancer (NSCLC), melanoma, cervix cancer and adenocarcinoma of unknown primary site (ACUP).

The performance status had to be $\leq$ 2 on the WHO scale (WHO Handbook, 1979), life expectancy $\geq$ 3 months and the age between 18 and 75 years. No previous chemotherapy with cisplatin or carboplatin was allowed and no radiotherapy for at least 4 weeks prior to entry in the study. Lesions had to be measurable according to WHO criteria (WHO Handbook, 1979). Each patient had a complete medical history and physical and neurologic examination, complete blood count, and determination of serum chemistries including albumin, total protein, electrolytes, urea (BUN), creatinine and complete liver function tests. The creatinine clearance was determined prior to each administration of cisplatin using the serum creatinine and 24-hour urinary creatinine excretion.

Neurologic evaluation was carried out as described previously (Goldberg, 1979, van der Hoop, et al, 1990) prior to entry in the study, at 2 weeks and at 3 and 6 months after the end of the cisplatin therapy. Briefly: the severity of neuropathy was evaluated by a questionnaire of neurologic symptoms, by performing a sensory neurologic examination and by measurement of the vibration perception threshold (VPT).

All patients had to have adequate renal and liver function, i.e. serum creatinine $\leq$ 1.4 mg/dl (120 μmol/l) or clearance $\geq$60 ml/min and serum bilirubin $\leq$ 1.5 mg/dl (25 μmol/l), WBC $\geq$ $3.0x10^9$/l and platelet count $\geq$ $100x10^9$/l.

The tumour response was scored after 6 courses as complete (CR) or partial response (PR), stable disease (SD) or progressive disease (PD). CR and PR were grouped as responders and SD and PD as nonresponders. The response was determined earlier during treatment if there was any indication of early progressive disease. Toxicity was scored according to the common toxicity criteria (Common Toxicity Criteria). Complete blood count, serum chemistries, urinalysis and determination of the creatinine clearance were repeated weekly.

H/N cancer was treated with weekly courses of cisplatin at a dose of 80 mg/m^2 on days 1, 8, 15, 22, 29 and 36 according to a previously established schedule (Planting, et al, 1993). The treatment was used as an induction regimen, preceding surgery and/or radiotherapy. All other tumour types were treated with weekly cisplatin at a dose of 70 mg/m^2 on days 1, 8, 15, 29, 36 and 43 plus 50 mg of oral etoposide from day 1-15 and 29-43 according to a previously established schedule (Planting, et al, 1994, Planting, et al, 1991). In the latter group, in case of a response etoposide was to be continued thereafter for up to 4 cycles at an oral dose of 50 mg/m^2 from day 1-21 every 4 weeks. Cisplatin was dissolved in 250 ml of 3% sodium chloride and administered as a 3-hour infusion with standard pre- and posthydration.

Pharmacologic studies

Sample collection

During the first course heparinized blood samples were collected at 0, 1, 2, 3, 4, 6, 8 and 18 hours after start of the infusion. The samples were of 4 ml each except at 0, 4 and 18 hours which were of 16 ml each. During all subsequent courses samples of 16 ml were collected at 0, 4 and 18 hours after start of the infusion with cisplatin. During the first course all urine was collected up to 24 hours after start of the infusion with cisplatin.

Analysis of cisplatin in plasma and DNA-adduct levels in WBC

Total and nonprotein bound cisplatin and the total DNA-adduct levels of cisplatin were determined with atomic spectroscopy (AAS) according to the method of Reed et al. (Reed, et al, 1988), with modifications (Ma, et al, 1995).

Data analysis

The area under the plasma concentration-time curve (AUC μg.hr/ml) of unbound cisplatin (measured with AAS as platinum [Pt]) was determined with extended least squares regression analysis (Sheiner, 1985). Plasma clearance (CL) of unbound cisplatin was calculated by dose/AUC (ml/min). The terminal half-life of unbound cisplatin was calculated by ln2/k (min), where k is the rate constant of the terminal phase. The renal clearance of cisplatin was calculated by multiplying the fraction of the dose of cisplatin excreted in the urine by the CL of unbound cisplatin. The DNA-adduct level 1 hour post-infusion was denoted Amax (Ma, et al, 1995) and expressed as picogram of platinum/μg DNA (pgPt/μgDNA). The area under the DNA-adduct-time curve (AUA, pgPt.hr/μgDNA) was calculated up to 15 hours post-infusion with the trapezoidal method, using the 3 DNA-adduct-time points (figure 1). The Siphar software package was used for pharmacologic calculations (version 4.0, SIMED, Creteil, Cedex, France).

Statistical analysis

Linear regression analysis and Pearson correlation analysis were used to quantitate the relationship between AUC and AUA and AUC and Amax. The Pearson correlation coefficient was used for calculation of the correlation between the creatinine clearance and the renal and plasma clearance of cisplatin. The unpaired two-sided student t-test was used to test for differences between responders and nonresponders in Amax, AUA, and AUC. In addition, this test was used to assess any significant differences in AUC, plasma clearance and terminal half-life of unbound cisplatin and AUA and Amax between the 2 subgroups who were treated with 70 or 80 mg/m^2.

Logistic regression analysis (Hosmer, 1989) was applied to establish the relationship between AUC, as well as AUA and Amax and the likelihood of a response. The equation can be written as:

Likelihood of a response $= [1 + \exp\{-(A + B*X)\}]^{-1}$

where: the dependent parameter is the likelihood of a tumour response, A and B are coefficients and X is the independent parameter (AUC, AUA or Amax). Goodness-of-fit of each logistic model was assessed with the Hosmer-Lemeshow test (Hosmer, 1980).

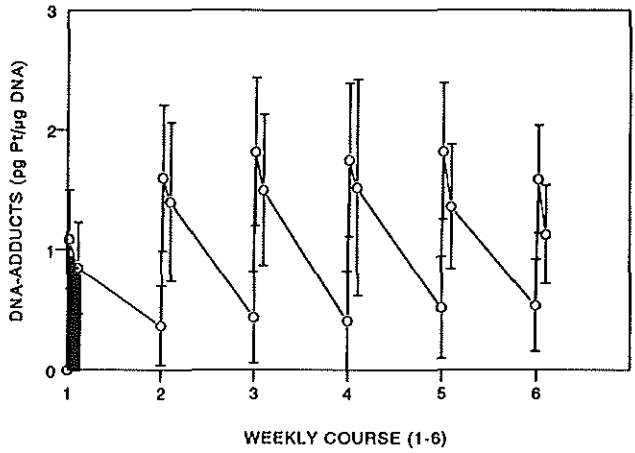

Figure 1. DNA-adduct-time curve of cisplatin during 6 weekly courses of 70-80 mg/m^2 in 45 patients (mean ± SD). The DNA-adduct-time-points [o] per course were: base line, 1 hour and 15 hours post-infusion. Shaded area = area under the DNA-adduct-time-curve (AUA), calculated using the 3 time points and the trapezoidal method.

The Pearson and Spearman rank correlation coefficient and chi-square test were applied to test for relationships between myelosuppresion, renal and neurotoxicity and AUC, AUA and Amax. For statistical analysis of neurotoxicity the maximal sum score post-treatment of the neurologic questionnaire and sensory examination were used, as well as the logarithm of the maximal VPT post-treatment (log VPT).

Multiple linear regression analysis was used to test for differences in the AUC-AUA relationship (i.e. exposure to cisplatin and DNA-adduct formation) between the 2 subgroups treated with 70 or 80 mg/m^2 of cisplatin. The statistical analysis was carried out by application of Stata (version 3.1, Statistics/Data Analysis, Computing Resourse Center, Santa Monica, CA, USA).

RESULTS

Population demographics

Patient demographic characteristics are shown in table 1. A total of 50 eligible patients were entered in the study. Eight patients had previously received radiotherapy and 2 patients chemotherapy. One received isolated regional limb perfusion with melphalan for melanoma 4 years prior to entry into the study and one had systemic cyclophosphamide for adenocarcinoma of unknown primary site 5 years

prior to entry. Five patients were not evaluable for tumour response. Three of the nonevaluable patients developed renal toxicity (2 patients grade 1 and one grade 3, after 1, 2 and 1 course, respectively) preventing further treatment. One patient stopped because of grade 3 gastrointestinal toxicity after 4 courses and one patient refused further treatment after 2 courses. Data of these 5 patients were included in the evaluation of renal toxicity. The 45 patients who were evaluable for response received a total of 237 courses. All patients received at least 1 course and were followed for at least 3 months. The mean number of courses per patient was 5.3 (88% of planned). The dose-intensity in the subgroup treated at 70 mg/m^2 cisplatin plus VP16 was 53.5 mg/m^2/week (89% of planned) and in the subgroup treated at 80 mg/m^2 cisplatin as single agent 71.2 mg/m^2/week (89% of planned). Overall there were 20 responders (44%; 2 CR and 18 PR) and 25 nonresponders (56%; 16 SD and 9 PD). In the subgroup with cisplatin and VP16 there were 10 responders (34%; all PR) and 19 nonresponders (66%; 12 SD and 7 PD).

Table 1. Patient characteristics

Characteristics	cisplatin 70 mg/m^2 + VP 16	cisplatin 80 mg/m^2	All
Total entered			
male	24	16	40
female	6	4	10
Median age, yrs (range)	61 (39-70)	53 (44-73)	59 (39-73)
Median performance score (range)	1 (0-2)	1 (1-2)	1 (0-2)
Prior therapy			
chemotherapy	1	0	1
radiation therapy	5	3	8
chemotherapy and radiation	1	0	1
no prior therapy	23	17	40
Diagnosis			
head and neck		20	20
mesothelioma	12		12
NSCLC	10		10
ACUP	6		6
cervix	1		1
melanoma	1		1

Performance score according to WHO criteria
NSCLC = non-small cell lung cancer
ACUP = adenocarcinoma of unknown primary site

Pharmacokinetics, DNA-adduct formation and tumour response

The AUC of unbound cisplatin showed substantial interpatient variability (table 2). The AUC varied from 1.1 - 3.82 μg.hr/ml and the coefficient of variation (%CV) was 21%. The plasma clearance of unbound cisplatin was 635 ± 217 ml/min (range 312-1477) and the half-life 38 ± 10 min (range 23-72). The volume of distribution of unbound cisplatin was 34 ± 13 liters (range 15-86). The renal clearance quantitated using the first 24-hour urine portion was 167 ± 71 ml/min (range 102-338).

The correlation coefficient between the creatinine clearance and renal clearance of unbound cisplatin was 0.70 ($p<0.01$, $n=20$), between creatinine clearance and plasma clearance of unbound cisplatin 0.46 ($p<0.01$, $n=20$) and between renal and plasma clearance of unbound cisplatin 0.92 ($p<0.0001$, $n=50$).

Also the AUA and Amax varied considerably (table 2). The %CV of the first course AUA was 25% and of the Amax 27%. The variability of the AUA and Amax during the subsequent courses was of the same order as during the first course.

There was a highly significant correlation between the AUC and the AUA and Amax. The correlation coefficient was 0.78 ($p<0.0001$, $n=44$) between AUC and AUA (figure 2) and 0.73 ($p<0.0001$) between AUC and Amax. Of note, there was no significant correlation between the absolute dose given and the AUC ($R=0.1$, $p=0.53$). No significant correlations were observed between the kinetics of total, i.e. bound plus unbound cisplatin and DNA-adduct formation (AUA and Amax).

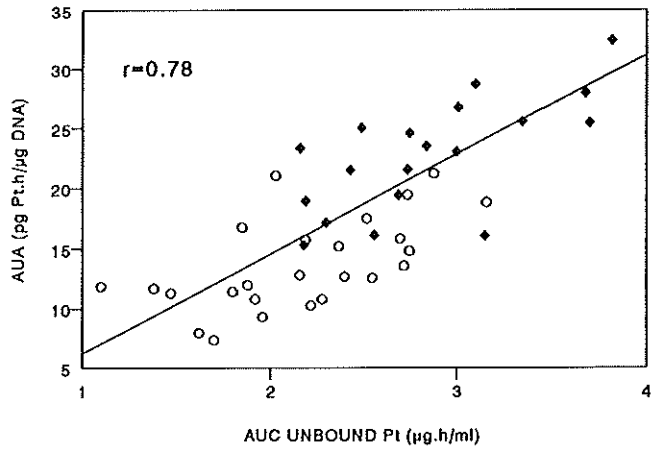

Figure 2. Relationship between the magnitude of exposure to unbound cisplatin (AUC) and AUA during the first course of cisplatin ($R=0.78$, $p<0.0001$). ♦ response, ○ non- response

The AUC, AUA and Amax were significantly higher in responders than in nonresponders (table 2, figure 3). This was evident in the total population as well as in the 2 subgroups treated with cisplatin at a dose of 70 mg/m^2 (various tumour types) and 80 mg/m^2 (H/N). In addition, the mean value of the AUA and Amax of all administered courses was also significantly higher in responders than in nonresponders. The AUC in the subgroup treated at 80 mg/m^2 of cisplatin (2.85 $\pm$ 0.55 μg.hr/ml) was significantly higher than in the subgroup treated at 70 mg/m^2 (2.28 $\pm$ 0.54 μg.hr/ml, p=0.002). The AUA and Amax were also significantly higher in the 80 mg/m^2 subgroup as a results of the dose difference. VP16 did not appear to influence the pharmacokinetics of cisplatin, as there were no statistically significant differences between the 2 treatment groups in plasma clearance, renal clearance or terminal half-life of cisplatin. In addition, VP16 did not affect the DNA-adduct formation significantly, as reflected by the slope of the linear regression relationship between AUC and AUA, which was not significantly different between the two subgroups treated with and without VP16 ($p>0.2$). An influence of VP16 on the DNA-adduct formation could not be tested directly, because the 2 subgroups did receive a different dose of cisplatin.

Logistic regression analysis

Logistic regression analysis revealed highly significant sigmoid relationships between AUC, AUA and Amax, and the likelihood of a response. This was evident in the total population and in the subgroup treated with 70 mg/m^2 of cisplatin (p value of coefficients A and B <0.01 for the total population of 45 patients and $\leq$ 0.02 in the subgroup of cisplatin + VP16). The corresponding 'p' values of the goodness-of-fit tests were all >0.50, indicating good fits. The likelihood of a response reached 100% in the three relationships with AUC, AUA and Amax.

Pharmacokinetics, DNA-adduct formation and toxicity

Myelosuppression was the most frequently encountered side-effect. CTC grade 1 anemia was observed in 9 of 45 evaluable patients (20%), grade 2 in 26 (58%) and grade 3 in 6 patients (13%). Grade 1 leucopenia was observed in 11 patients (24%), grade 2 in 9 (20%), grade 3 in 16 (35%) and grade 4 in one patient (2%). Grade 1 thrombocytopenia was found in 4 patients (9%), grade 2 in 10 (22%), grade 3 in 4 (9%) and grade 4 in 2 patients (4%).

Table 2. Pharmacologic parameters of cisplatin in 45 patients treated with 6 weekly courses of 70 mg/m^2 + oral VP16 daily 50 mg or 80 mg/m^2 of cisplatin as single agent.

Patients	Response	N	AUC [μg.hr/ml]	Amax 1st [pgPt/μgDNA]	Amax 1-6 [pgPt/μgDNA]	AUA 1st [pgPt.hr/μgDNA]	AUA 1-6 [pgPt.hr/μgDNA]
cisplatin + VP16	yes	10	2.64 ± 0.40 2.16 - 3.22	1.21 ± 0.28 0.84 - 1.61	1.55 ± 0.28 1.19 - 1.90	20.0 ± 3.7 15.3 - 25.6	23.5 ± 4.6 16.1 - 28.0
	no	19	2.08 ± 0.51 1.10 - 3.16	0.78 ± 0.19 0.34 - 1.15	1.32 ± 0.24 0.69 - 2.30	13.0 ± 2.9 8.0 - 19.5	18.8 ± 3.1 10.8 - 33.1
	p		0.006	$< 10^{-4}$	0.03	$< 10^{-4}$	0.003
cisplatin	yes	10	3.09 ± 0.53 2.30 - 3.82	1.58 ± 0.26 1.10 - 1.81	1.95 ± 0.28 1.60 - 2.67	25.3 ± 4.2 17.2 - 32.4	30.4 ± 3.8 24.9 - 37.9
	no	6	2.47 ± 0.45 2.16 - 2.88	0.92 ± 0.22 0.58 - 1.15	1.49 ± 0.43 1.07 - 1.52	16.6 ± 4.5 10.3 - 21.3	24.3 ± 6.1 14.5 - 26.5
	p		0.03	0.0001	0.02	0.001	0.03
ALL	yes	20	2.86 ± 0.51 2.16 - 3.82	1.38 ± 0.36 0.64 - 1.81	1.75 ± 0.34 1.24 - 2.67	22.6 ± 5.1 11.5 - 32.1	27.0 ± 5.4 16.1 - 37.9
	no	25	2.17 ± 0.51 1.10 - 3.16	0.81 ± 0.21 0.30 - 1.15	1.36 ± 0.30 0.69 - 2.30	13.7 ± 3.8 7.4 - 21.3	20.1 ± 4.5 10.8 - 33.1
	p		$<10^{-4}$	$< 10^{-7}$	0.0001	$< 10^{-7}$	$< 10^{-4}$

Mean ± SD and range are given.

AUC = Area under unbound cisplatin plasma concentration-time curve
Amax = cisplatin-DNA-adduct level in WBC 1 hour after 3-hour-infusion
AUA = Area under cisplatin-DNA-adduct-time curve in WBC [0-18hrs]

1st = 1st course of cisplatin
1-6 = mean of all courses
Response = CR+PR; No response = SD+PD

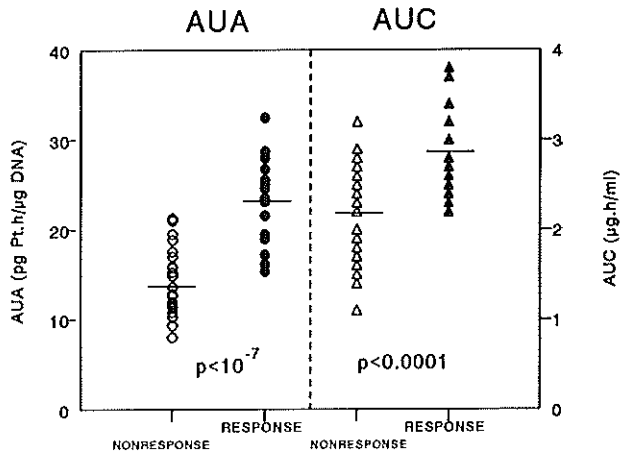

Figure 3. Area under the DNA-adduct-time curve (AUA) and area under the plasma concentration-time curves (AUC) in responders and nonresponders to cisplatin chemotherapy.

The AUC and AUA were significantly correlated with the CTC-grade of thrombocytopenia (Spearman rank R= 0.38, p=0.01 [AUC]; R=0.43 p=0.005 [AUA], n=45). These relationships were also significant in the subgroup treated with cisplatin as single agent, hence without the influence of VP16. In this subgroup the correlation coefficient between AUC and thrombocytopenia was 0.62 (p=0.02, n=16) and AUA and thrombocytopenia 0.70 (p=0.007). The correlation coefficient between dose/m^2 or absolute dose given and thrombocytopenia was not significant (p=0.11). Correlation coefficients between AUC/AUA and anaemia or leucocytopenia were not statistically significant.

Eight patients developed grade 1 nephrotoxicity (16% of 50 patients), one grade 2 (2%) and one patient grade 3 (2%). No significant Spearman rank correlation coefficients were observed between AUC, AUA or absolute dose given and CTC-grade of nephrotoxicity (n=50).

Forty-five patients were evaluable for the sum score of neurotoxicity and in 21 patients the log VPT was determined. Fifteen patients developed grade 1 neurotoxicity (33%). No grade 2 or higher was observed. The log VPT varied between -0.05 and 0.65 (mean 0.23 and SD 0.21). No significant correlation was observed between the cumulative dose nor dose/m^2 and sum score or log VPT.

The cumulative AUC (i.e. AUC of course 1 times number of administered courses) was significantly correlated with the log VPT (Spearman rank R=0.52, p=0.01). The AUA and cumulative AUA were not significantly correlated with the log VPT (p=0.63).

DISCUSSION

For our pharmacologic analyses, we applied a dose-intensive schedule of weekly cisplatin, which was previously developed in our department. Presently over 200 patients with solid tumours have been treated in phase I/II trials according to this schedule (Planting et al., 1991,1993,1993a,1994). The importance of the weekly administration was recently stressed by Logothesis and Amato (Logothetis, 1992). The results clearly indicate that the AUC of unbound cisplatin and the DNA-adduct formation in WBC are closely correlated. The relationship can best be described by a linear relationship (figure 2). In addition, the likelihood of a tumour response was strongly determined by the magnitude of the AUC of cisplatin (figure 2 and 3). Not unexpected, because of the close correlation with the AUC, also the AUA and Amax were strong predictors of response (figure 2 and 3). The AUC of unbound cisplatin was highly variable, despite the small dose range of cisplatin of 70-80 mg/m^2. Also in the two subgroups treated at 70 or 80 mg/m^2 the AUC range was high (table 2). The pharmacokinetic parameters of cisplatin were of the same magnitude as reported previously (Himmelstein, et al, 1981, Reece, et al, 1987, Reece, et al, 1989). The highly significant correlation between the AUC and the level of DNA-adduct formation combined with the strong predictive power of the AUC gives evidence that the variability in the dose-response relationship of cisplatin in our patient population is mainly determined by pharmacokinetic variability. The results were obtained in a heterogeneous population with a variety of solid tumours. It implies that clinical resistance to cisplatin in these tumours is determined to a substantial extent by the magnitude of exposure to unbound cisplatin. We speculate that pharmacokinetic variability contributes significantly to clinical resistance of other tumour types which are potentially sensitive to cisplatin.

Two DNA-adduct parameters were defined and used throughout the study: Amax and AUA. The AUA may reflect processes leading to induction of DNA-adduct formation shortly post-infusion and DNA-repair in the 15 hours post-infusion of cisplatin. The correlation coefficient between AUC and AUA (0.78) was slightly higher than between AUC and Amax (0.73).

Although the AUA is theoretically more of interest, the difference in AUA between responders and nonresponders was only marginally greater than in the Amax (table 2). The DNA-adduct levels did not show a significant accumulation with increasing number of courses, although the mean of the level during the first course was slightly lower than during the subsequent courses (figure 1, table 2). The DNA-adduct levels in responders were consistently higher than in non-responders throughout the study (table 2), which supports the results of Reed et al. (Reed, et al, 1993). The most reasonable explanation for the overlap in DNA-adducts and AUC between responders and nonresponders is pharmacodynamic variability.

The relationships between the AUC of cisplatin or DNA-adduct formation (AUA and Amax) and the response were almost similar in the two subgroups treated at 70 or 80 mg/m^2.

The addition of VP16 had no measurable influence on the relationship between AUC and DNA-adduct formation or on the pharmacokinetics of cisplatin. The response rates in the present study are comparable with those reported by Planting et al. (Planting, et al, 1993a, Planting, et al, 1994, Planting, et al, 1991, Planting, et al, 1992).

The weekly schedule was overall well tolerated. Significant but manageable myelosuppression was encountered. The AUC and AUA were significantly correlated with the CTC-grade of thrombocytopenia. The nephrotoxicity was manageable in almost all patients. No significant correlations were observed between nephrotoxicity and AUC or DNA-adduct formation. One third of the patients developed grade 1 neurotoxicity. This incidence is of the same order as reported in previous studies (Cavaletti, et al, 1992, Roelofs, et al, 1984). The cumulative AUC of cisplatin was more closely correlated with the log VPT than the cumulative dose. Of note, the cumulative dose was not significantly correlated with any of the neurotoxicity parameters, which is in contrast to a previous study (Cavaletti, et al, 1992). It is important to note that the AUC of unbound cisplatin was more closely correlated with any toxicity parameter than the dose, cumulative dose or dose/m^2. These relationships, however, need affirmation in future studies.

The outlined results clearly confirm that a standardized dose/m^2 results in wide interpatient variation in the AUC of cisplatin (Himmelstein, et al, 1981, Reece, et al, 1987, Reece, et al, 1989). Considering the relationship between the AUC and the likelihood of a tumour response in a population with a variety of solid tumours,

the pharmacokinetic variability has major implications for the treatment with cisplatin. Patients should benefit from individualized dosing of cisplatin, to increase the response rate. Based on the significant correlations between AUC and toxicity parameters this will also lead to more frequent, but mostly predictable toxicity. Drug monitoring applying a limited sampling strategy is indicated to achieve target levels of AUC or DNA-adducts. The presented study provides support for tumour-type specific trials, for example in non small cell lung cancer. This procedure is currently investigated in a prospective study.

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CHAPTER 10

SAMENVATTING
CONCLUSIES EN PERSPECTIEF

SAMENVATTING

In **hoofdstuk 1** wordt de achtergrond van de studies die het onderwerp zijn van dit proefschrift beschreven. De cytostatica cisplatin en etoposide worden geïntroduceerd. Cisplatin is wellicht het belangrijkste cytostaticum bij de behandeling van solide tumoren; het kent echter ook vele bijwerkingen, zoals misselijkheid en braken, beenmergdepressie en beschadiging van nieren, zenuwbanen en het gehoor. Om deze bijwerkingen te voorkomen wordt cisplatin meestal toegediend in lage dosering in combinatie met andere cytostatica. Resistentie tegen cisplatin is soms relatief, dat wil zeggen: met een hogere dosis kan een tumor alsnog tot regressie worden gebracht. Dit is onder andere waargenomen bij eierstokkanker. Of dit bij andere tumortypes ook geldt is nog niet duidelijk. Etoposide is veel minder toxisch dan cisplatin. Beenmergdepressie en haaruitval zijn de belangrijkste bijwerkingen. Verduidelijkt wordt waarom laag gedoseerd oraal etoposide de voorkeur verdient boven hoog gedoseerd etoposide intraveneus. De patiëntengroepen waarin de wekelijkse cisplatin studies zijn verricht worden besproken. De huidige behandelingsresultaten zijn niet optimaal. Iedere kleine verbetering in de behandeling bij deze patiënten is belangrijk.

In **hoofdstuk 2** wordt de fase 1 studie met wekelijks cisplatin gepresenteerd. Gestart werd met een dosis van 50 mg/m^2/week welke werd geëscaleerd tot 85 mg/m^2/week. Op dit dosisniveau bleek trombopenie de dosis limiterende toxiciteit te zijn. Opvallend was het geringe risico op nefrotoxiciteit en neurotoxiciteit, hetgeen wij toeschrijven aan de toediening van cisplatin in hypertoon zout. Op grond van de resultaten van deze studie werd een cisplatin dosis van 80 mg/m^2/week bij niet-voorbehandelde patiënten haalbaar geacht.

Hoofdstuk 3 beschrijft de fase 2 studie bij lokaal uitgebreide hoofd-halstumoren met een cisplatin dosis van 80 mg/m^2/week. In deze studie werden 59 patiënten behandeld; het response percentage bedroeg 60% bij 50 evalueerbare patiënten, een van de hoogste respons percentages met cisplatin monotherapie ooit bereikt bij deze ziekte. Toch bleek slechts een klein deel van de patiënten de geplande behandeling zonder vertraging te kunnen volbrengen, vooral door trombopenie.

Hoofdstuk 4 behandelt de volgende studie bij hoofd-halstumoren. De mogelijkheid om binnen de EORTC hoofd-hals groep de chemoprotector amifostine te bestuderen

leidde na een feasibility studie, tot een gerandomiseerde studie waarin een lagere dosis cisplatin, 70 mg/m^2/week werd vergeleken met dezelfde dosis voorafgegaan door amifostine. Amifostine bleek een beschermend effect op de niertubulus te hebben zich uitend in een verminderd risico op hypomagnesiëmie. Tevens trad minder trombopenie op. De omvang van de studie was echter te gering om duidelijke uitspraken te doen over andere bijwerkingen. Opvallend is wel dat met een lagere geplande cisplatin dosis-intensiteit uiteindelijk in werkelijkheid een hogere cisplatin dosis-intensiteit werd bereikt vergeleken met de studie beschreven in hoofdstuk 3.

In **hoofdstuk 5** wordt de fase 2 studie met wekelijks 80 mg/m^2 cisplatin beschreven bij maligne mesothelioom van de pleura. Vijf van de 14 patiënten respondeerden, echter de responsduur van mediaan 6 maanden was kort. Het ontbreken van een onderhoudsbehandeling na de zesde cisplatin toediening werd hiervoor verantwoordelijk geacht. Om deze reden bleef de omvang van de studie beperkt.

Hoofdstuk 6 beschrijft de fase 1 studie met wekelijks cisplatin gecombineerd met oraal etoposide. Gekozen werd voor oraal etoposide vanwege het synergisme met cisplatin en het gebruiksgemak voor de patiënt. Oraal etoposide werd ook voor onderhoudsbehandeling geschikt geacht aangezien hiermee bij diverse tumortypes al gunstige ervaring bestond. Met de combinatie bleek behalve trombopenie ook granulopenie frequent tot uitstel van de therapie te leiden. Uiteindelijk kon door het inlassen van een pauzeweek na de derde cisplatin dosering en het verlagen van de etoposide dosis een schema worden bereikt waarin minder beenmerg toxiciteit optrad terwijl toch een hoge cisplatin dosis-intensiteit van 52.5 mg/m^2/week werd bereikt. Dit schema: cisplatin 70 mg/m^2/week in week 1-2-3 en week 5-6-7 gecombineerd met 15 dagen 50 mg etoposide per kuur is nader bestudeerd in fase 2 studies.

Hoofdstuk 7: rapporteert een fase 2 studie in maligne mesothelioom van de pleura met het schema uit hoofdstuk 6. Een respons werd bereikt bij 6 van de 25 patienten; niet beter dan met cisplatin alléén doch de responsduur was iets langer.

Hoofdstuk 8 beschrijft een fase 2 studie met hetzelfde behandelschema bij stadium III en IV niet-kleincellig longcarcinoom. De behandeling werd in deze patiëntengroep goed verdragen. Van de 18 evalueerbare patiënten met stadium III tumoren

respondeerden er 11. Nadere bestudering van dit schema bij stadium III tumoren lijkt daarom geïndiceerd. Bij stadium IV (gemetastaseerde ziekte) was het behandelingsresultaat niet beter dan met minder intensieve schema's kan worden bereikt.

In **hoofdstuk 9** wordt een brug geslagen naar de toekomst. Dit hoofdstuk beschrijft een studie naar de correlatie van farmacokinetische parameters en het resultaat van de behandeling. De parameters AUC (area under the curve van vrij platina), AUA (area under the DNA-adduct time curve) en Amax (DNA-adduct gehalte in leucocyten 1 uur na beëindiging van het infuus) bleken hoger bij patiënten met een respons dan bij patiënten die niet respondeerden. Deze correlaties dienen nader te worden onderzocht in prospectieve studies. Bij bevestiging van de uitkomsten zal optimalisering van de behandeling kunnen plaatsvinden op geleide van de AUC en AUA; een lage AUA betekent een te lage dosis. Ophogen van de dosis kan een verhoogd risico op bijwerkingen betekenen. Door gelijktijdige meting van de AUC kan worden gewaakt tegen een te hoog opvoeren van de dosis.

Perspectief: Wekelijks toegediend cisplatin (en dagelijks oraal etoposide) is een zeer actieve behandeling in verschillende tumortypes met over het algemeen een hanteerbare toxiciteit. Het verder ontwikkelen van een effectievere behandeling met beperking van het risico op bijwerkingen lijkt mogelijk. Dit ideale doel wordt realistisch door farmacologische ondersteuning van cytostatische behandelingen, hetgeen zal leiden tot individualisering van de chemotherapie en hopelijk daardoor tot verhoging van de kans op een respons. Momenteel bestuderen wij deze veronderstelling reeds prospectief. Het verder incorporeren van chemoprotectieve stoffen, zoals amifostine of natriumthiosulfaat (of combinaties van chemoprotectiva), zal het risico op bijwerkingen doen afnemen waardoor de therapeutische breedte van cisplatin toeneemt. De waarde van cisplatin als radiosensitizer in solide tumoren is nog onvoldoende geëxploreerd. Weliswaar is voordeel aangetoond bij het niet kleincellig longcarcinoom en leidt gelijktijdige chemo-radiotherapeutische behandeling bij hoofd-halstumoren tot hoge respons percentages, de acute bijwerkingen zijn echter aanzienlijk en over lange termijn bijwerkingen bestaat nog onvoldoende informatie. Studies ter vermindering van toxiciteit met behulp van chemoprotectiva in chemo-radiotherapie schema's zijn dringend nodig. Juist de categorie patiënten, met lokaal uitgebreide tumoren, waarvan een deel lang zal overleven, is gebaat bij inspanningen die de responskans zo hoog mogelijk en de kans op toxiciteit zo laag mogelijk houden.

CHAPTER 10

SUMMARY
CONCLUSIONS AND PERSPECTIVE

SUMMARY

Chapter 1 describes the background of the studies presented in this thesis, introduces the cytotoxic drugs cisplatin and etoposide and the dose-intensity concept. The tumor types head and neck cancer, non-small cell lung cancer and pleural mesothelioma and the results of chemotherapy in these tumors are discussed.

Chapter 2 presents the results of the phase 1 study with weekly administration of cisplatin. Trombocytopenia was the dose limiting toxicity at 85 mg/m^2/week. Non-haematological toxicities were considered very acceptable.
Based on the results of this study a dose of cisplatin of 80 mg/m^2/week for 6 weeks was considered feasible in previously untreated patients.

Chapter 3 presents the results of this schedule tested as a neoadjuvant chemotherapy regimen in patients with locally far advanced head and neck cancer. The response rate of 60% is high for single agent treatment. Toxicities were, however, more frequent than expected and due to treatment delays mainly because of trombocytopenia the planned high dose intensity could not be reached.

Chapter 4 presents the study performed by the EORTC Cooperative Head and Neck Group with the combination of cisplatin and amifostine. Amifostine is a chemoprotective agent which was studied in a randomized fashion with cisplatin 70 mg/m^2/week for 6 administrations versus the same cisplatin schedule preceded by amifostine. A protective effect was shown on the development of hypomagnesaemia as well as a reduction of risk of trombocytopenia. The small sample size did not allow a reliable analysis of other toxicities.

Chapter 5 describes the phase 2 study with weekly cisplatin in pleural mesothelioma. Although 5 out of 14 patients responded the study was terminated because the response duration was short, probably related to the lack of maintenance treatment.

Chapter 6 describes the phase 1 study of weekly cisplatin combined with oral etoposide followed by oral etoposide as maintenance treatment. Trombocytopenia, but also granulocytopenia, were dose limiting toxicities and necessitated treatment delays. Introduction of a one week interval between cycle 3 and 4 and a decrease

of the etoposide dose led to the schedule used in the studies described in the next chapters.

Chapter 7 discusses the activity of this regimen in pleural mesothelioma. Although the response rate was comparable to the cisplatin single agent regimen the responses were more durable.

Chapter 8 presents the data of the phase II study in stage III and IV non-small cell lung cancer. The activity was high in stage III tumors with a response in 11 of 18 evaluable patients, with very acceptable toxicity. Further exploration is thus indicated in locally advanced lung cancer. In stage IV tumors the response rate was not better compared to what can be achieved with less intensive regimens.

Chapter 9 opens perspectives for future refinement of treatment. In patients on weekly cisplatin the cisplatin AUC was determined as well as DNA-adducts levels in leucocytes. Patients responding to treatment had a significant higher AUC (Area Under the Curve) of unbound platinum, AUA (Area Under the DNA-Adduct time curve) and Amax (DNA-adduct levels in leucocytes at one hour after completion of the infusion) compared to non-responding patients. These pharmacological studies are extended. If these correlations are confirmed, optimization of treatment can be achieved by dose adjustments of cisplatin based on the AUC and AUA. A low AUA will lead to an increase of the cisplatin dose in consecutive administrations, whereas the AUC will indicate the threshold associated with unacceptable toxicity.

Perspective: Weekly cisplatin (and daily oral etoposide) is a highly active antitumor regimen in several solid tumor types with overall manageable toxicity. The treatment results may be further improved by individualisation of the cisplatin dosage based on pharmacological parameters. In an ongoing study we are testing this concept prospectively. Further reduction of cisplatin toxicity, by chemoprotective agents such as amifostine or sodiumthiosulphate or the combination of chemoprotective agents, will allow cisplatin treatment with less toxicity and hopefully a better preservation of the quality of life of the patients. Cisplatin is an excellent radiosensitizer and its value should be explored further. The response rates with concomitant chemo-radiotherapy in head and neck cancer are encouraging. The acute toxicities of these regimens are, however, considerable and information on late toxicities is still scanty. Exploration of the activity of chemoprotective agents

in high-dose chemo-radiotherapy schedules is therefore warranted. Only when the complete response rate can be improved with simultaneous reduction of toxicity, we can say that "progress has been made".

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CURRICULUM VITAE

André Simon Theodoor Planting

3 maart 1948	: geboren te Haarlem
1966	: H.B.S.-B te Rotterdam, St. Franciscus College, diploma 1966.
1972	: Studie medicijnen aan de medische faculteit te Rotterdam. Arts diploma behaald op 15 september 1972. Tijdens militaire dienst werkzaam als arts-assistent op de afdeling anaesthesiologie van het "De Wever" ziekenhuis te Heerlen (hoofd dr. J. Lelkens) Opleiding tot internist te Rotterdam, St. Franciscus Gasthuis (hoofd dr. M. de Jong) Tijdens het "vrije jaar" werkzaam in de dr. Daniël den Hoedkliniek binnen de RRTI-mammagroep o.a. aan studies met Tamoxifen.
1979	: Inschrijving in het specialisten register als internist per 1 augustus 1979.
1979 - heden	Sedert september 1979 werkzaam in de dr. Daniël den Hoed Kliniek als internist.

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