Anti-Cancer Drugs 2001, **12,** pp. 667–675

Clinical report

Adaptive intrapatient dose escalation of cisplatin in patients with advanced head and neck cancer

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The purpose of this study was to explore the feasibility and toxicity of intrapatient dose adjustment using predefined levels of exposure to cisplatin, with the ultimate goal to further improve the antitumor activity of the treatment. The primary parameter for adaptive dosing was the level of platinum DNA adducts in peripheral white blood cells (WBC) and the secondary parameter the area under the curve (AUC) of unbound platinum in plasma, which were determined during the applied courses. Target levels had been defined in a previously performed pharmacologic study. The concept of adaptive dosing was tested in 16 patients with locally advanced head and neck (H/N) cancer who would receive six weekly courses of cisplatin at a starting dose level of 80 mg/m^2, which was previously investigated in a phase II study. Forty-seven percent of patients received a dose increase varying from 10 to 40%. Only two patients had exposure levels significantly below the defined target levels for DNA adducts and AUC. The majority of patients reached the defined target levels by modest dose increases of 10–20% during course 2. Relevant but reversible ototoxicity (temporary grade 3 in two patients) and renal toxicity (temporary grade 2 in two other patients) were observed. The pattern and severity of the toxicity was comparable to that encountered in the previous phase II study in H/N cancer patients. We conclude that the strategy of intrapatient dose adjustment for cisplatin is practically feasible in a research setting even when a short turn around time of 1 week is the limit for reporting results. Although in some patients the dose increase that had to be applied to reach target levels was substantial (up to 40%), this approach in H/N cancer patients is not expected to improve the response rate significantly, because these significantly underdosed patients represented only a small percentage of the investigated population. The great majority of patients needed only limited (10–20%) dose increases which very likely will not improve the response rate to a clinically significant extent. The outlined concept is currently being explored in other tumor types and schedules of cisplatin. [© 2001 Lippincott Williams & Wilkins.]

Key words: Adaptive dose adjustment, cisplatin, DNA adducts, head and neck cancer, pharmacokinetics.

Introduction

Cisplatin is one of the most active agents in the treatment of head and neck (H/N) cancer.[1,2] H/N cancer that cannot be cured by local therapy, consisting of radical resection combined with postoperative radiotherapy, most often has a poor prognosis and patients die of metastatic disease. The median survival after diagnosis of advanced incurable disease is of the order of 4–7 months.[3] In locally advanced inoperable and metastatic tumors cisplatin, given as single agent or in combination with methotrexate or 5-fluorouracil (5-FU), is the most often applied anticancer drug for palliative treatment. Traditionally, cisplatin was used in 21-day schedules at doses of 75–100 mg/m^2 per course. Dose intensities in these schedules are often low and of the order of 25–35 mg/m^2/week. Associated response rates were also found to be relatively low and varied from 3 to 40%.[4–11] However, for cisplatin there may exist a dose–response relationship in H/N cancer and clinical studies have been performed to increase the dose intensity of cisplatin in advanced disease.[1,9,12,13] Studies also performed in other tumor types aimed at optimizing the dose intensity of cisplatin by increasing the dose per course revealed that doses significantly higher than 100 mg/m^2 per course are intolerable due to acute toxicity. In phase I and II studies, Planting *et*

This study was supported by the Dutch Cancer Society grant NKI 95-1059.

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al. have shown that the dose intensity of cisplatin can significantly be increased by shortening the treatment interval from 21 to 7 days without compromising the dose per course.[12–16] In H/N cancer where cisplatin was used as single agent the maximum tolerated dose (MTD), and recommended dose for further testing, was 80 mg/m^2 per week for six cycles.[12] The achieved dose intensity at this dose level was 70 mg/m^2/week, which is 87.5% of the planned dose intensity. In the phase II study, 22 (37%) or the patients received the planned six courses.[13] The dose intensity reached was 68 mg/m^2/week in patients who had 1 week delay and 60 mg/m^2/week in patients who had 2 weeks delay.[13]

In a pharmacokinetic–dynamic study in 16 patients, which supported the phase II trial, a significant correlation was found between the area under the unbound plasma concentration–time curve (AUC) of cisplatin [measured as platinum by atomic absorbance spectroscopy (AAS)] and the likelihood of tumor response.[17] In addition, a highly significant difference in DNA adduct level, as measured in peripheral white blood cells (WBC) by AAS, was found between responders (n=10) and non-responders (n=6). The adduct level in responders was 72% higher compared with non-responders at 1 h after the end of the 3-h infusion of cisplatin. Also at later time-points the responders had significantly higher WBC DNA adduct levels than non-responders. There was also a highly significant correlation ($p<0.01$) between the AUC of cisplatin and the DNA adduct levels in WBC, indicating that variation in the adduct levels is largely determined by pharmacokinetic variability of cisplatin. This has resulted in a feasibility study to adapt doses of cisplatin during treatment in order to achieve better antitumor activity, of which the results are presented.

Methods

Selection of patients

Patients were eligible if they had a histologically confirmed squamous cell carcinoma of the head and neck, they were >18 and <80 years, had a life expectancy of at least 3 months, measurable disease according to WHO criteria,[18] a WHO performance score of $\geqslant 2$, adequate bone marrow function (WBC $>3.0\times10^9$/l and platelets $>100\times10^9$/l), adequate liver (serum bilirubin <25 μmol/l and serum albumin >25 g/l) and renal function (serum creatinine <140 μmol/l or creatinine clearance >45 ml/min). They were not eligible if they had received radiotherapy on the indicator lesion or when any radiotherapy was given within 4 weeks prior to start of the study. New measurable metastases in previously irradiated areas were accepted as indicator lesions. Patients were also ineligible if they had neurologic disease that could cause an increased risk for peripheral or central neurotoxicity, if they had uncontrolled infections, if they were pregnant or were lactating, or if they had known cerebral or leptomeningeal metastases. Pretreatment with cisplatin or carboplatin was not allowed. Patients had to give written informed consent. The study was approved by the local ethics committee.

Treatment schedule

Cisplatin was administered in six weekly courses on days 1, 8, 15, 22, 29 and 36. Cisplatin was administered in 250 ml 3% NaCl as a continuous i.v. infusion of 3 h. Patients were prehydrated with 0.75 l dextrose/saline plus 20 mmol KCl and 2 g $MgSO_4$ administered 3 h prior to the 3-h infusion of cisplatin. After the end of the cisplatin infusion patients received posthydration with 2 l of dextrose/saline plus 40 mmol KCl and 4 g $MgSO_4$ administered over 14 h.

Blood sampling for pharmacokinetic and platinum DNA adduct measurements

During the first three courses blood samples were to be taken at 0, 1, 2, 3, 3.5, 4, 5, 6 and 21 h after start of the infusion. The volume of each sample was 4 ml except at time-points 0, 4 and 21 h where a volume of 16 ml was collected. Samples at these three time-points were also used for collection of WBC and measurement of platinum DNA adduct levels, according to a previously validated quantitative assay.[19] Unbound cisplatin concentrations in plasma were measured as platinum according to a previously validated assay employing AAS.[20]

During the last three courses only three blood samples were taken of 16 ml at time-points 0, 4 and 21 h after start of the infusion of cisplatin.

Urine collection

During the first three courses 24 h urine was collected in two portions for measurement of platinum excretion.

Dose individualization

The dose of cisplatin to be administered during the second course depended on the pharmacokinetic measurements of cisplatin in plasma and the DNA

adduct levels measured in WBC during course 1. The dose to be administered during the third and subsequent courses depended on the pharmacokinetic and DNA adduct parameters as determined during course 1 and 2.

The primary target for dose individualization was the level of DNA adducts in WBC. The secondary target was the AUC of unbound platinum in plasma. The algorithm for dose adaptation is summarized in Figure 1. The starting dose in all patients was 80 mg/m^2 according to the previously performed phase II study.[13] As a basis for dose individualization, the pharmacologic data were used from a large pharmacokinetic–pharmacodynamic study in 45 patients who received cisplatin at a dose of 70 or 80 mg/m^2.[17] In that study, the mean area under the adduct concentration–time curve (AUA) in the group of responders to cisplatin therapy was rounded off to 23 [mean 22.6, range 11.5–32.1 (pgPt·h/μgDNA)]. In the non-responders the mean AUA was rounded off to 14 [mean 13.7, range 7.4–21.3 (pgPt·h/μgDNA)]. The AUA level of 23, the mean value observed in the responders, was taken as the target value for the current dose-individualization study.

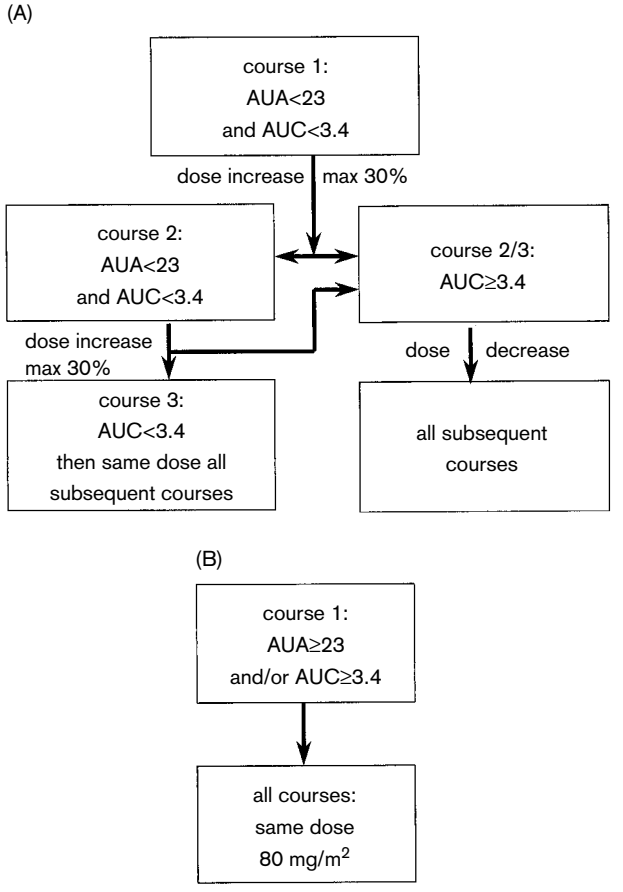

Figure 1. Algorithm for dose adaptation of cisplatin. (A) If the observed AUA during course 1 is below the target of 23 (pgPt·h/μgDNA) and the AUC is below the safety limit of 3.4 (μg·h/ml). (B) If the observed AUA during course 1 is already higher than the target of 23 (pgPt·h/μgDNA and/or the AUC is higher than or equal to the safety limit of 3.4 (μg·h/ml). For further details, see Methods.

If the observed AUA during course 1 was below this defined target value of 23, the patient received a subsequent dose increase in order to achieve an AUA value of 23 during the second course. If the observed AUA during the second course was found to be below 23 again, then a second dose increase was applied. The maximum allowable dose increase was set at 30% per course for safety reasons. If the observed AUA during the first course was found to be higher than 23 then no dose reduction was applied and the patient continued treatment at the starting dose of 80 mg/m^2 during all courses.

In the previous pharmacologic study the mean AUC in the responders was 3.0 [range 2.30–3.82 (μg·h/ml)] and the AUC in non-responders was 2.2 [range 1.10–3.16 (μg·h/ml)].[17] If, in the current study, for any reason the AUA could not be determined then a target AUC value of 3.0 was used for adaptive dosing. Hence, if the observed AUC was below 3.0 during course 1 a dose increase was applied during course 2 and if the observed AUC during course 2 was still below 3.0, then a second dose increase was applied with a maximum increase per course of 30%, exactly according to the approach as outlined for the AUA. If the observed AUC during course 1 was higher than the defined target of 3.0 then no dose reduction was applied.

In the previous pharmacologic study a significant relationship was also found between the AUC as well as the AUA and the toxicity, in particular thrombocytopenia. The AUC, but not the AUA, was also significantly correlated with neurotoxicity (in particular the log vibration perception threshold). For this reason a maximum value of the AUC was accepted, which was arbitrary set at 3.4 (the mean value in the responders + SD, as observed in the pharmacologic study). If, for example, a patient needed a dose increase, because the observed AUA was below the defined target, but the AUC after the planned dose increase was expected to exceed the safety limit of 3.4, then no or a lower than planned dose increase was applied for safety reasons in order not to exceed the limit of 3.4.

Follow-up studies

Prior to start and every week during treatment a physical examination was performed and the toxicity score (according to the Common Toxicity Criteria[21])

and WHO performance score were determined. In addition, hematologic parameters (hemoglobin, leukocyte, granulocyte and platelet counts), serum chemistry [liver (ASAT, ALAT, γ-GT, LDH, alkaline, phosphatase, bilirubin) and renal function (serum creatinine and measured creatinine clearance), serum albumin, and Na, K, Mg and Ca] were determined weekly.

Neurologic examination (including vibrametry) and audiometry were performed prior to the start and 2 weeks and 3 and 6 months after the end of cisplatin treatment.

Pharmacokinetic and pharmacodynamic calculations

The AUC of cisplatin was determined using the non-compartmental trapezoidal method. The elimination rate constant k (h^{-1}) was determined using the time-points at 4, 5 and 6 h after start of the infusion. Curves were extrapolated to infinity by using $C(t)/k$, where $C(t)$ is the plasma concentration at the latest time-point 't' (mostly 6 h after the start of infusion). The terminal half-life was calculated by $\ln 2/k$ (h). The total plasma clearance (CL) of unbound platinum was calculated by dose/AUC (ml/min).

The area under the AUA was determined up to the last measured time-point at 21 h after start of the infusion (i.e. by using the time-points 0, 4 and 21 h) by applying the trapezoidal method. The parameter AUA has previously been defined.[17]

Urinary platinum excretion was used to calculate the renal clearance of unbound platinum during the first 24 h after start of treatment.

Toxicity and retreatment

At any subsequent cycle leukocyte counts had to be $\geqslant 2.0 \times 10^9$/l and platelets $> 100 \times 10^9$/l. Patients were to be taken off study in case of treatment delay due to drug related toxicity for more than 2 weeks, and any irreversible grade $\geqslant 2$ non-hematologic toxicity (in particular neuro-, nephro- and ototoxicity), excluding untreated nausea, vomiting and alopecia. In case patients were taken off study, further treatment was left to the discretion of the responsible physician.

Endpoints of the study

The study had a primary pharmacologic endpoint, which was to determine the feasibility of adaptive intrapatient dose adjustment to achieve the desired exposure to cisplatin defined by DNA adducts in WBC and AUC of unbound platinum in plasma.

The secondary clinical endpoints were the toxicity and response rate of the treatment. Patients were considered evaluable for response if they had received a minimum of three cycles of cisplatin.

It was anticipated that approximately 15 evaluable patients would be necessary to determine the feasibility of the adaptive dosing strategy.

Statistical analysis

Pearson correlation coefficients were calculated between dose and exposure parameters where appropriate. Spearman rank correlation coefficients were calculated between exposure parameters and toxicity scores. $p < 0.05$ was defined as statistically significant.

Results

In total 16 patients were entered in the study. The main characteristics are given in Table 1. All patients were eligible and were evaluable for pharmacokinetics and toxicity. Ten patients were also evaluable for tumor response. Six patients were not evaluable for response, because they did not receive the required minimum number of three cycles of cisplatin. In one patient early disease progression after the first cycle developed and treatment was stopped. In two other patients reversible grade 3 ototoxicity developed after course 2, which after discontinuation of cisplatin therapy resolved to grade 2. In two patients temporary grade 2 nephrotoxicity developed, which decreased to grade 1 after the second cycle. In one patient treatment was stopped after the second cycle because of gastrointestinal toxicity, which consisted of vomiting grade 3. This was completely reversible after treatment was stopped.

Treatment

The 16 patients received a total of 58 courses, which means that on average 3.6 courses were administered per patient. The achieved number of courses was 60% of the planned maximum of six courses. In the 10

Table 1. Patient characteristics

Total entered	16
Male	11
Female	5
Median age (range)	59 (39–73)
Median WHO performance score (range)	1 (0–1)
Prior chemotherapy	0
Prior radiotherapy	3

patients evaluable for response the administered number of courses was 78% of the planned maximum.

Pharmacokinetic data, DNA adduct levels and dose adaptations

Of the 15 patients who received more than one course in total, eight (53%) patients received a dose increase, because the initial pharmacokinetic parameters were below the defined target level during course 1. The magnitude of the dose increases versus the percentage of patients is shown in Figure 2. In individual patients the dose increase varied from 0 to 40%. On average a moderate dose increase of close to 10% (9.8%) was applied (Table 2). In one of the patients the AUC was applied as the exposure parameter for determination of dose adjustments, because in this patient for technical reasons the DNA adduct levels could not be determined. Five of the seven patients who received a dose increase after the first course reached the target value of DNA adducts during the second course and in two patients a modest (10%) further dose increase was necessary. One patient reached an AUC value higher than the safety cut-off value of 3.4 (μg·h/ml). However, the AUC of 3.5 was already achieved during course 1 and therefore no dose reduction was applied during subsequent courses. The AUA and AUC data are given in Tables 2 and 3.

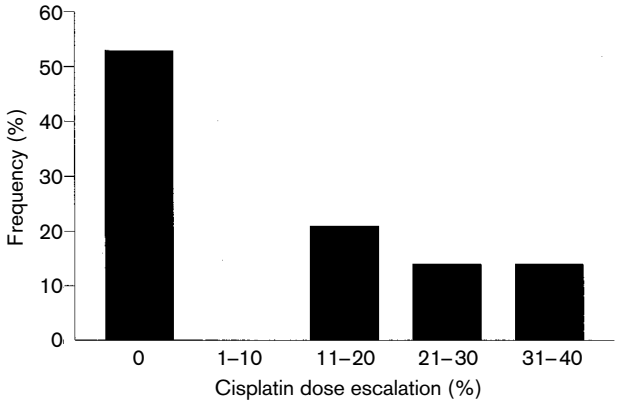

Figure 2. Magnitude of the dose increase of cisplatin expressed as percentage of the starting dose versus the percentage of patients.

Table 2. Cisplatin dose during course 1 and 2

	Course	
	1	2
Cisplatin dose (mg)		
mean	143	157
SD	16	18
range	120–175	130–190
N	16	15

The main pharmacokinetic data of cisplatin during course 1 are given in Table 4. Total plasma clearance of unbound platinum was 643 ± 143 ml/min and renal clearance was 139 ± 39 ml/min. The clearance data obtained during course 2 and 3 were of the same order as those of course 1.

The correlation coefficient between AUC and AUA during course 1 was 0.61 ($p < 0.05$; N=15). The correlation coefficient between dose and AUC was 0.34 (not significant, NS; N=16) and between dose and AUA 0.29 (NS; N=15).

Toxicity

As described, five of the 16 patients discontinued cisplatin therapy because of toxicity. One of the patients refused further therapy because of vomiting, the other four because of toxicity that was not compatible with continued dose intensive cisplatin therapy, such as renal toxicity and ototoxicity. The observed CTC grade 2 renal toxicity in two patients reversed to grade 1 within 3 weeks after the end of therapy and the grade 3 ototoxicity, with temporary partial hearing loss, in two other patients reversed to grade 2 within 4 weeks after discontinuation of therapy. The main toxicities observed are summarized in Table 5. Most toxicities started to develop after two or three courses. Mild anemia (grade 1), mild to moderate leukocytopenia (grade 1–3) and mild thrombocytopenia (grade 1–2) were frequently observed (Table 5), and developed gradually after three courses. Also, mild to moderate nausea (grade 1–2) and vomiting (grade 1–2) developed frequently. Reversible grade 1 renal electrolyte disturbances (hyponatremia and hypomagnesia) developed in 75–80% of the patients. Ototoxicity (grade 2; 69%) and neurotoxicity (grade 1; 62%) also developed frequently. Neurotoxicity consisted of mild to moderate pareasthesias and sensory neuropathy.

No significant relationships were found between exposure parameters (dose, AUC and AUA) and toxicity scores including the neurotoxicity scores.

Tumor response

Ten of the 16 patients were evaluable for response according to the definitions of the study protocol. One patient developed a complete remission (CR) and five patients developed a partial remission (PR). In three patients stable disease (SD) was noted and in one

Table 3. AUA in WBC and AUC of unbound platinum in plasma in 16 patients

		Course					
		1	2	3	4	5	6
AUA	mean	18.6	25.3	31.1	30.1	26.7	33.9
(pgPt·h/μgDNA)	SD	4.1	7.8	11.7	3.7	3.8	7.5
	range	11.4–25.1	19.6–50.4	24.4–61.6	24.9–36.1	22.6–30.1	28.6–39.2
	N	15	14	10	6	4	2
AUC	mean	2.6	3.1	3.2	ND	ND	ND
(μg·h/ml)	SD	0.6	0.4	0.4			
	range	1.7–3.5	2.4–4.1	2.6–4.1			
	N	16	14	10			

ND, not determined.

Table 4. Total plasma clearance of unbound platinum (Pt), urinary excretion (0–24 h after start of infusion), renal clearance and terminal half-life ($t_{1/2}$ of Pt in plasma during course 1

	CL unbound Pt (ml/min)	Urinary Pt excretion (% dose)	Renal CL Pt (ml/min)	$t_{1/2}$ (h)
Mean	633	22	139	0.55
SD	143	5	39	0.16
Range	447–952	11–30	94–221	0.33–1.20
N	16	14	14	16

Table 5. Main CTC graded toxicities in 16 patients which are probably or definitively related to cisplatin therapy (one patient received only one course due to early progressive disease): toxicities are scored as worst grade per patient

Toxicity	Grade			
	1	2	3	4
	N (%)	N (%)	N (%)	N (%)
Leukocytopenia	3 (19%)	6 (38%)	5 (31%)	0
Neutropenia	1 (7%)	6 (38%)	2 (13%)	0
Thrombocytopenia	6 (38%)	4 (25%)	0	0
Neurotoxicity	10 (62%)	0	0	0
Ototoxicity	2 (13%)	11 (69%)	2 (13%)	0
Nephrotoxicity	4 (25%)	2 (13%)	0	0
Alopecia	3 (21%)	0	–	–
Nausea	8 (50%)	6 (38%)	0	–
Vomiting	6 (38%)	4 (25%)	1 (7%)	0
Diarrhea	2 (13%)	0	0	0
Anorexia	5 (31%)	2 (13%)	0	0
Fatigue	6 (38%)	1 (7%)	0	0

patient disease progressed (PD). The overall response rate was 60%. As outlined, one patient was not evaluable because of early disease progression after one cycle and five patients were not considered evaluable because treatment was discontinued for toxicity reasons before a third cisplatin course could be administered.

Discussion

In previous studies in advanced H/N cancer, cisplatin was found to be one of the most active anticancer agents. Traditionally cisplatin is applied as single agent or in combination therapy at 3-weekly intervals. In order to optimize therapy with cisplatin in advanced

H/N, studies have been performed at increased dose intensity. In previous phase I and II studies in H/N cancer and other solid tumor types, Planting *et al*. has extensively explored the concept of increased dose intensity by shortening the treatment interval to 7 days.[12–16, 22–24] The schedule was primarily developed as a short-lasting induction schedule prior to radiotherapy in locally advanced disease. In a larger phase II study, applying a dose of 80 mg/m^2/weekly × 6, the response rate in 50 evaluable patients with locally advanced disease was 50% (16% CR, 44% PR, overall 60%).[13] Dose-limiting toxicity in the phase I study was mainly bone marrow suppression, with significant leukocytopenia and thrombocytopenia. With adequate support by 5-HT$_3$ blockers in combination with dexamethasone gastrointestinal toxicity could be limited and only incidentally patients stopped treatment prematurely because of intolerable nausea or vomiting.

In an extensive pharmacologic study in patients with a variety of solid tumors, including H/N cancer, the pharmacokinetics of cisplatin were found to vary substantially between patients. In contrast, the variation within patients was limited.[17] Importantly, in this retrospective analysis, the AUC of unbound platinum in plasma was significantly correlated with the likelihood of tumor response. The correlation between platinum DNA adduct levels in WBC, expressed as AUA, was even better correlated with tumor response. DNA adduct levels in WBC (AUA) and AUC were found to be significantly correlated in that study, indicating that the level of DNA-adducts is to a large extent determined by the level of exposure of leukocytes to active cisplatin in plasma.

A second phase II study in locally advanced, recurrent or metastatic H/N cancer has been performed using a weekly dose of 70 mg/m^2 × 6.[15] This was a randomized study of cisplatin plus amifostine versus cisplatin alone. The median dose intensity turned out to be equal to the planned dose intensity of 70 mg/m^2, illustrating that such dose-dense schedules are very well feasible if adequate support is given to the patients, including 5-HT$_3$ blockers plus dexamethasone as anti-emetics and pre- and post-hydration of patients. The response rate in this second large, randomized, phase II study was relatively high. The overall response was 63% in the amifostine arm and 50% in the cisplatin-alone arm (NS).

These results were used to design the current adaptive dosing strategy to test the feasibility of this approach. The ultimate goal is to further improve the tumor response rate in patients with advanced H/N cancer. The primary parameter used to monitor exposure was the level of DNA adducts of platinum in WBC. Theoretically this parameter, although determined in a surrogate tissue, was found to be more of interest than the AUC, because DNA adducts are considered the lesion through which cisplatin exerts its cytotoxic action.[26,27] Also in several other different clinical pharmacologic studies significant relationships could be described between levels of DNA adducts of cisplatin in WBC or buccal smears and likelihood of tumor response.[28–33] The results of the feasibility study reveal that it is possible to apply intrapatient dose adjustment even when courses are given with a short treatment interval of 1 week. The sample work up, assays for unbound platinum in plasma and DNA adducts in leukocytes and pharmacokinetic calculations were ready in all patients within the time interval of 1 week. Only in one patient could adduct levels not be determined for technical reasons (inadequate sample work up resulting in too low DNA content). Prior to the execution of the study a dosing algorithm was designed allowing maximally 30% dose escalations, which was arbitrarily chosen for safety reasons.

In two patients a maximum dose increase was used during course 2 and in these two patients an additional dose increase of 10% was needed during course 3 to reach the defined target for the AUA during the subsequent courses.

In five patients treatment with cisplatin was discontinued after two courses. Two of these patients had received small increases of 10% of the starting dose and in the other three no dose adjustment during course 2 had been applied. This indicates that the adaptive dosing was not the reason for the early discontinuation of therapy. The toxicity profile was significant, but manageable, as may be expected for dose intensive cisplatin therapy. Also, in the previous phase II study with weekly cisplatin dosed at 80 mg/m^2/week significant but manageable, toxicity was reported.[13,15] The pattern and severity of the toxicity in the current study and the previous phase II study were largely comparable. Significant (temporary grade 3) ototoxicity was observed in two patients in the present study. Combined with the high percentage of patients who developed grade 2 ototoxicity, this side-effect may be a major limiting factor in dose increases of cisplatin in the weekly schedule. However, additional data of a larger cohort of patients are needed to confirm this observation. Given the present and previous results, this dosage schedule seems to be at the edge of tolerance.

The overall response rate in this small cohort of patients was 60%, which is comparable with results obtained in previous studies with the same schedule.

In these studies response rates were reported of 60–80%.[13,15]

In contrast to the previous pharmacologic study in which significant relationships could be described between exposure parameters and toxicity, in this study no such relationships became evident. This is not surprising, because a significant percentage of patients received small to large dose increases and exposure parameters during subsequent courses were influenced, thereby obscuring possible relationships between exposure and toxicity.

The magnitude of the pharmacokinetic parameters described in this study at the applied starting dose of 80 mg/m^2 (AUC, CL, renal CL and $t_{1/2}$) were of the same order as previously published by us and by others, indicating that apparently a representative patient population was investigated.[34–36] Also, the DNA adduct levels were comparable with levels previously reported.[17]

If the current strategy of intrapatient dose escalation is going to be applied at a wider scale in the future, then the study design should be simplified. The AUA may be replaced by the AUC of cisplatin, because both parameters were highly correlated as shown in the retrospective study. In the current study this is confirmed; however, in a relatively low number of patients. This relationship will also be investigated in an ongoing analysis of the same approach in patients with other solid tumor types, treated with a lower dose of cisplatin in combination with daily low dose etoposide. In addition, the number of samples for estimation of the AUC of cisplatin may be reduced. At present the data of this and other studies are being used to design a limited sampling model in order to further improve the practical application of adaptive dosing for cisplatin.

In conclusion, the strategy of intrapatient dose adjustment for cisplatin is practically feasible in a research setting even when a short-turn around time of 1 week is the limit for reporting of results. At the applied dose level of 80 mg/m^2 in H/N cancer patients 47% of the patients needed a dose increase to reach predefined exposure levels. Although in some patients the dose increase that had to be applied to reach target levels was substantial (up to 40%), this approach in H/N cancer patients is not expected to improve the response rate significantly, because these significantly underdosed patients represented only a small percentage of the investigated population. The great majority of patients needed only small (10–20%) dose increases, which very likely will not improve the response rate to a clinically significant extent. The outlined concept is currently being explored in other tumor types and schedules of cisplatin.

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(Received 25 May 2001; accepted 20 June 2001)