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ORIGINAL ARTICLE

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Nephrotoxicity of heptaplatin: a randomized comparison with cisplatin in advanced gastric cancer

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Abstract *Purpose:* Heptaplatin is a newly developed platinum derivative which has been reported to be less toxic than cisplatin. This study was designed to evaluate the nephrotoxicity of heptaplatin in comparison with that of cisplatin. *Methods:* Previously untreated advanced gastric cancer patients with normal renal function were randomly assigned into either group I (heptaplatin 400 mg/m^2 i.v. over 1 h on day 1 plus 5-fluorouracil (5-FU) 1000 mg/m^2 per day continuous i.v. from day 1 to day 5), or group II (cisplatin 60 mg/m^2 i.v. over 1 h on day 1 plus 5-FU 1000 mg/m^2 per day continuous i.v. from day 1 to day 5), with the cycles repeated every 4 weeks. Renal function parameters before, during, and after the chemotherapy were compared between the two groups. *Results:* A total of 99 patients were enrolled in the study, 51 in group I and 48 in group II. The 24-h proteinuria on day 5 was markedly increased in group I (95 ± 108 mg/day to 9098 ± 4514 mg/day, means $\pm$ SD) in comparison with the increase observed in group II (104 ± 148 mg/day to 151 ± 102 mg/day), and creatinine clearance showed a greater decrease in group I (83.1 ± 23.6 ml/min to 44.9 ± 17.3 ml/min) than in group II (89.6 ± 22.1 ml/min to 72.8 ± 21.0 ml/min). The differences in these parameters between the two groups were statistically significant throughout the subsequent cycles. *Conclusions:* Our findings show that nephrotoxicity was more severe in patients treated with heptaplatin 400 mg/m^2 than with cisplatin 60 mg/m^2 when it was combined with 5-FU. Measures to more effectively prevent nephrotoxicity should be developed for the safe use of heptaplatin.

Keywords Heptaplatin · Cisplatin · Nephrotoxicity · Proteinuria · Gastric cancer

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Introduction

Although cisplatin is one of the most potent anticancer drugs for a variety of human cancers, undesirable effects such as severe nephrotoxicity, high emetogenicity, and neurotoxicity, along with the development of drug resistance, limit its clinical usefulness [6, 18, 20, 23]. Thus, there has been a continuing effort to develop new platinum analogues with equivalent or greater antitumor activity and/or lower toxicity than cisplatin.

Heptaplatin, *cis*-malonato[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (SKI-2053R, Sunpla) is a recently developed platinum derivative. In vitro studies have shown this new analogue to have high antitumor activity against various cancer cell lines, including cisplatin-resistant cancer cell lines [10, 11, 12]. A preclinical study has also indicated that heptaplatin has a favorable toxicity profile in general pharmacological evaluation and that it might produce less nephrotoxicity than cisplatin [16]. In a phase I clinical trial all three patients who received a dose of 480 mg/m^2 heptaplatin developed severe nephrotoxicity (grade 2 azotemia and proteinuria), and the maximal tolerated dose was determined to be 480 mg/m^2 [15]. A phase II study also demonstrated that this agent is active in the treatment of patients with advance gastric cancer (AGC) and has a favorable toxicity profile [14]. In that

study, the most common nonhematological toxicity was proteinuria (grade 1 or 2) seen in 80% of patients, but it was concluded that the proteinuria was mild and reversible.

However, after widespread use of heptaplatin, a few cases of severe proteinuria and/or acute renal failure have been identified, and the necessity for accurate evaluation of the nephrotoxicity of heptaplatin has become apparent. To our knowledge, despite the indication of its low nephrotoxicity in several in vitro and in vivo studies, there have been no clinical trials in which the nephrotoxicity of heptaplatin has been directly compared with that of cisplatin. This study was designed to evaluate the nephrotoxicity of heptaplatin in comparison with that of cisplatin in patients with previously untreated AGC.

Materials and methods

Patient selection

All patients were required to have a histological diagnosis of gastric adenocarcinoma. Prior surgical treatment, such as gastrectomy, was allowed, if it had been performed at least 3 weeks before enrollment in this study, but no prior chemotherapy, immunotherapy, or radiotherapy was allowed. The eligibility criteria were as follows: age $\leq$ 75 years; performance status (PS) $\leq$ 2 according to Eastern Cooperative Oncology Group (ECOG) criteria; adequate hematological function with a white blood cell count of $\geq$4000/mm^3 and a platelet count of $\geq$100,000/mm^3, adequate renal function demonstrated by serum creatinine concentrations $\leq$ 1.5 mg/dl or a creatinine clearance of $\geq$60 ml/min, and adequate hepatic function with serum bilirubin levels $<$2 mg/dl and transaminase levels less than twice the upper normal value. Patients with uncontrolled infections, medical instability, pregnancy, or cerebral metastasis were excluded from the study. Written informed consent was obtained from all patients, and the study was approved by the Institutional Review Board of Asan Medical Center.

Treatment plan

All patients eligible for this study were randomly assigned to receive either heptaplatin plus 5-FU (group I) or cisplatin plus 5-FU (group II). Randomization was performed using a blocked randomization technique in sealed envelopes, stratifying patients by age and ECOG performance status. Patients in group I received heptaplatin 400 mg/m^2, which was diluted with 500 ml 0.9% normal saline, by intravenous infusion over 1 h on day 1 and 5-FU 1000 mg/m^2 per day by continuous infusion using an infusion pump on day 1 to day 5. Patients in group II received cisplatin 60 mg/m^2 on day 1 and 5-FU 1000 mg/m^2 per day on day 1 to day 5 using the same administration schedule as in group I. A uniform hydration procedure was followed for the prevention of nephrotoxicity in both groups. Prehydration with 1.5 l isotonic saline mixed with 20 mEq KCl and 8 mEq $MgSO_4$ was infused prior to the administration of heptaplatin or cisplatin, and an additional 1.5 l was given after administration. On days 2 to 5, at least 1 l of isotonic saline was administered in both groups. The therapeutic cycles were repeated every 4 weeks.

To prevent acute emesis associated with heptaplatin or cisplatin, 8 mg ondansetron was given by intravenous injection twice on the first day, and intravenous dexamethasone with or without metoclopramide was used to control delayed emesis in all patients. None of the patients received other drugs known to be nephrotoxic during or after chemotherapy. Treatment was stopped if disease progression such as the development of a new lesions or obvious aggravation of evaluable disease was observed, if unacceptable toxicities such as persistent nonhematological toxicity of greater than grade III occurred, or if the patient refused further treatment. Otherwise, all patients were scheduled to receive a maximum of six cycles of chemotherapy and they were followed up until progression of disease was observed.

Evaluation of nephrotoxicity and dose modification

Routine pretreatment evaluation included physical examination, complete blood cell count, serum chemistries, electrolyte analysis and urinalysis with microscopy. Baseline renal function including serum creatinine, 24-h urinary protein, and creatinine clearance were measured before the start of the first cycle of chemotherapy. A colorimetric method using a pyrogallol-red molybdate complex (Hoffmann-La Roche, Basel, Switzerland) was used to determine 24-h urinary protein levels. Follow-up measurements of these three parameters were performed on days 2 and 5 of the first cycle to evaluate acute nephrotoxicity, and before the start of each new cycle to evaluate cumulative renal toxicity. Because the contrast dye used in imaging studies may be measured as a proteinuria if it is excreted during urine collection, any imaging study using contrast dye was planned for at least 5 days before the urine collection [22].

Toxicity was graded according to the National Cancer Institute (NCI) common toxicity criteria (http//ctep.info.nih.gov/CTC3/ctc.htm). Chemotherapy was delayed until recovery if the white blood cell count decreased to less than 3000/mm^3, platelets decreased to less than 75,000/mm^3, or in cases of significant nonhematological toxicity. In cases of grade I neutropenia or thrombocytopenia, the dose of 5-FU was reduced by 25%. The dose of heptaplatin or cisplatin was modified according to the serum creatinine measured just before the new cycle. The dose was reduced by 50% if serum creatinine was between 1.6 and 2.5 mg/dl, and chemotherapy was stopped if serum creatinine was still greater than 2.5 mg/dl after a delay of 1 week.

Statistical analysis

The results are shown as means $\pm$ SD. The chi-square test and two-sample *t*-test were used for comparing the categorical and continuous variables between the two groups, respectively. Logarithmic transformation was used for the statistical analysis of 24-h proteinuria. Changes over time of the three renal function parameters within each group and between the two groups were compared with mixed linear models, and a family-wise multiple comparison was performed using Bonferroni's correction method. Statistical significance was defined as *P*-values less than 0.05. Statistical analysis was done using SAS (version 6.12) software.

Results

Patient characteristics

Patient characteristics are shown in Table 1. Between April 2000 and March 2001, a total of 99 patients were enrolled in this study, 51 patients in group I and 48 patients in group II. The median age of the patients was 53 years in both groups. About two-thirds of all patients had undergone gastric resection and were diagnosed as stage IV including tumor invading adjacent structures or metastasis in more than 15 regional lymph nodes. The other patients had locoregionally advanced disease or peritoneal seeding and ascites which were not measurable (defined as at least one diameter of more than 2 cm on clinical examination, chest radiography or conven-

Table 1. Patient characteristics and baseline renal function. Group I received heptaplatin plus 5-FU; group II received cisplatin plus 5-FU

	Group I ($n=51$)	Group II ($n=48$)
Sex		
Male	29 (56.9%)	33 (68.8%)
Female	22 (43.1%)	15 (31.2%)
Age (years)		
Median	53	53
Range	27–72	25–69
Performance status (ECOG)		
0	6 (11.8%)	2 (4.2%)
1	42 (82.4%)	43 (89.5%)
2	3 (5.8%)	3 (6.3%)
Gastric resection		
No	17 (33.3%)	15 (31.3%)
Yes	34 (66.7%)	33 (68.7%)
Number of chemotherapy cycles		
Median	4	4
Range	1–6	1–8
Three or more cycles	34 patients	35 patients
Six or more cycles	21 patients	27 patients
Total cycles	204	216
Baseline renal function (mean ± SD)		
24-h proteinuria (mg/day)	95 ± 108	104 ± 148
Serum creatinine (mg/dl)	0.79 ± 0.2	0.85 ± 0.2
Creatinine clearance (ml/min)	84.3 ± 24.0	83.0 ± 19.1

tional computed tomography scan) but evaluable disease. There was no significant difference in baseline values of 24-h proteinuria, serum creatinine and creatinine clearance between the two groups.

The median number of administered chemotherapy cycles was four per patient in group I (range one to six) and group II (range one to eight). A total of 204 cycles were administered in group I, and 216 in group II. In group I 34 patients and in group II 35 patients completed at least three cycles, but only 21 patients in group I and 27 patients in group II were able to complete the planned six cycles of chemotherapy. Thus, 51 patients could not complete the planned six cycles, 30 in group I, and 21 in group II. The reasons were as follows: in group I 11 refused further treatment, 9 suffered disease progression, 5 were lost to follow-up, 4 had chemotherapy-induced toxicity, including 3 with grade III nausea and vomiting and 1 with renal impairment, and there was 1 early death; in group II 9 suffered disease progression, 7 refused further treatment, and 5 were lost to follow-up.

Acute nephrotoxicity

Interim analyses showed that serum creatinine and 24-h proteinuria on day 5 of the first cycle were consistently higher than on day 2, and the same results were also obtained during the second cycle (Table 2). Therefore, we decided not to continue with the day-2 measurements from the 35th patient. On day 5 of the first cycle, serum creatinine and 24-h proteinuria had increased, and creatinine clearance had decreased in both groups. However, as shown in Fig. 1, patients in group I had significantly greater degrees of 24-h proteinuria and renal dysfunction than those in group II ($P<0.05$). In particular, the 24-h proteinuria, which was 95 ± 108 mg/day in group I and 104 ± 148 mg/day in group II, showed a more marked increase in group I than in group II (group I, 9098 ± 4514 mg/day; group II, 151 ± 102 mg/day; $P<0.0001$). According to the NCI toxicity criteria, proteinuria occurred in all 51 patients in group I, including 18 patients (35.6%) with grade 3 and 25 patients (48.9%) with grade 4 toxicity. Grade 1 proteinuria occurred in only 14 patients (30.2%) in group II. Urinary protein electrophoresis was performed in one patient in group I, and the proteinuria was shown to be mainly tubular in origin.

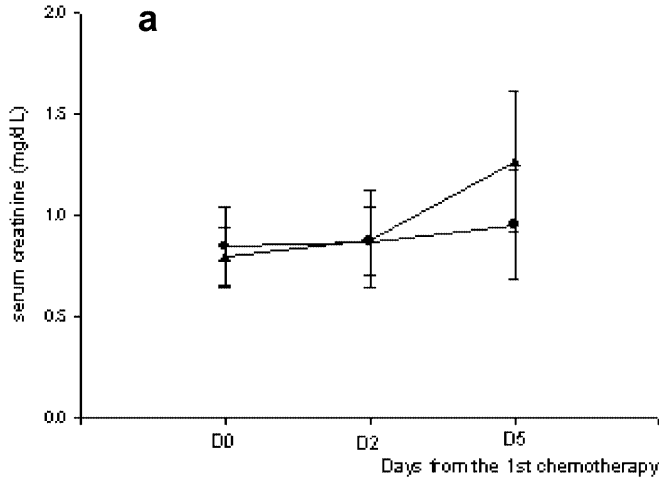
Table 2. Interim analysis during the first cycle in the first 34 patients. The differences between group I and group II on day 2 and day 5, and between day 2 and day 5 within each group were significant ($P<0.05$)

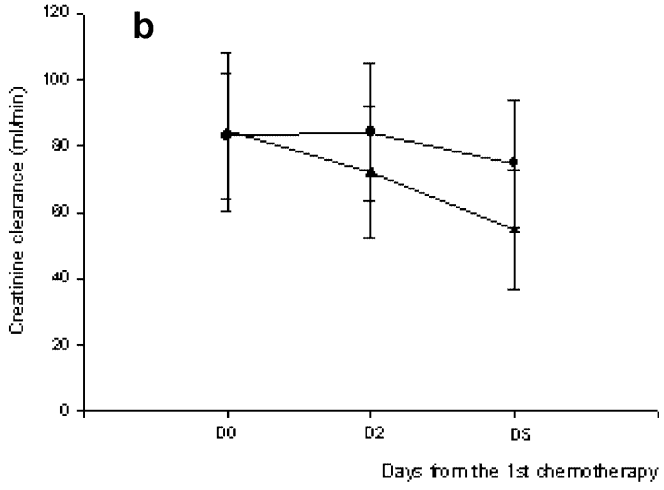
	Baseline	Day 2	Day 5
24-h proteinuria (mg/day)			
Group I ($n=19$)	122 ± 167	1710 ± 2990	8019 ± 4691
Group II ($n=15$)	82 ± 17	92 ± 24	114 ± 43
Serum creatinine (mg/dl)			
Group I ($n=19$)	0.80 ± 0.2	0.88 ± 0.2	1.3 ± 0.4
Group II ($n=15$)	0.88 ± 0.1	0.88 ± 0.2	0.96 ± 0.2
Creatinine clearance (ml/min)			
Group I ($n=19$)	80.8 ± 25.0	72.0 ± 19.6	50.0 ± 16.5
Group II ($n=15$)	85.4 ± 19.5	86.6 ± 20.4	78.2 ± 16.2

Creatinine clearance, which was 83.1 ± 23.6 ml/min in group I and 89.6 ± 22.1 ml/min in group II, was lower in group I than in group II (group I, 44.9 ± 17.3 ml/min; group II, 72.8 ± 21.0 ml/min). Transient azotemia, with elevation of serum creatinine to above normal limits (> 1.5 mg/dl), occurred in 15 patients (32%) in group I, but in only two patients (4.2%) in group II. In two patients in group I, serum creatinine levels were above 4.0 mg/dl after 7 days of heptaplatin administration. Although serum creatinine levels were decreased after 1 month, one patient refused further chemotherapy because he felt it too hard to tolerate, and the other delayed the next round of chemotherapy and required a 50% dose reduction. At the time of this report, no patient in group II had developed more than grade I azotemia.

Cumulative nephrotoxicity

Acute nephrotoxicity, noted on day 5 of the first cycle, improved to nearly normal after 3 weeks in most of the patients in both groups. However, statistically significant differences were noted only in group I when the renal function results during each cycle were compared with the pretreatment results. In patients who completed all six cycles, 24-h proteinuria (341 ± 251 mg/day vs 98 ± 58 mg/day) and serum creatinine (1.12 ± 0.2 mg/dl





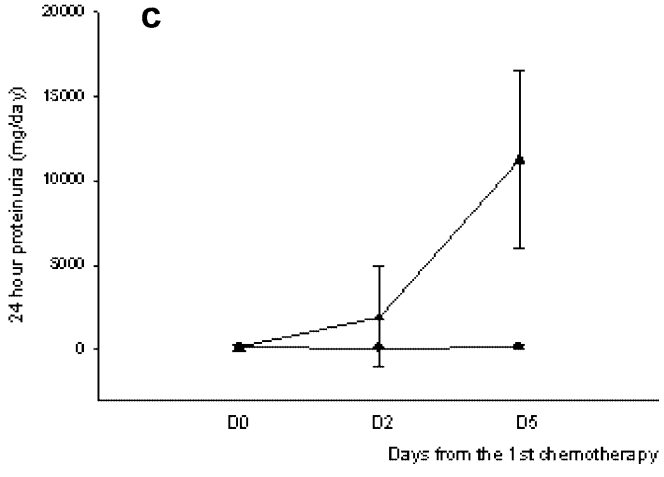
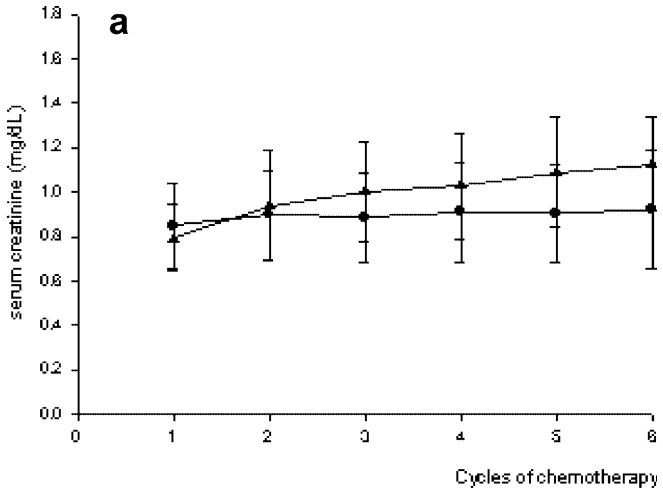
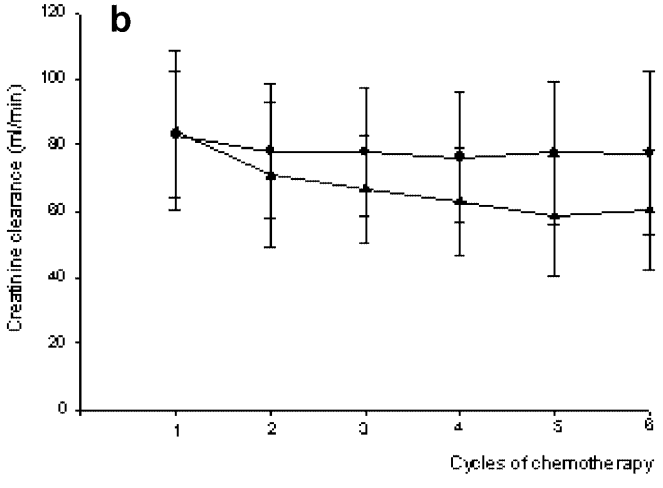


Fig. 1A–C. Acute nephrotoxicity between group I (*triangles*; heptaplatin plus 5-FU) and group II (*circles*; cisplatin plus 5-FU) during the first chemotherapy ($P < 0.05$). Serum creatinine (**A**), creatinine clearance (**B**) and 24-h proteinuria (**C**) were used as renal function parameters. The data are presented as means ± SD





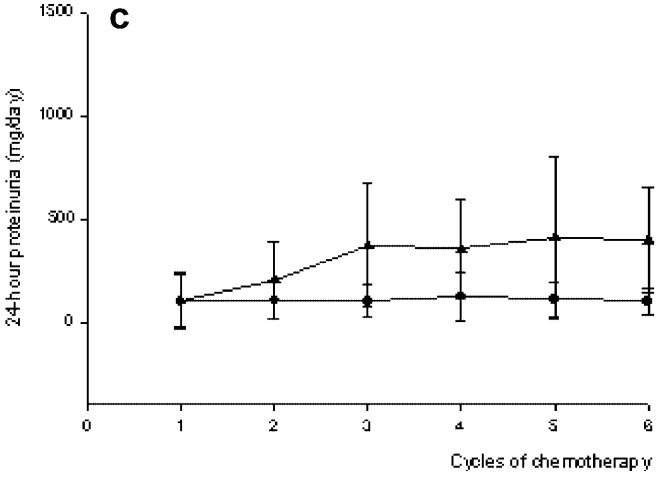


Fig. 2A–C. Cumulative nephrotoxicity between group I (*triangles*; heptaplatin plus 5-FU) and group II (*circles*; cisplatin plus 5-FU) during the six cycles of chemotherapy ($P < 0.05$). The renal function parameters serum creatinine (**A**), creatinine clearance (**B**) and 24-h proteinuria (**C**) were measured before the start of each new cycle

vs 0.93 ± 0.2 mg/dl) were all higher in group I than in group II. Creatinine clearance was also lower in group I than in group II (60 ± 18 ml/min vs 77 ± 24 ml/min). Figure 2 shows that differences in these three renal function parameters between the two groups continued to be significant through the subsequent cycles.

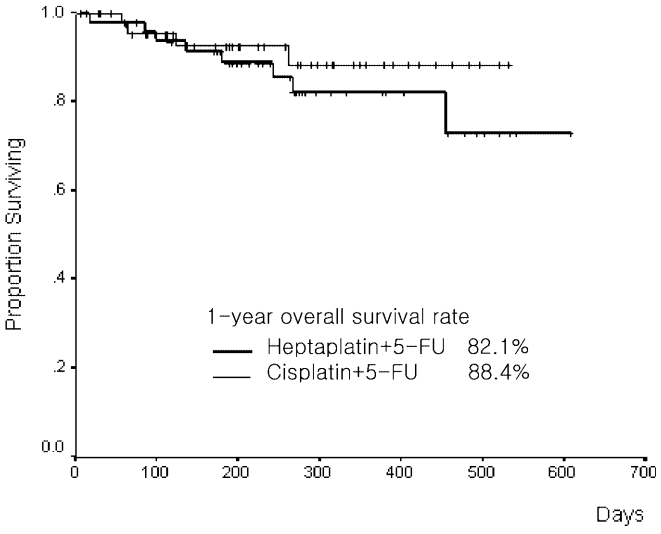


Fig. 3. Overall survival

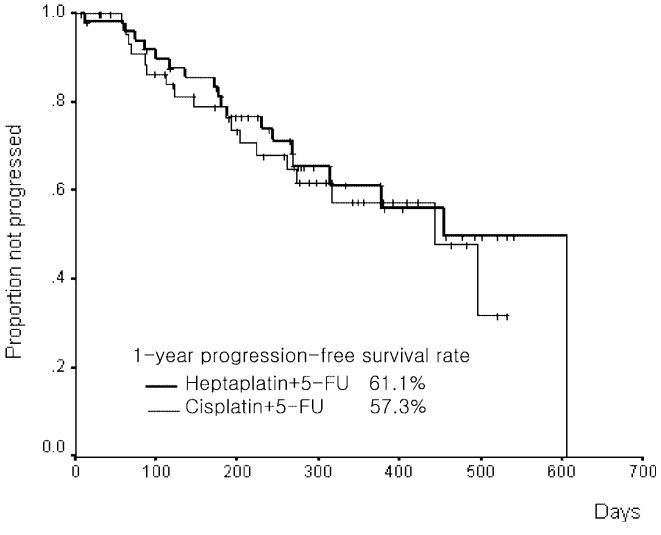


Fig. 4. Progression-free survival

Survival

Median progression-free survival was 14.6 months in group I and 14.2 months in group II. There was no significant differences in 1-year progression-free survival rate (61.1% vs 57.3%) and in 1-year overall survival rate (82.1% vs 88.4%) between the two groups (Figs. 3 and 4).

Discussion

This study showed that heptaplatin 400 mg/m^2 was more nephrotoxic than cisplatin 60 mg/m^2 in terms of azotemia and proteinuria. This result is not consistent with previous reports. Previous preclinical and clinical studies of heptaplatin have suggested that it has no marked toxicities in general pharmacological evaluation and has lower nephrotoxicity than cisplatin, even though mild and transient proteinuria is frequently observed [14, 15, 16]. However, our experience of severe proteinuria in many patients on heptaplatin led us to investigate its nephrotoxicity more accurately. To our knowledge, this is the first study in which the nephrotoxicities of heptaplatin and cisplatin have been directly and quantitatively compared.

The nephrotoxicity of cisplatin has been well studied, and has been shown to be dose-related in both animals and humans [1, 19]. Acute and cumulative renal toxicities associated with histological changes, including tubular necrosis, dilatation of the tubules, and cast formation, have been shown in kidneys from patients treated with cisplatin [7, 24]. However, in general, simple hydration provides adequate protection against nephrotoxicity of cisplatin at doses up to 100 mg/m^2 per cycle. Although hyperosmolar mannitol was routinely used in a phase I/II study of heptaplatin, its role as a nephrotoxicity-modulating agent is still not clear except in experimental high-dose cisplatin therapy [2, 3]. So patients of both groups were treated with a uniform hydration procedure of at least 3500 ml/day with the heptaplatin or cisplatin infusion.

In this study, severe proteinuria on day 5 of the first cycle was the most prominent feature in patients treated with heptaplatin. We adjusted the amount of 24-h urinary protein excretion in terms of the urinary creatinine excreted to correct for the adequacy of urine collection, and found the same result of severe proteinuria (data not shown). All three patients in a recent phase I study who received a dose of 480 mg/m^2 heptaplatin developed severe nephrotoxicity (grade 2 azotemia and proteinuria), with one patient developing a Fanconi-like syndrome with glucosuria and severe tubular damage [15]. In a phase II study, the most frequent toxicity was grade 1 or 2 proteinuria, but the investigators suggested that it was mild and transient [14]. However, they used a urine stick test, which detected mainly albuminuria, and failed to measure 24-h proteinuria on day 5 of chemotherapy for the evaluation of the degree of proteinuria. Hence, proteinuria may have been underestimated in their study. Goren et al. [8] stated that proteinuria after cisplatin treatment increases because low molecular mass plasma proteins are less efficiently reabsorbed by dysfunctional cells and protein exudes from the denuded tubular epithelium. They suggested that the degree of urinary excretion of proteins and enzymes may indicate the degree of renal damage and, especially, of proximal tubular dysfunction. We also suspect that the markedly increased proteinuria observed on day 5 of the first cycle in patients treated with heptaplatin might have originated mostly from tubular injury, based on the findings from urinary protein electrophoresis that demonstrated a tubular origin.

On day 5 of the first cycle, serum creatinine showed a greater elevation and creatinine clearance a greater decrease in patients treated with heptaplatin than in those

treated with cisplatin. Theoretically, the reason for this difference, measured on day 5 of the first cycle, might be explained by the difference in the emetogenicity and the consequent volume status between the two groups. However, even though three patients treated with heptaplatin refused further chemotherapy because of severe nausea and vomiting, emetogenicity was generally mild and no statistically significant difference was noted between the two groups. In addition, because continuous hydration of more than 1 l of isotonic saline was infused daily during the 5 days of chemotherapy, and 24-h urine output was equal in both groups, it is unlikely that a difference in volume status accounted for this difference. We rather believe that acute tubular damage is more likely to have caused the difference in the serum creatinine levels. We found a slowly progressive elevation in serum creatinine, and a reduction in creatinine clearance during only heptaplatin treatment. The important clinical question that was not addressed in this study was whether those patients who demonstrate a sudden increase in proteinuria and elevation in serum creatinine after heptaplatin therapy eventually develop significant long-term renal damage. However, repeated severe proteinuria is known to be a highly sensitive indicator of renal tubular damage, and one of the causes of renal deterioration is now believed to be the tubulotoxic effects of proteinuria itself [4, 5, 9].

Heptaplatin is a recently developed platinum derivative designed to overcome the drawbacks of cisplatin, mainly nephrotoxicity. In general, for any newly developed chemotherapeutic agent to be an attractive alternative to an established agent, the new analogue needs to have an advantage in terms of toxicity and/or efficacy. We monitored both hematological and nonhematological toxicities after each cycle. There was no difference in the degree of myelosuppression or in the degree of nausea/vomiting, ototoxicity, or neurotoxicity (data not shown) between the two groups in our study. Hepatotoxicity which was one of the dose-limiting toxicities in patients treated with heptaplatin in the phase I study [13], was mild, and there was no difference between the two groups (grade I, 14.0% vs 12.5%). Nephrotoxicity, however, was shown to be greater in patients treated with heptaplatin than in those treated with cisplatin, although the long-term toxicity results are not yet fully evaluated.

Because this study did not focus on efficacy but on toxicity profiles and most of the patients did not have measurable disease, efficacy is hard to compare between the two groups. However, we were able to determine disease progression if new lesions developed or obvious aggravation of evaluable disease was noted. We were not able to detect any difference in 1-year survival rates or 1-year progression-free survival rates between the two groups. However, the results of this study do not allow a definite conclusion on the difference in efficacy between the two drugs to be drawn. A phase III study comparing treatment efficacy between heptaplatin and cisplatin is now underway.

In a literature review we found another example of a cisplatin analogue that showed a more favorable toxicity profile in early clinical development but proved to be more nephrotoxic than cisplatin in later clinical studies. In animal studies, spiroplatin [TNO-6; 1,1-diaminomethylcyclohexane sulphatoplatinum(II)] showed less nephrotoxicity than cisplatin at therapeutic doses [17]. However, in clinical studies in the late 1980s and early 1990s, spiroplatin-induced nephrotoxicity was recognized as serious and dose-limiting [21, 25, 26]. Spiroplatin's nephrotoxicity was mainly massive proteinuria which was maximal on day 5 and mostly recovered before the next cycle, as in our study. Azotemia was less common and mostly transient, but a few cases of overt renal failure were reported [21, 25, 26]. Based on the low antitumor activity and unpredictable occurrence of acute renal failure, this drug has been withdrawn from further clinical testing [25, 26].

A recent preclinical study has demonstrated that exposure to low concentrations of heptaplatin for 24 h produces a greater kill of cancer cells than a 1-h or a 4-h exposure [13]. That study also suggested that severe glomerular and tubular damage by heptaplatin may be caused by high peak plasma concentrations at the higher dose level. In case of spiroplatin, it was reported that the prolongation of infusion could diminish the degree of proteinuria [25]. On the basis of this observation, a phase I study of heptaplatin given by continuous 24-h infusion is currently being conducted in Korea. We hope that the results of this ongoing phase I study will indicate whether this modification of the administration schedule will reduce the nephrotoxicity of heptaplatin.

In conclusion, our data showed that nephrotoxicity was more severe in patients treated with heptaplatin 400 mg/m^2 than in those treated with cisplatin 60 mg/m^2 when it was combined with 5-FU. Further efforts to detect and minimize the nephrotoxicity of heptaplatin seem to be warranted.

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