DISCUSSION

Cisplatin is one of the most effective agents available for treating a variety of carcinomas. However, its dose-related and cumulative nephrotoxicity is a common clinical complication that limits its usefulness. Previous studies of its nephrotoxic effects on the morphology and physiology of the kidney have demonstrated that the renal tubule system is the site of maximal damage, especially the proximal tubule. Based on the laboratory data, increasing in urinary NAG activities which exist maximally in the lysosomal fraction of the proximal tubular cells correlates with cisplatin-induced nephrotoxicity. The nephroprotetive effects of fosfomycin on cisplatin-induced nephrotoxicity have been widely demonstrated. However, the nephroprotective effects of 4 gm dose of fosfomycin given just few hours before high doses of cisplatin have never been reported. Therefore, we conducted the study to determine the protective effect of fosfomycin given as 2 gm twice daily, started in concurrent with single high dose/cycle of 100-mg/m^2 cisplatin and continued for 5 days in NSCLC cisplatin naïve patients. Urinary excretion of the lysosomal enzyme of which the NAG activity was measured as a specific indicator of tubular cell damage as in other studies. NAG is renal tubule specific enzyme and is a valid indicator of tubular cell damage and the measurement of urine NAG activity can be employed to detect in early stage of nephrotoxicity. Nevertheless, the errors of urine NAG evaluation are due to factor of circadian variation, renal hydration and incompleteness of individual urine collection. To prevent falsification in urine NAG measurement

due to these errors, NAG activities were determined in the pooled urine of each patient and set in relation to urine creatinine [94]. Therefore, NAG activities in this study were presented in unit/gram creatinine. Our results contrasted with previous studies that reported the protective effects of fosfomycin on cisplatin nephrotoxicity by inhibiting the rising of urinary NAG activities. The reasons may be due to differences in dosages of cisplatin and fosfomycin. In this study, a single high dose of 100 mg/m^2 cisplatin per cycle was given as a treatment schedule. This dose was approximately double the doses of cisplatin used in previous studies (20-70 mg/m^2). The dose of fosfomycin (4 gm per day) in this study was minimal dose to those studies (4-8 gm per day), however, time and duration of drug administrations were different. In our study, the first dose of fosfomycin was given within 2-3 hours before cisplatin while Hayashi and Yogi [44] gave fosfomycin 2 days prior to cisplatin. Nevertheless, in this study fosfomycin did not fully protect the elevation of NAG levels, but significantly reduced the increasing of NAG levels in terms of severity and duration. Therefore, higher dose of fosfomycin prior to high dose cisplatin administration may be a better alternative. Fosfomycin given few days before cisplatin may result in a better induction of competitive inhibition of cisplatin excretion and decreasing the nephrotoxic effect. In addition, higher doses of fosfomycin should be titrated when dealing with high dose cisplatin therapy and clinical trials on these approaches are warranted.

Another possibility of the discrepancy may be the different statistic method of data analysis. Our method of analysis was a non-

parametric Mann-Whitney test since our raw data was not normally distributed. Contradictory, the method of data analysis used in previous report was *t*-test. Theoretically since our data was not normally distributed, the use of *t*-test in our study would lead to a wrong conclusion.

Since no significant changes in CL_{cr} and Scr from baseline (Day 0) after cisplatin therapy or cisplatin in combination with fosfomycin, these results suggest that cisplatin-nephrotoxicity may not be associated with glomerular damage. Moreover, our study was conducted in cisplatin naïve patients with prior normal renal function who developed nephrotoxicity after both cisplatin regimen but the toxicity was mild and reversible since the NAG activities soon returned toward normal on Day 6. A long wash out period of 28 days between each cycle also minimized the risk of loss of kidney function in the present study. Nevertheless, although CL_{cr} is considered a useful index of glomerular filtration rate, it is not a sensitive measure of early renal impairment. Moreover, since creatinine production is related to muscle mass and our cancer patients were marantic, the CL_{cr} may be a misleading indicator.