INTRODUCTION

Cisplatin is a chemotherapeutic agents used in the treatment of various solid tumors including lung cancer [1]. It is the most important compound on the basis of combination chemotherapy with a great impact on improving patient's survival, especially in patients with advanced non-small cell lung cancer (NSCLC) [2,3].

Although cisplatin has shown a high anticancer activity, its application in large dosage is limited by several toxic effects including nephrotoxicity, ototoxicity, and neurotoxicity [2,4]. In a single dose per cycle schedule, the dose related toxicity is primarily nephrotoxicity, which is related to peak plasma levels and cumulative dose of cisplatin [5-7]. Nephrotoxicity is a common clinical problem and has been noted in 28% to 36% of patients treated with a single dose of 50 mg/m^2 . The renal damage usually become evident during the second week after the dose and increase in severity with repeated courses of the drug [1]. Since these nephrotoxic effects are clearly dose-related and cumulative, most patients never regain their pretreatment level of renal function. To alleviate renal impairment, adequate saline hydration and intravenous mannitol diuresis are indicated in concurrent with high dose cisplatin administration [1]. However, renal dysfunction still occurs and remains a common cause of morbidity after cisplatin therapy [8-14]. Cisplatin-induced nephrotoxicity may manifest as acute or chronic renal failure, polyuria and chronic hypomagnesemia [15-18]. In addition to renal magnesium wasting, hypercalciuria, hypocalcemia and

hypophosphatemia may develop and may be severe to provoke tetany in some patients [19-22]. A tendency to develop hypokalemia, hyponatremia and metabolic alkalosis has also been reported [20,23-27]. These serum electrolyte disturbances associated with impaired renal function are primarily due to tubular damage caused by cisplatin [24,26,28]. The vulnerability of the kidney to cisplatin is related to its primary role in the excretion of the drug [1]. During renal elimination, greater accumulation of intracellular platinum to the proximal tubules is evident and suggest that renal tubular cell is a vulnerable site [28,29]. The majority of intracellular platinum is bound to macromolecules including protein and DNA due to its high affinity to bind the sulfhydryl groups of various enzymes. Consequently it may induce changes in cytochrome P450, lipid peroxidation and drug metabolizing enzyme activities in the kidney [30]. Evidence of renal tubular injury such as detection of renal tubular epithelial cells or tubular cell casts in the urine sediment examination have been observed [31]. The tubular damages result in enzymuria, proteinuria, tubular salt wasting and polyuria follow by a decrease in glomerular filtration [32,33].

Since cisplatin has been implicated in renal tubular toxicity and in causing renal enzymuria, early diagnosis of its nephrotoxicity include sensitive assays for elevated tubular enzymes, such as N-acetyl-β-D-glucosaminidase (NAG), alanine aminopeptidase (AAP), β-galactosidase (βGAL) and leucine aminopeptidase (LAP) [34,35] can serve as sensitive biomarkers for cisplatin-induced nephrotoxicity. Serum creatinine (Scr) and/or creatinine clearance (CL_{cr}) which

measured the glomerular filtration rate (GFR) are not a sensitive marker during early renal dysfunction caused by cisplatin [35-37]. Although a large number of enzymes are excreted in urine, urinary NAG has emerged as the enzyme of choice for assessment and monitoring of cisplatin-induced nephrotoxicity [35-39]. The reason may be due to the stability of the enzyme in urine and the availability of rapid assay procedures which are non-invasive techniques in a clinical setting [39]. After damage of the tubular cells, the NAG is released in increased amounts into the urine. It is recognized as an early index of tubular damage since not all patients with increased enzymuria have clinically apparent nephrotoxicity. Other conditions causing increase in urinary NAG activity include diabetic nephropathy, rheumatic diseases, nonsteroidal antiinflammatory drugs (NSAIDs) therapy, nephrotic syndrome, renal hypertension, glomerulonephritis, tubulointerstitial disease, urinary tract infection, and acute renal failure [39-42]. NAG is found predominantly in the lysosomal and cytoplasmic fractions of the proximal tubules of the kidney. Each dose of cisplatin induces proximal tubular damage and a transient increase in NAG excretion, followed by proteinuria [43]. The mean peak NAG excretion approaches 2-3 times higher than the pretreatment level on day 3 and 4 and tends to decline thereafter [44]. Transient enzymuria after the last cisplatin dose is significantly greater than that of the first dose [11-13]. This cumulative harmful effect produces persistent increase in urinary NAG and Scr which indicates chronic renal damage.

Methods such as aggressive hydration with diuresis and avoidance of other nephrotoxic agents are routinely used to prevent cisplatin-induced nephrotoxicity. However, these methods are partially protective and irreversible deterioration of renal function will become evident [45,46]. A variety of agents have been investigated in order to ameliorate cisplatin-related nephrotoxicity, however, fosfomycin is the most promising agent which is available and less expensive. Previous clinical studies have shown successful protective effects of fosfomycin on cisplatin-induced nephrotoxicity in cancer patients [44,47,48]. The protective effect is demonstrated by a decline in urinary NAG levels. Moreover, fosfomycin does not interfere with antitumor activity of platinol base on clinical studies and the cell line assay [49,50]. In addition the drug has been shown effective in inhibiting aminoglycoside-induced nephrotoxicity in animals and humans. The mechanism underlying the protective effect of fosfomycin on renal dysfunction is unknown. However, prevention rather than reversal of cellular damage is likely. In an aminoglycoside nephrotoxicity model, fosfomycin prevents renal lysosomal accumulation of aminoglycosides when co-administered, but not following aminoglycoside administration [51,52]. This observation suggests a competitive inhibition effect of fosfomycin against aminoglycoside-induced nephrotoxicity.

Fosfomycin (1, 2-epoxypropylphosphonic acid) is a phosphonic acid antibiotic that inhibits phosphoenolpyruvate transferase which is involved in the early steps of bacterial cell wall synthesis [53,54]. Approximately 90% of fosfomycin is rapidly

excreted by glomerular filtration within 24 hours after administration [55]. Conversely, the urinary excretion of cisplatin in cancer patients is proved to be very slow [1]. The first 24-hour urine excretion rate for cisplatin is 10-40% and the excretion rate during the first 5 days is 35-51%. Nevertheless, the mean renal clearance of cisplatin and free platinum exceed that of glomerular filtration rate and creatinine clearance indicating that the drug is actively secreted by the kidney [1]. Similar to cisplatin, fosfomycin is actively secreted by the renal tubule. The mean serum half-lives of both drugs (approximately 1-2 hours) are also similar. These might presume protective effect of fosfomycin by competitive inhibition of cisplatin secretion and limitation of progressive platinum accumulation in the kidney after concurrent administrations. However, the extract mechanism of nephroprotective action against cisplatin remains unknown.

Even though beneficial effects of fosfomycin on cisplatin-induced nephrotoxicity have been reported, its role as an adjunctive protective agent is still debated. In addition, prior studies of the nephroprotective effects has been conducted in a small number of patients and in patients who previously exposed to various doses of cisplatin, further study on higher doses in large number of patients who are chemonaive is required. Therefore, the goal of this study was to assess the nephroprotective effects of fosfomycin in patients with non-small cell lung cancer who were due to receive high dose of cisplatin according to our present chemotherapeutic schedules.