LITERATURE REVIEW

Lung cancer is a common malignant cancer in northern Thailand. The risk factors involved in the etiology of the disease include tobacco smoking (cigarette and local tobacco Khiyo) as well as chronic respiratory disease caused by the infection of fungi such as *Microsporum canis* [56]. Histological variations in lung cancer have been recognized. The WHO classification distinguishes four major cell types; squamous cell carcinoma, adenocarcinoma, large cell and small cell carcinoma [57]. However, since small cell lung cancer is highly sensitive to chemotherapy and radiotherapy, lung cancer are usually reclassified into 2 groups; small cell and non-small cell lung cancer (NSCLC). Squamous cell carcinoma, one of the NSCLC is the most frequent cell type found in patients with lung cancer in the north. As mention earlier, the reason may be related to tobacco smoking that predisposed to the development of squamous cell malignant change. NSCLC is commonly diagnosed from symptoms related to primary tumor or its metastastic lesions. Some patients may be diagnosed from an incidental finding on chest radiograph, or rarely from paraneoplastic syndromes such as hypercalcemia and hypertrophic pulmonary osteoarthropathy. The definite diagnosis is usually established by pathological finding from fiberoptic bronchoscopy, percutaneous fine-needle aspiration, biopsy of a regional or distant metastatic lesions, or thoracotomy. Staging must be made for appropriate treatment plan [58]. Stages I and II NSCLC, which are confined within the pleural

reflection, are managed by surgical resection whenever possible, with approximately 5-year survival of 45% and 25%, respectively. Patients with stage IIIa cancers, in which the primary tumor has extended through the pleura or metastasized to ipsilateral or subcarinal lymph nodes, can occasionally be surgically resected but are often managed with definitive thoracic irradiation and have 5-year survival of approximately 15% [59,60]. For the remaining non-operable patients (about 80% of cases) denote as advanced NSCLC (stage IIIb and IV), radiotherapy has limited evidence of the survival benefit, therefore, chemotherapy is used primarily to palliate disease symptoms [59,61,62]. Nevertheless, the use of chemotherapy requires careful judgment to balance potential benefits and toxicity. The response rate of NSCLC to single agent; cisplatin, vinblastine, ifosfamide, and mitomycin-C range from 5-20%. Cisplatin is generally considered the most active agent, therefore, this drug is often used in combination with vinblastine or etoposide [61-63].

CISPLATIN

Physicochemical Properties

Cisplatin (cis-dichlorodiammine platinum, cis-DDP), is an inorganic platinum complex surrounded by two ammonia molecules and two chloride leaving atoms in the cis-position. The molecular formula of cisplatin is $Pt(NH_3)_2Cl_2$ with a molecular weight of 300.1. It is a

white lyophilized powder, soluble in water or saline at 1 mg/mL, and has melting point at 207° C [1].

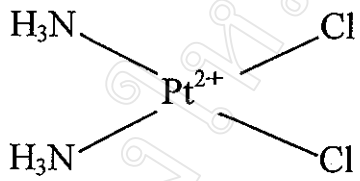

Figure 1 Structure of cisplatin.

Pharmacological Properties

The major target of cisplatin cytotoxic effect is DNA. Cisplatin pharmacological behavior is determined largely by an initial aquation reaction in which the chloride groups are replaced by water molecules. High concentration of water and low concentration of chloride in the tissues activate cisplatin aquation reaction to produce reactive electrophile molecules that can covalently bind to a variety of macromolecules including DNA. Cisplatin binds to RNA more extensively than to DNA and to DNA more extensively than to protein [64].

Cisplatin seems to bind preferentially to the N-7 position of guanine and adenine of intact DNA [65]. This may due be to the high nucleophilicity at this position. The predoninant lesions that occur in the reaction of cisplatin with DNA *in vitro* or in cultured cells are the d(GpG)Pt, d(ApG)Pt, and d(GpNpG)Pt intrastand cross-links

approximately 60%, 15%, and 20% [66], respectively. The reaction of monoadducts and $d(G)_2$ interstand cross-links occur less than 5%. The specificity of cisplatin with regard to the phases of cell cycle appears to differ among cell types, however, the effects on cross-linking are most pronounced during the S phase. The platinum-DNA adduct results in cisplatin cytotoxic effect in processes of DNA replication and transcription, and leads to breaks and miscoding [67].

Pharmacokinetic Properties

Pharmacokinetics of cisplatin is studied by measurement of platinum antitumor compound include ultrafiltrable platinum and total platinum. Untrafiltrable platinum consists of non-protein-bound intact drug and metabolites, which contribute to cisplatin antitumor activity and toxicity. Total platinum represents all platinum species in plasma after cisplatin infusion. There are various regimens, doses and schedules in studies of cisplatin pharmacokinetics. However, the kinetics of total plasma platinum depends on both the doses and the schedule after infusion during only in the initiation period. Peak levels are dependent on both the doses and the schedule but half-lives are only schedule-dependent [66].

After rapid intravenous administration of 100 mg/m^2 cisplatin, a peak plasma level of approximately 6 μg/mL is reached immediately and decreases to less than 2 μg/mL within 2 hours [68]. More than 90% of the platinum in the blood is bound to plasma

proteins. High concentrations of cisplatin are found in the kidney, liver, intestine, and testis, but it penetrates poorly into the cerebrospinal fluid [69]. In pharmacokinetic studies of short-term cisplatin infusion demonstrate declining of total plasma platinum in triphasic manner with half-lives of 14.4 min., 273.7 min., and 5.3 days, respectively. Concentrations of free-platinum decline in biphasic manner with half-lives of 9.7 ± 0.2 and 40.4 ± 2.5 min, respectively [70]. Approximately 25% of cisplatin dose is eliminated from the body during the first 24 hours, with renal clearance accounting for more than 90%. Then, renal clearance of cisplatin is due mainly to the glomerular filtration and is also eliminated partly by active tubular secretion, whereas less than 1% of dose is detected in the bile [71].

Therapeutic Uses

Cisplatin is one of the most effective agents for treating solid tumors, including testis, ovary, bladder, oropharynx and lung cancer. Combination chemotherapy of cisplatin with bleomycin, etoposide, and vinblastine is curative for 85% of patients with advanced testicular cancer. Its beneficial effects in carcinoma of the ovary has been shown when used with paclitaxel, cyclophosphamide, or doxorubicin [72]. The drug also sensitizes cells to the cytotoxic effects of radiation therapy [73].

Cisplatin is available for intravenous administration. The usual dose is 20 mg/m^2 per day for 5 days or 100 mg/m^2, given once every 4

weeks. Doses as high as 40 mg/m^2 for 5 consecutive days have been used alone or together with cyclophosphamide for the treatment of patients with advanced ovarian cancer, but result in greater renal, hearing, and neurological toxicity [74]. In order to prevent renal toxicity, hydration by the infusion of 1 to 2 liters of normal saline and mannitol diuresis prior to cisplatin administration is recommended. Cisplatin should be diluted in dextrose or saline solution and administered intravenously over a period of 6 to 8 hours after. Since aluminum reacts with and inactivates cisplatin, it is important not to use needles or other equipment that contain aluminum when preparing or administering the drug [1]. Serum creatinine as a guide to cisplatin dose selection is generally recommended. Cisplatin should be withheld if serum creatinine values are greater than 1.5 mg/dL since in the presence of elevated serum creatinine the use of cisplatin can result in irreversible damage of the kidney. Nevertheless, serum creatinine levels vary base on age body weight and gender, reliance on the serum creatinine can underestimate renal toxicity especially for women. Calculation of creatinine clearance that takes these variables into account then can provide an important monitoring parameters for renal dysfunction.

Toxicities

Nephrotoxicity

Dose-related and cumulative renal toxicity is the major dose-limiting toxicity of cisplatin. Its renal toxicity is primarily involved proximal renal tubule. In a study of 30 patients, Daugaard et al. [33] found significant impairment of proximal tubular reabsorption, despite a significant decrease in glomerular filtration rate. Study in male rats treated with cisplatin showed that the proximal tubules have patchy changes and are partially lined by flattened epithelium cells that contain hyperchromatic nuclei [75]. The pathology of the renal damage is also characterized by focal acute tubular necrosis, dilatation of convoluted tubules, thickened tubular basement membranes, formation of casts, and epithelium atypia of the collecting duct [28]. Moreover, cisplatin has been found to interfere with endoplasmic reticulum calcium pump activity that regulates cytosolic calcium homeostasis [76]. Simulation of the renal endoplasmic reticulum calcium pump may be potential a possible biomarker for platinum toxicity. In addition, because of its affinity for the sulfhydryl groups of various enzymes, cisplatin can induce a decrease in mitochondrial respiratory function, enzymatic activity in the respiratory chain and glutathione peroxidase in rat kidney. Clinical signs of toxicity manifested by elevated of BUN, creatinine serum uric acid and/or a decrease in CL_{cr} usually occur during the second week after a dose. Decreases in serum electrolytes due to renal salt

wasting have been reported, including hypomagnesemia, hypocalcemia, hypokalemia, hypophosphatemia and metabolic alkalosis. Excessive urinary magnesium excretion is due to disruption of renal tubular active transport system at the thick ascending limb of Henle's loop and collecting ducts by platinum compounds. In addition, volume expansion and mannitol diuresis may cause greater fractional excretion of magnesium and calcium. The consequence of hypomagnesemia and hypocalcemia tetany may be severe that requires replacement therapy and close monitoring, especially in alcoholic patients [77]. The effects of chronic disease such as diabetes mellitus and hypertension, which are more common in the elderly, may increase the risk of cisplatin nephrotoxicity [78]. Other risk factors contributing to nephrotoxicity include renal radiation before cisplatin therapy that may result in acute nephritis.

Vigorous hydration and osmotic diuresis can diminish renal toxicity of cisplatin. Al-Sarraf et al. [79] showed a protective effect on kidney function by adding mannitol to cisplatin-plus-hydration regimen. The mechanism underlying this effect is unknown, however, the effect probably is not mediated via an increase in renal blood flow since animal studies showed that high urine flow does not reduce cisplatin nephrotoxicity. Nevertheless, reduction in the time during which cisplatin and renal tubule are in contact has been implicated as possible contributing factor.

Other toxicity

Ototoxicity caused by cisplatin is characterized by tinnitus and hearing loss. The hearing loss is usually in the high frequency range from 4,000 to 8,000 Hz, but may also occur in the lower ranges which include the speech frequencies [80,81]. The ototoxicity can be unilateral or bilateral and tends to be more severe with repeated doses. Gastrointestinal toxicity especially intense nausea and vomiting are also a major problem for patients receiving cisplatin. The symptoms can usually be controlled with ondansetron or high dose corticosteroid. Animal models indicate that chemoreceptor trigger zone, abdominal visceral innervation and 5-hydroxytrptamine receptors on visceral afferent nerve play a role in mediating this toxicity [82,83]. Neurotoxicity has been seen in patients receiving high doses or multiple doses of cisplatin. Symptoms consist of peripheral neuropathy involving both the upper and lower extremities, with parenthesias, weakness, tremors, and loss of taste [84]. Myelosuppression, hemolytic anemia, hyperuricemia, seizures, cardiac abnormalities and anaphylactic-like reactions have been reported.

N-Acetyl-β-D-Glucosaminidase

NAG is a hydrolytic enzyme with a molecular weight of 130-140 kilodaltons. It is normally located in the lysosomal fraction of the proximal renal tubule where it plays a role in the breakdown of

glycoproteins. It is generally not filtered at the glomerulus, however, low levels of NAG may be found in normal urine results from the exocytosis and pinocytotic activity of the epithelial cells [85-87]. If changes in urinary NAG are to be meaningful, it is essential to compare its activities against age-matched normal reference ranges. Moreover, careful interpretation must be taken in pregnant women and transplant patients since increase in NAG activity is found in these individuals. Abnormal elevation of NAG activity in the urine is not specific for any particular condition and the pattern of excretion varies with the site and intensity of damage. For example, increase in NAG activity may occur in renal diseases and systemic diseases such as nephrotic syndrome, hypertension, diabetes and rheumatoid arthritis. Indeed, increased NAG activity reflects the severity of the disease and the residual functional capacity of the kidney. Damage of the renal tubules will initially affect the lysosomal/plasma membrane interaction resulting in an increased loss of the NAG enzyme into the urine. Further increases in enzyme excretion will accompany structural breakdown of the cells that leads ultimately to cell necrosis. Removal of toxic stimulus or recovery from disease will result in a decrease in NAG activity [39-42]. Since increase in urinary NAG activity is a sensitive index of renal tubular damage, it is a useful indicator for early detection of cisplatin-induced nephrotoxicity. It appears to be a more sensitive indicator than Scr and BUN levels. Moreover, the NAG is stable in urine and the urine sample can be stored for several months at

-20 °C. [35-37,39]. Normal reference value in our study is 0.93-2.39 unit/gram creatinine.

FOSFOMYCIN

Physicochemical Properties

Fosfomycin sodium, (Figure 2) a phosphonic acid derivative, is a synthetic antibacterial agent. It was first discovered in 1967 by a culture of *Streptomyces fradiae* isolated from Spanish soil samples. Fosfomycin sodium is a white crystalline powder having a slightly salty taste. It is very soluble in water, sparingly soluble in methanol and practically insoluble in ethanol, ether and chloroform. The molecular formula of fosfomycin sodium is $C_3H_5Na_2O_4P$ with a molecular weight of 182.02. Fosfomycin is very stable when dissolved in distilled water for injection, physiological saline or 5% glucose solution. After dissolving, fosfomycin can be kept for 7 days [53,54].

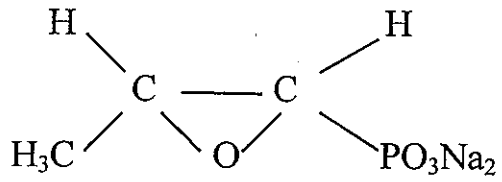

Figure 2. Structure of fosfomycin sodium.

Pharmacological Activity

Fosfomycin, a broad-spectrum bactericidal antibiotic, has *in vitro* activity against a range of gram-positive and gram-negative aerobic microorganisms. The bactericidal action of fosfomycin is to inactivate of the enzyme enolpyruvyl transferase, thereby irreversibly blocking the condensation of uridine diphosphate N-acetylglucosamine with p-enolpyruvate in the first step of bacterial cell wall synthesis. It also reduces adherence of bacteria to uroepithelial cells [88]. It is effective in treating both gram-positive and gram-negative infections including penicillinase-resistant staphylococci, proteus species *Pseudomonas aeruginosa*, most enterobacteriaceae, *Haemophilus influenzae* and *Neisseria spp.* As far as rates of efficacy are concerned, it is more effective against these bacterial infections in surgical, urological, ophthalmic and some other fields [89].

Fosfomycin has been reported to demonstrate antimicrobial synergy with a wide range of antibiotics against organisms such as enterococci, methicillin-resistant *Staphylcoccus aureus*, and the enterobacteria. Such synergistic effects have been reported particularly with the beta lactams, but also with aminoglycosides, macrolides, tetracyclines, chloramphenicol, rifamycin, and lincomycin [90].

Pharmacokinetic Properties

Absorption of fosfomycin depends on the route of its administration. Oral fosfomycin (Fosfomycin trometamol) is partially absorbed and low levels of fosfomycin in blood are found. Intramuscular injection gives fosfomycin levels in the blood 3-5 times higher than oral administration while intravenous injection gives serum concentration almost twice as high as intramuscularly. The distribution volume of fosfomycin sodium is 0.183 L/kg, serum half-life is 1.5-2 hours and renal clearance is 0.0737 L/hr/kg [54,91]. Fosfomycin is mainly excreted by glomerular filtration, in which the 6-hour urinary recovery reaching about 20% and 90% in the cases of oral and of intravenous administration, respectively [92]. Fosfomycin is not bound to serum proteins, diffusion into tissues and body fluids is good. Fosfomycin is not metabolized in human body and therefore is excreted into urine with its original form [54].

Uses and Administration

Fosfomycin sodium has been given intravenously in the treatment of a variety of bacterial infections caused by susceptible organisms. The usual daily doses of intravenous drip infusion for adult are 2 to 4 gm of fosfomycin and 100 to 200 mg/kg for children are given in 2 divided doses. Each dose of fosfomycin is prepared by dissolving in 100 to 500 mL of infusion fluid and infused over a period of 1 to 2 hours. For intravenous injection, the usual daily doses are the

same as for intravenous drip infusion, but given in 2 to 4 divided doses by dissolving 1 to 2 gm of fosfomycin sodium in 20 mL of water for injection. The injection must be performed over 5 minutes. The dosage may be adjusted according to the age of patients and the severity of symptoms [53,54].

Fosfomycin trometamol is given to adults as a single dose equivalent to 3 gm of fosfomycin; children over 5 years may be given 2 gm in the treatment of acute uncomplicated infections of the urinary tract. It is also used for the prophylaxis of infection in transurethral surgical procedures; the equivalent of 3 gm of fosfomycin is given by mouth 3 hours before and 24 hours after the procedure [92].

Adverse Reactions

The incidence of adverse reactions occurs in clinical trials at a rate of <1%. These include anorexia, constipation, dry mouth, dysuria, flatulence, flu syndrome, haematuria, infection, insomnia, lymphadenophathy, menstrual disorder, migraine, myalgia, nerversness, paresthesia, pruritus, increased ALT, skin disorder, somnolence and vomiting. In post-marketing experience, the adverse events are 1.75% include elevation of ALT, AST and LDH, exanthema, itching, urticaria, diarrhea, nausea, vomiting, abdominal pain, anorexia, facial flush, fever, malaise, renal disorders, hypoesthesia and leucopenia [53,88].

Fosfomycin is one of the most promising agents in ameliorating cisplatin nephrotoxicity demonstrated by a measuring

urinary NAG activity. According to Umeki et al., [93] fosfomycin given 2 gm 2 times a day from the 1st to 4th day of cycle protects the kidney from cisplatin nephrotoxicity in lung cancer patients [53,88,93]. Fosfomycin, 4 gm twice daily given 2 days before and 5 days after cisplatin administration is beneficial in ovarian cancer patients [44]. Other authors also observed this protective effect; however, most studies were conducted in a small number of patients and the doses of cisplatin and fosfomycin varied among different studies.