Study of Cisplatin-Vinblastine Plus Amifostine in Patients with Locally Advanced or Metastatic Non-small Cell Lung Cancer

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Objective : *To determine whether pretreatment with amifostine would reduce the toxicity of cisplatin with no reduction in antitumor efficacy in patients with advanced non-small lung cancer*
Patients and Method : *Patients with locally advanced or metastatic non-small cell lung cancer, aged less than 75 years, with an Eastern Cooperative Oncology Group (ECOG) performance status 0-2 were enrolled in the study. Amifostine was administered at a dose of 740 mg/m^2 before chemotherapy. Then cisplatin at100 mg/m^2 was administered on day 1 and vinblastine 5 mg/m^2 given on days 1, 8 and 15 in a 28 day cycle.*
Results : *Forty one patients were enrolled.Baseline characteristics included; a median age of 58 years (range, 28-72); 23 males and 18 females; performance status of 0 (1 patient), 1 (38 patients) and 2 (2 patients); stage IIIa (1 patient), stage IIIb (10 patients) and stage IV (30 patients).The predominant histology was adenocarcinoma (60.97%). A median of 4 cycles (range, 1-6) were administered. Thirty six cases out of forty one patients were assessable for response. The response rate was 38%. All those responding gave partial response. The median survival time was 33 weeks. One and two years survival were 23.9% and 9% respectively. Grade 3/4 toxicity was primarily hematologic. Grade 3/4 leukopenia occurred in 12.4%. Grade 3/4 thrombocytopenia occurred in 1.2%. Anemia grade 3/4 occurred in 7.5%. The observed grade 3/4 non-hematological toxicities were hypertension, hypocalcemia, nausea and vomiting and sensory neuropathy. Other toxicities were grade 2 or below.*
Conclusion : *This study demonstrated that amifostine has the potential to be a broad spectrum cytoprotectant of normal tissues from toxicity caused by chemotherapy and no effect on therapeutic outcome in lung cancer patients.*

Keywords : *Amifostine, Lung cancer, Cisplatin toxicity*

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Lung cancer is one of the leading causes of cancer death throughout the world[1]. It is the most common malignancy in men and women of ChiangMai, Thailand[2]. Approximately 75-80% of all lung cancer cases are of the non-small cell subtype. Most patients with newly diagnosed non-small lung cancer (NSCLC) have locally advanced or metastatic disease at the time of diagnosis[3]. Chemotherapy prolongs survival in patients with locally advanced and distant metastases NSCLC. Platinum based chemotherapy is one of the commonly used regimens and it has shown a statistical improvement in survival and disease-related symptoms when compared with best supportive care[4,5]. Cisplatin induced toxicites include nephrotoxicity, ototoxicity, neurotoxicity, in addition to severe nausea and vomiting in patients and it is usually dose limiting[6]. Because of the important role of cisplatin in cancer treatment, a method for attenuating or preventing of its toxicity would be a useful adjunct. Amifostine, S-2-(3-amino propylamino) ethylphosphorothioic acid, is a sulfhydryl compound, which selectively protects normal tissues against the cytotoxicity of radiation and alkylating agent in the animal model[7]. From a

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preclinical study, amifostine exerts its protective effect on a wide range of normal tissue, such as bone marrow, oral mucosa, gastrointestinal epithelium, heart, salivary glands, lungs,kidneys, etc[8]. It was the first cytoprotective drug to enter clinical practice[9] and showed protection against platinum induced nephrotoxicity, as well as reduced neurotoxicity[10-12]. A randomized phase III trial showed that pretreatment with amifostine provided a statistically significant reduction in the accurate and cumulative hematological and renal toxicites associated with cyclophosphamide and cisplatin regimen, with preservation of tumor response and equivalent survival[13]. The American Society of Clinical Oncology have developed recommendations regarding the use of amifostine and recommended that it might be considered for the prevention of nephrotoxicity and reduction of neutropenia-associated events in patients who receive cisplatin-based chemotherapy[14]. Regarding amifostine dosage, a dose of 910 mg/m^2 was used in the phase III clinical trial, but pharmacologic data and controlled studies evaluated that a dose of 740 mg/m^2 results in a similar degree of cytoprotection and lower toxicity[15-17].

Therefore, the present study was to determine whether pretreatment with amifostine would reduce the toxicity of cisplatin with no reduction in antitumor efficacy in lung cancer patients with advanced non-small cell lung cancer.

Patents and Method

Patient selection

Lung cancer patients with inoperable locally advanced or metastatic disease were enrolled in the study, if they had a histological or cytological diagnosis of non-small cell lung cancer. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, age of less than 75 years,measurable disease, adequate bone marrow reserve (white blood cell count $\geq$ 3000 / mm^3,platelet count $\geq$ 100,000/ mm^3), adequate renal function (creatinine $\leq$ 1.5 mg/dl), and adequate hepatic function (SGOT $\leq$ 3 times the upper limit of normal and serum bilirubin $\leq$ 2 mg/dl). Prior radiation therapy was allowable. If patients had had prior radiotherapy, they must have had measurable disease outside the radiation port and $\geq$ three weeks recovery from radiation with a resolution of all radiation-induced toxicities.

Patients were not eligible for study enrollment if they had any of the following: active or uncontrolled infection: significant cardiovascular disease (uncontrolled hypertension, symptomatic ischemic heart disease, history of congestive heart failure or myocardial infarction within the preceding 6 months and uncontrolled serious arrhythmias); prior malignancies within the preceding 5 years other than previously treated basal carcinoma of the skin or carcinoma in situ of the cervix; pregnancy; lactation; refusal to use effective contraception; hypocalcemia; evidence of peripheral neuropathy; intercurrent medical or psychological conditions that would preclude informed consent or compliance with the protocol; brain or other central nervous system metastases; and any previous chemotherapy or biological treatment.

Treatment schedule

The treatment regimen consisted of cisplatin at 100 mg/m^2 administered intravenously on day 1 followed by vinblastine at 5 mg/m^2 given intravenously on day 1, 8 and 15. Amifostine at 740 mg/m^2 was diluted in 50 ml of normal saline and given intravenously over 15 minutes. It was administered 30 minutes prior to the administration of cisplatin. These cycles were repeated every 4 weeks for six cycles or until patients had disease progression, developed unacceptable drug toxicity or did not respond to dosage modification. All patients were hydrated intravenously at a rate of 200 ml/hour with normal saline solution (added with potassium 20 mEq KCl per liter) starting 12 hours prior to amifostine and cisplatin infusion and for 12 hours after administration. The patients also received 1 liter of normal saline solution 1 hour prior to initiation of amifostine/cisplatin in order to avoid hypotension.

Patients were then placed in a supine position, and their blood pressures were taken prior to and every 5 minutes during amifostine infusion and 5 minutes after the infusion had been completed. The infusion was interrupted if systolic blood pressure decreased significantly from the baseline (i.e. decreased blood pressure at 20,25,30,40 and 50 mmHg from baselline systolic blood pressure at <100, 100-119, 120-139, 140-179 and $\geq$ 180 mmHg respectively) or if the patients developed symptoms related to decreased cerebral or cardiovascular perfusion. If a decrease in blood pressure occurred, the patient received a rapid infusion of normal saline solution and was kept in a supine position until the blood pressure returned to the baseline. If the patient's blood pressure returned to a level above the threshold value (defined as the baseline minus the relevant decrease, which would necessitate interrupting the infusion within 5 minutes of stopping the amifostine infusion, and the patient

was asymptomatic, the amifostine infusion might be restarted with continued blood pressure monitoring every 3 minutes. If the patient's blood pressure did not return to above threshold within 5 minutes, the infusion will not be restarted. After amifostine infusion, mannitol at 20 g was infused followed by cisplatin at 100 mg/m^2 over 30 minutes, and vinblastine at 5 mg/m^2 over 4 minutes. Chemotherapy dose modification was based on subsequent toxicites. Dose of chemotherapy in subsequent cycles of treatment were to be adjusted according to the type and severity of toxicity observed in the prior cycle. Doses of chemotherapy was reduced by 25% for a nadir platelet counts between 75,000 and 99,999 /mm^3 and reduced dose by 50% for a nadir white blood cell count between 1,000 and 1,499/mm^3 and platelet count between 50,000 and 74,999/mm^3. Initiation of a subsequent cycle of chemotherapy was delayed until patients achieved an absolute neutrophil count $\geq$ 1000/ mm^3 and platelet count $\geq$ 100,000/ mm^3.

Prophylactic antiemetics were given to all patients. The schedule for this protocol was dexamethasone at 20 mg given intravenously 12 hours prior to therapy and 10 mg intravenously 1 hour prior to therapy, lorazepam at 1 mg given 1 hour prior to therapy and ondansetron at 8 mg given orally 1 hour prior to therapy and 2 hours after cisplatin infusion. Routinely administered antihypertensives were withheld for 24 hours before or after the amifostine infusion, and all potentially nephrotoxic agents were prohibited for 4 days prior to cisplatin administration.

Patient evaluation

Prior to treatment, the patients underwent a medical history and physical examination, an electrocardiogram, audiogram, laboratory evaluation (complete blood count with differential and platelet count, serum chemistry included glucose, Blood urea nitrogen (BUN), serum creatinine, calcium, phosphorus, total protein, albumin, total bilirubin, alkaline phosphatase, SGOT, LDH, sodium, chloride, potassium, phosphorus and magnesium and baseline tumor measurements (computerized scan of chest and abdomen or chest radiograph). The medical history and physical examination, and serum chemistries were repeated every 4 weeks prior to each cycle of therapy. Serum creatinine and complete blood count with differential and platelet counts were obtained weekly throughout treatment.

Tumor response was assessed according to the World Health Organization criteria. The tumor was reassessed during treatment after every 2 courses until disease progression was documented. With the documentation of disease progression or completed chemotherapy, patients were followed every 3 months for survival. Toxicities were graded using the National Cancer Institute (NCI) Common Toxicity Criteria, and toxicity assessments were made prior to each cycle of therapy. In addition, duration of response and survival were determined.

Statistics

Patient characteristics, the response rate and safety profile were characterized using descriptive statistics. The probability of survival at one and two years' survival were estimated by using Kaplan-Meier methods.

Results

Between August 1999 and May 2001, a total of 41 patients were enrolled in the study. All patients were evaluable for toxicity, while 36 were evaluable for tumor response. One patient was not included in the analysis for response because she developed brain metastases after one course of chemotherapy and three patients had early death. Baseline patient characteristics are shown in Table 1. The median number of given courses per patient was 4. Response was evaluated after completion of chemotherapy. Objective response is shown in Table 2. All responders had partial response. Overall median survival was 33 weeks with a 1 and 2 year survival rate of 23.9 and 9% respectively. A

Table 1. Patient characteristics

Characteristics	No. of patients
Total number of patients	41
Median age (yr)	58
Range	28-72
Sex	
Male	23 (56.1%)
Female	18 (43.9%)
Histology	
Adenocarcinoma	25 (60.97%)
Squamous cell carcinoma	8 (19.51%)
Large cell carcinoma	2 (4.88%)
Undifferentiated carcinoma	2 (4.88%)
NSCLC	4 (9.76%)
Staging	
IIIa	1 (2.44%)
IIIb	10 (24.39%)
IV	30 (73.17%)
ECOG performance status	
0	1 (2.44%)
1	38 (92.68%)
2	2 (4.88%)

Kaplan-Meier survival curve for all patients entered in this trial is shown in Fig. 1. Median response duration time was 27 weeks (range 7 to 52 weeks). Toxicities are listed in Table 3. The major toxicity was hematological toxicity. Non-hematological toxicities were mild to moderate. The observed grade 3/4 non-hematological toxicities were hypertension, hypocalcemia, nausea and vomiting and sensory neuropathy. Other toxicities were grade 2 or below.

Discussion

Amifostine (ethyol), a cytoprotective agent selected for development by the Walter Reed Army Institute of Research for protection against radiation injury to cells in the late 1950's[18], has been effective in protecting normal tissues from chemotherapy and radiation toxicities without interfering with chemotherapy effects[19,20]. Following amifostine administration it rapidly leaves the blood and distributes rapidly into tissues[9]. Amifostine is converted to its active interfering WR-1065 by enzyme alkaline phosphatase. WR-1065 exerts its protective action by scavenging free radicals, thus enhancing the chemical and enzymatic repair of the damaged DNA[18,19,21,22]. Amifostine may also upregulate the expression of a variety of proteins related to DNA repair and apoptosis inhibition,directly or indirectly through hypoxia[22-24]. The selective protection mechanism of normal tissue results from the preferential uptake of WR-1065 by normal cells in a higher concentration than tumor cells. This is because of the reduced activity of alkaline phosphatase in malignant cells and relative hypovascularity of tumor and alkaline pH necessary for WR-1065 generation[25]. Amifostine is generally well tolerated and is associated with transient side effects, including nausea, vomiting, sneezing, flushing and allergic reaction, etc. The most clinically significant toxicity is hypotension. With the use of repetitive doses of cisplatin, one of the most active drugs used in the treatment of various cancers, treatment limiting toxicity usually occurs and, from the documentation, toxicities prohibit further courses of cisplatin[12,26,27]. With prolonged administration of cisplatin, potentially debilitating nonhematologic toxicities occur, most notably renal, neurologic and ototoxicities. Renal dysfunction has been the major dose-limiting toxicity of cisplatin. It is manifested by a reduction in the glomerular filtration rate and a rising serum creatinine level. Renal toxicity associated with a dose of cisplatin ranging from 50 to 100 mg/m^2 has been diminished by vigo-rous hydration and osmotic diuresis, but life-threaten-ing renal toxicity and death still occur[12].

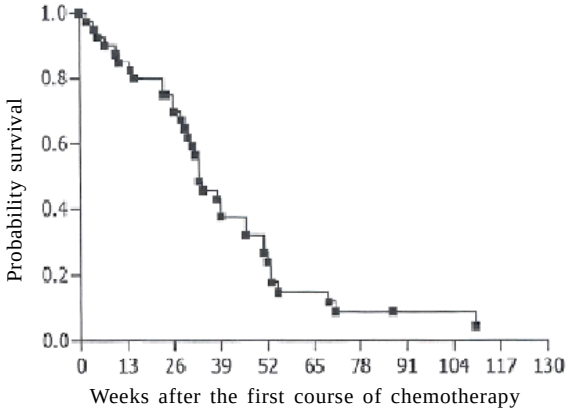

Fig. 1 Kaplan-Meier analysis of survival: median survival = 33 weeks, one-year survival = 23.9% and two year survival = 9%

Table 2. Objective Response

Response	No. of patient	(%)
Response assessable	36	
Complete response	0	(0%)
Partial response	14	(38.88%)
Stable diseases	9	(25.00%)
Progressive disease	13	(36.11%)

Table 3. Toxicity

Toxicity type	Percent		
NCI Grade	1/2	3	4
Hematologic toxicity			
Anemia	55.5	7.5	-
Neutropenia	41.3	11.7	0.7
Thrombocytopenia	0.7	0.6	0.6
Non-hematologic toxicity			
Anorexia	1.2	-	-
Rising of creatinine	7.2	-	-
Diarrhea	2.7	-	-
Dizziness	3.1	-	-
Fatigue	5.3	-	-
Flushing	1.9	-	-
Hypertension	7.2	7.2	-
Hypotension	0.3	-	-
Hypocalcemia	9.4	4.1	0.7
Hypomagnesemia	5.3	-	-
Hiccup	3.1	-	-
Mucositis	3.1	-	-
Nausea/Vomiting	9.1	1.2	-
Sensory neuropathy	2.7	0.3	-
Sneezing	1.9	-	-
Tinnitus	6.9	-	-

The present study demonstrated that amifostine provides protection against cisplatin-induced toxicites with no effect on the efficacy of chemotherapy. This finding is consistent with reports from other studies[10,11,13,16,28,29].The study from phase II trials of amifostine showed higher than expected antitumor response rate[10,17]. The result from Shiller's study showed a response rate of 64% and median survival time of 17 months in non-small cell lung cancer patients who received amifostine with cisplatin and vinblastine[10]. Eventhough there has been no difference in the overall response rate to treatment, nor any difference in the overall survival from randomized clinical trials of amifostine, it can demonstrate a protective effect against cumulative nephrotoxicity and hematologic toxicity from cisplatin[13]. The usage of amifostine at a dose of 740 mg/m^2 including premedication with dexamethasone, adequate hydration and a 5-HT$_3$ receptor antagonist may be the reason for lower toxicities from amifostine in the present report.

The present study demonstrated that amifostine provided protection against cisplatin induced toxicities with no effect on efficacy of chemotherapy. However, there was insufficient data to recommend it for protection against thrombocytopenia or its routine use to prevent cisplatin associated neurotoxicity or ototoxicity[14]. Future clinical trials need to evaluate the role of amifostine in the prevention of these platinum toxicities and its benefit when combined with new chemotherapeutic agents.

Conclusion

This study demonstrates that amifostine has the potential to be a broad spectrum cytoprotectant of normal tissues from the toxicity of chemotherapy and has no effect on the therapeutic outcome in lung cancer patients.

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การศึกษาผลของ amifostine ร่วมกับการให้ยา cisplatin และ vinblastine ในผู้ป่วยมะเร็งปอดชนิดเซลล์ไม่เล็กระยะลุกลามเฉพาะที่หรือแพร่กระจาย

สุมิตรา ทองประเสริฐ, บุษยามาส ชีวสกุลยง

วัตถุประสงค์ *: เพื่อประเมินผลของการรักษาด้วย amifostine ต่อการลดผลข้างเคียงของยา cisplatin รวมทั้งผลกระทบต่อประสิทธิภาพของการรักษาผู้ป่วยมะเร็งปอดชนิดเซลล์ไม่เล็กระยะลุกลามเฉพาะที่ หรือ แพร่กระจาย*

ผู้ป่วยและวิธีการทดลอง *: ทำการศึกษาในผู้ป่วยมะเร็งปอดชนิดเซลล์ไม่เล็กระยะลุกลามเฉพาะที่ หรือ แพร่กระจายที่มี ECOG performance status 0 ถึง 2 ทั้งเพศชายและหญิง อายุน้อยกว่า 75 ปี โดยให้ยา amifostine ในขนาด 740 มิลลิกรัมต่อพื้นที่ผิวตารางเมตรก่อนแล้วให้ยา cisplatin ในขนาด 100 มิลลิกรัมต่อต่อพื้นที่ผิวตารางเมตร ในวันแรกของการรักษา และให้ยา vinblastine ในขนาด 5 มิลลิกรัมต่อพื้นที่ผิวตารางเมตร ในวันที่1, 8 และ 15 ของการรักษาที่ให้ทุก 28 วันรวมไม่เกิน 6 ชุด*

ผลการทดลอง *: ผู้ป่วยทั้งหมด 41 ราย เข้าร่วมการศึกษามีอายุในช่วง 28-72 ปี ค่ามัธยฐาน 58 ปี เป็นเพศชาย 23 ราย เพศหญิง 18 ราย ค่า performance status ระดับ 0 จำนวน 1 ราย ระดับ 1 จำนวน 38 ราย และระดับ 2 จำนวน 2 ราย ระยะของโรค IIIa 1 ราย ระยะ IIIb 10 ราย และระยะ IV 30 ราย ค่ามัธยฐานของจำนวนชุดของยาเคมีบำบัดคือ 4 ชุด (ช่วง 1ถึง 6 ชุด) อัตราการตอบสนอง คิดเป็นร้อยละ 38 โดยทั้งหมดเห็นการตอบสนองแบบ partial response ค่ามัธยฐานของการรอดชีวิต คือ 33 สัปดาห์ ส่วนร้อยละของการรอดชีวิตที่ 1 ปี และ 2 ปี คือ ร้อยละ 23.9 และ 9 ตามลำดับ ผลข้างเคียง เกรด 3 และ 4 ที่เด่นคือผลต่อระบบโลหิตวิทยา โดยเม็ดโลหิตขาวต่ำ เกรด 3 และ 4 พบร้อยละ 12.4 เกร็ดเลือดต่ำ เกรด 3 และ 4 พบร้อยละ 1.2 เม็ดเลือดแดงต่ำ เกรด 3 และ 4 พบร้อยละ 7.5 ส่วนผลต่อระบบอื่น ๆ ที่มีเกรด 3/4 ได้แก่ ความดันโลหิตสูง ภาวะแคลเซียมต่ำในเลือด คลื่นไส้อาเจียน และ ความผิดปกติทางด้านประสาทรับความรู้สึก ส่วนผลข้างเคียงนอกจากนี้มี เกรด 2 หรือต่ำกว่า*

สรุป *: การศึกษานี้ได้แสดงให้เห็นว่า amifostine สามารถลดผลข้างเคียงของ cisplatin โดยไม่ได้ลดประสิทธิภาพของการรักษาผู้ป่วยมะเร็งปอด*