Combination of Gemcitabine and Cisplatin in Advanced Non-Small Cell Lung Cancer

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Abstract

A prospectively designed phase II study of non-small cell lung cancer stage IIIb and IV treated by gemcitabine and cisplatin was studied. The dosage of gemcitabine was 1g/m^2 weekly on day 1, 8 and 15. Cisplatin 100 mg/m^2 was given on day 15 of each 28 day cycle.

Twenty-eight patients were treated and all cases were evaluated for response. Survival and toxicity were determined in all enrolled patients. Thirteen (46.4%) achieved partial response (PR). By using Kaplan Meier's method the mean survival time was 19.8 months. One year survival was 66.6 per cent. Non hematologic toxicity consisted of mild nausea, vomiting, alopecia and hyperpigmentation of the skin. Rising creatinine of grade I was seen in 1.6 per cent. Anemia and leukopenia were common hematologic side effects with 27.5 per cent and 14.2 per cent of patients experiencing grade III and IV toxicity respectively. Both side effects were usually short lived and responsible for the delay of gemcitabine administration on day 8 and 15 in 18.3 per cent and 23.3 per cent on day 15 alone of chemotherapeutic courses respectively. We conclude that the combination of gemcitabine and cisplatin at this dosage achieved good response with moderate side effects.

Key word : Gemcitabine, Cisplatin, Non-Small Cell Lung Cancer

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J Med Assoc Thai 2001; 84: 397-401

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Lung cancer is the leading cause of cancer related death throughout the world with the vast majority of patients having non-small cell lung cancer (NSCLC)[1,2]. Cisplatin-based chemotherapy represents the standard treatment for advanced NSCLC and shows modest improvement in the survival of patients compared with the best supportive care. In the last decades several new chemotherapeutic agents were shown to be as effective as or more effective than cisplatin. Gemcitabine a nucleoside analogue is one of these new drugs produced tumor response rates of 20 per cent or more with monotherapy. It is well tolerated and has a favorable toxicity profile[3-5]. From experimental data both *in vitro* and *in vivo* suggest that gemcitabine-cisplatin combination interact synergistically[6-9]. From phase II and III trials of NSCLC, gemcitabine/ cisplatin gave a better response rate and time to disease progression than etoposide and cisplatin. Randomized Phase III trials showed that gemcitabine combined with cisplatin had a better response rate, longer time to disease progression and improved median survival better than cisplatin alone. Several phase II studies of gemcitabine combination with cisplatin have been performed using different scheduling and dosage regimens. Response rate varied from 26 per cent to 65.3 per cent[12-16] and median survival was 8.4 to 15.4 months[12,16]. The schedule of cisplatin given on day 15 provided the longest duration of gemictabine exposure and associated with best dose intensity[16]. We, therefore, conducted a phase II study in a Thai population to examine the feasibility of using a combination of weekly gemcitabine on day 1, 8, 15 and cisplatin on day 15 of a 28-day cycle.

PATIENTS AND METHOD

Patients with stage IIIb or IV non-small cell lung cancer were entered into the study after giving informed consent. Criteria for study entry included histological or cytological confirmation of advanced non-small cell lung cancer, Karnofsky performance status ≥ 60 per cent, adequate bone marrow reserve (hemoglobin level >10 g/dl, leukocyte count >4000/mm^3 platelet count > 100,000/mm^3), normal liver and renal function (total bilirubin level <2.0 mg/dL, AST/ALT levels <2 x the upper normal limit, serum creatinine level <1.5 mg/dl), and no prior chemotherapy, immunotherapy or radiotherapy regimen. Age range of 18 to 75 years. Patients with brain metastases and/or second malignancy were excluded.

Gemcitabine 1 g/m^2 was administered on day 1,8 and 15 of a 28 day cycle. Cisplatin 100 mg/m^2 was given on day 15. Cycles were repeated every 4 weeks. A detailed medical interview, clinical examination, radiological finding together with laboratory studies were obtained before each cycle. Treatment was delayed for 1 week if leukocyte counts or platelet counts on day 8 or 15 were less than 3000/mm^3 or less than 100,000/mm^3 respectively. Cisplatin was omitted if serum creatinine level >1.5 mg/dl. Toxicity and response evaluation were based on World Health Organization (WHO) criteria. Survival time was calculated from the date of entry until death or last follow-up by Kaplan-Meier's method.

RESULTS

From April 1998 through November 1999, 28 enrolled patients received gemcitabine plus cisplatin. The characteristics of these patients are described in Table 1. All patients were evaluated for response and toxicity. Median course of chemotherapy was 4 courses (range 1-6). Table 2 and 3 summarize tumor response and hematologic toxicity. Fig. 1 shows the survival curve calculated by Kaplan-Meier's method. Median survival time was

Table 1. Patients' Characteristics.

Characteristics	No. of patients	%
Patients entered	28	
Patients evaluable	28	
Median age (years)	58.5	
Range	37-73	
Gender		
Male	17	60.7
Female	11	39.3
Karnofsky Performance status		
90%	1	3.6
80%	10	35.71
70%	10	35.71
60%	7	25
Histology		
Adenocarcinoma	20	71.4
Squamous cell carcinoma	3	10.7
Large cell carcinoma	2	7.1
Unspecified NSCLC	3	10.7
Stage		
IIIb	7	25
IV	21	75

Table 2. Response information.

Number of eligible patients	28	
Number of evaluable patients	28	
Response		
Complete response (CR)	0	(0%)
Partial response (PR)	13/28	(46.4%)
Stable disease (SD)	7/28	(25.0%)
Progressive disease (PD)	8/28	(28.6%)
Response duration (months)		
Median	6+ months	
Range	1+-22.7 months	
Median survival time (months)	19.8 months	

Table 3. WHO hematologic toxicities.

	WHO grade (% of all patients, all cycles)
Hematologic (grade III & IV)	
Anemia	27.5
Leukopenia	14.2
Thrombocytopenia	5.0

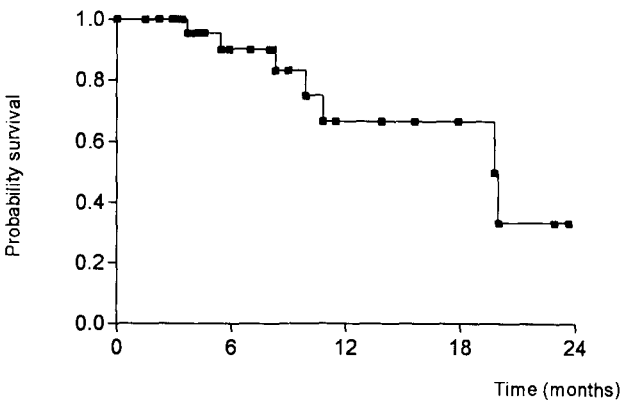

Fig. 1. Survival curve of 28 patients treated with combination of Cisplation plus Gemcitabine (Kaplan-Meier's method).

19.8 months and one-year survival was 66.6 per cent. Because of hematologic toxicities treatment schedules were delayed. Delayed on day 8 and 15 were 18.3 per cent and 23.3 per cent delayed on day 15 only. Non hematologic toxicity composed of grade I nephropathy 1.6 per cent (sererm creatinine rising >1.5 mg/dL). Two patients had persistent rising creatinine and the chemotherapy regimen was changed to carboplatin plus gemcitabine. Others had nausea, vomiting, alopecia and hyperpigmentation of skin.

DISCUSSION

Gemcitabine (2´, 2´ -difluorodeoxycytidine) is a new pyrimidine nucleoside analogue. It exhibits an extraordinary acray of self – potentiating mechanism that increased the concentration and prolonged the retention of its active nucleosides in tumor cells. Gemcitabine monotherapy appears to have similar efficacy to cisplatin / etoposide which is the standard regime for NSCLC treatment. Based on gemcitabine and cisplatin synergism, the mechanism may be due to the ability of gemcitabine to potentiate cisplatin cytotoxicity by inhibition of cisplatin-induces DNA interstrand cross-link removal. Objective response rates ranging from 26 to 65.3 per cent[12,13,15,16] were recorded when gemcitabine was combined with cisplatin, and 1-year survival duration ranged from 34 to 61 per cent [13,15,16].

When gemcitabine schedule was given once a week for 3 weeks followed by a rest of one week, combination of both activity and tolerability were superior to other schedules. About the cisplatin schedule it has been proposed that administration of gemcitabine 24 hours before cisplatin may favor drug synergy, so that gemcitabine is incorporated within DNA at the time of cisplatin administration and facilitates platinum DNA adduct formation. The day 2 regimen allowed the possibility of increased renal toxicity. The day 15 cisplatin schedule had the longest platelet recovery time and the subsequent predictable administration of the planned three infusions of gemcitabine per cycle[16].

Our study showed a response rate which is similar to previous studies[11,12]. Thrombocytopenia in our study was very low and did not effect the treatment course. Delayed treatment occurred due to leukopenia. Febrile neutropenia was not seen. Further randomized studies would be required to find out the most promising schedules of these two drugs in combinations to meet the best efficacy and acceptable toxicity.

SUMMARY

Gemcitabine/ cisplatin is an active regimen in advanced non-small cell lung cancer. The toxicity is modest and manageable. The results from

this study represent that the combination was one of the promising regimens for the treatment of non-small cell lung cancer.

ACKNOWLEDGEMENT

Lilly Co. Thailand branch for supplying part of the gemcitabine.

(Received for publication on September 22, 2000)

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การรักษามะเร็งปอดชนิดไม่ใช่เซลล์เล็กด้วยยาเจมซัยตาบีนร่วมกับซิสพลาติน

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การศึกษาประสิทธิผลของการให้ยาเคมีบำบัดแบบ Phase II ของยาเจมซัยตาบีนร่วมกับซิสพลาติน ในผู้ป่วยมะเร็งปอดชนิดไม่ใช่เซลล์เล็กในระยะที่ IIIb และIV ขนาดของยาเจมซัยตาบีน คือ 1 กรัมต่อพื้นที่ผิวหนึ่งตารางเมตรให้ยาทุกสัปดาห์ในวันที่ 1, 8 และ 15 ส่วนยาซิสพลาติน ให้ขนาด 100 กรัมต่อพื้นที่ผิวหนึ่งตารางเมตรในวันที่ 15 ยาทั้ง 2 ขนานให้ทางหลอดเลือดดำแต่ละชุดห่างกัน 28 วัน ผู้ป่วยทั้งหมด 28 รายได้รับการศึกษาและถูกประเมินผลของการรักษา ผลข้างเคียงและระยะการรอดชีวิต ผู้ป่วย 13 ราย (46.4%) มีการตอบสนองแบบ partial response ค่ามัธยฐาน ของการรอดชีวิตของผู้ป่วยทั้งหมดมีค่า 19.8 เดือนซึ่งประเมินโดยวิธีของ Kaplan Meier's method อัตราการรอดชีวิตที่ 1 ปี คือ 66.6% ผลข้างเคียงที่ไม่เกี่ยวกับทางโลหิตวิทยาประกอบด้วยอาการคลื่นไส้ อาเจียนเล็กน้อย ผมร่วง ผิวสีคล้ำและการเพิ่มขึ้นของค่า creatinine เพียงเล็กน้อย (Grade I) พบ1.6% ภาวะโลหิตจางและเม็ดเลือดขาวต่ำเป็นผลข้างเคียงทางโลหิตวิทยาที่เกิดขึ้นบ่อยด้วยเกรด 3 และ 4 พบ 27.5% และ 14.2% ตามลำดับซึ่งผลข้างเคียงดังกล่าวมีผลทำให้มีการให้เจมซัยตาบีน ตามกำหนดเลื่อนออกไปให้วันที่ 8 และ 15 จำนวน 18.3 % และเลื่อนในวันที่ 15 23.3% จากผลการศึกษาสรุปได้ว่ายาเจมซัยตาบีนร่วมกับซิสพลาติน ในขนาดดังกล่าวได้ผลการตอบสนองต่อการรักษาดีและมีผลข้างเคียงปานกลาง

คำสำคัญ : เจมซัยตาบีน, ซิสพลาติน, มะเร็งปอดชนิดไม่ใช่เซลล์เล็ก

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