Preliminary Study of Efficacy of Intravenous Cisplatin Plus Oral Etoposide in Small Cell Lung Cancer

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Abstract

Twenty-three patients with small cell lung cancer were treated with combination chemotherapy consisting of Cisplatin at 100 mg/m^2 given by 2 hours intravenous infusion on day 1 and oral etoposide 25 mg/caplet given twice a day for 21 days repeated every 28 days for 6 cycles. Of 23 cases, four cases were not evaluable due to early death (three of them died from febrile neutropenia). Median age of the patients was 59 years (range = 45-76 years). Five cases were female and eighteen cases were male. Median Karnofsky performance status was 70 per cent (range = 50-90%). Five cases were extensive disease and eighteen cases were limited disease. Of 5 extensive disease cases, 1 complete response (20%) and 3 partial responses (60%) were achieved. Of 14 limited disease patients, 1 complete response (7.1%) and 11 partial responses (78.6%) were achieved. Hematologic toxicities were severe causing three patients to die because of febrile neutropenia, nine cases (10.7%) had grade 3 and 4 neutropenia. Grade 3 and 4 anemia and thrombocytopenia were seen in 28.6 per cent and 8.3 per cent respectively. Median survival time of all cases was 7 months.

Thus, the combination of intravenous cisplatin and prolonged administration of oral etoposide could be administered to small cell lung cancer patients with high response rate, however, because of its severe toxicities, special caution should be considered and the optimal duration of oral etoposide should be evaluated.

Small cell lung cancer (SCLC) is one of the most chemotherapy-responsive malignancies. Among the available antineoplastic drugs against SCLC, etoposide (VP-16) is one of the most active (1,2). However, its dose and schedule dependent activity has not been well established(1), so several studies exploring these issues are ongoing(3). From clinical data there have been documented the superiority of a 5 day schedule *versus* 3 or 1-day schedule, therefore etoposide is best administered over several days(4,5). Several studies demonstrated that the efficacies of oral etoposide were comparable to the efficacies of intravenous (IV) etoposide. Etoposide administered by either way

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was well tolerated, similar or less in toxicity, as well as no difference in response rate, time to progression and survival[6,7]. Thus, the oral administation of etoposide could be substituted for the IV form. Prolonged oral etoposide administration has raised the possibility of enhancing its efficacy in several tumors including small cell lung cancer. Data from phase I trial, the maximum tolerated dose of chronic oral etoposide was 50 mg/m^2/d for 21 consecutive days[8]. Subsequently, data obtained from phase II studies suggested that this prolonged schedule may be more active and less toxic than the standard intravenous schedule[4]. Based on the *in vitro* and *in vivo* data, cisplatin was shown to be synergistic with etoposide and cisplatin was less myelosuppressive drugs than the other chemotherapeutic agents[1,9,10]. The combination of cisplatin and etoposide is considered to be a standard and excellent induction regimen for SCLC[2]. Because of the above reasons, we designed our treatment protocol consisting of prolonged low dose oral etoposide combined with cisplatin in previously untreated SCLC patients. This study aimed to determine the efficacy and toxicity of the two drugs in our small cell lung cancer patients.

MATERIAL AND METHOD

All patients were required to have measurable or evaluable disease, histologically or cytologically confirmed small cell carcinoma of the lung. Patients had to have adequate bone marrow [white blood cells (WBC) > 4000/mm^3, platelet count > 100,000/mm^3], normal hepatic (bilirubin < 1.5 mg%) and renal function (creatinine < 1.5 mg%) and a Karnofsky's performance status of 50 or more. Patients with cardiac disease, a second primary cancer or active infection were excluded. Patients with previous chemotherapy or radiotherapy were excluded. For staging workup complete blood count, platelet count, chest X-ray, ultrasound abdomen and bone scan were performed in all cases. Computerized scan of chest, and abdomen were performed in some cases. Computerized scan of brain was done only when subjects had neurological signs and symptoms, and bone marrow study was not done.

Patients were treated with oral etoposide and intravenous (i.v.) cisplatin for six cycles. Each cycle consisted of etoposide 50 mg/day administered orally divided into two doses (bid) for 21 consecutive days, providing white blood cell and platelets counts were adequate. Cisplatin was administered at a dosage of 100 mg/m^2 giving by i.v. drip over 2 hours on day 1. Chemotherapy was recycled every 28 days. Maximal use of antiemetics was encouraged, but no specific regimen was defined.

Etoposide was discontinued at any time during the cycle if the WBC fell below 3000/µl and/or the platelet count fell below 100,000/µl. On day 1 of each cycle, no therapy was given if the WBC was below 3,000/µl and/or the platelet count was below 100,000/µl. Therapy was resumed 1 week later if the counts were adequate at 100 per cent dosage. Patients were taken off the study if the treatment was delayed greater than two weeks. Cisplatin was discontinued for a serum creatinine > 1.5 mg/100 ml. Patients were evaluated for response following six cycles of therapy. A complete reponse (CR) to therapy was defined as the complete disappearance of all clinically detectable malignant disease for at least 4 weeks. A partial response (PR) was defined as greater than or equal to 50 per cent decrease in tumour size for at least 4 weeks, without an increase in size of any known malignant disease or appearance of new lesions. A no change (NC) was defined as no significant change in measurable or evaluable disease for at least 4 weeks, and progression of disease (PD) was defined as 25 per cent or more increase in the tumor size of one or more measurable lesion[11]. In case of limited disease, radiation therapy was given to the chest for complete or partial responders. Prophylactic cranial irradiation was provided to complete responders only.

WHO grades 1 ,2, 3 and 4 leukopenia were defined as WBC counts of 3.0-3.9, 2.0-2.9, 1.0-1.9 and < 1.0 (x10^9/1), respectively. Grades 1, 2, 3 and 4 thrombocytopenia were defined as platelet counts of 75-99, 50-74.9, 25-49.9 and < 25 (x10^9/1), respectively. Grades 1, 2, 3 and 4 anemia were defined as haemoglobin levels of 10.0-normal, 8.0-10.0, 6.5-7.9 and less than 6.5 (g/dl), respectively[12].

RESULTS

Twenty-three patients were entered into the study. Patient's characteristics are summarized in Table 1. Four patients did not complete the first cycle of therapy because of early death and were considered evaluable for toxicity. Characteristics of all 23 patients are reported in Table 1.

Table 1. Patient's characteristics.

Number of entered	23 cases
Number of evaluable	19 cases
Age (years)	
Median	59
Range	45-76
Sex	
Female	5 cases
Male	18 cases
Performance status (Karnofsky)	
Median	70%
Range	50-90%
Stage	
Extensive disease	5 cases
Limited disease	18 cases
Sites of metastatic disease	
Liver	1 cases
Bone	3 cases
Liver+Bone	1 cases

Table 2. Patient's outcome (19 Evaluable cases).

Responses	Extensive disease cases (%)	Limited disease cases (%)
Complete (CR)	1 (20%)	1 (7.1%)
Partial (PR)	3 (60%)	11 (78.6%)
Progressive disease (PD)	1 (20%)	2 (14.3%)
Duration of response (mos.)	4 (3-9)	6.5 (1-10)
Survival (mos.)	6 (3+-11)	7 (1-18+)

Therapeutic activity

Nineteen patients were evaluable for response (Table 2), there were fourteen limited disease, five extensive disease. One complete responder (7.1%) and eleven partial responders (78.6%) were achieved, for an overall response rate of 85.7 per cent in the limited disease group. One complete responder (20%), three partial responders (60%) were achieved, for an overall response rate of 80 per cent in the extensive disease group. The duration of response for limited disease was 6.5 months, and was 4 months for extensive disease. The median survival for all cases was 7 months (19 evaluable patients.)

Toxicity

Six of the 23 eligible patients completed all six cycles of therapy. Most common toxicity was myelosuppression, of the 84 courses of chemotherapy grade 3 and 4 leukopenia were 10.7 per cent (9 episodes). Grade 3 and 4 thrombocytopenia were 8.3 per cent (7 episodes). Four patients developed febrile neutropenia and died after the first course of treatment. Treatment was delayed in 5 patients due to leukopenia, anemia or thrombocytopenia and in 3 patients it was delayed due to severe nausea and vomiting.

DISCUSSION

Prolonged administration of etoposide, with its increased efficacy and decreased toxicity, leads one to view this regimen almost as a new drug. There are several reasons to explain etoposide's schedule dependency. A more prolonged exposure should affect more cells than the same dose given over a shorter period; the second reason is more likely due to persistently and substantially inhibited enzyme than a short, higher dose of exposure and may be because the drug or it's active metabolite bound to plasma protein for a prolonged period[1,13]. Currently cisplatin combination with etoposide administered intravenously is considered to be a standard induction regimen for small cell lung cancer therapy[2]. In limited and extensive stage overall response of 82-100 per cent (CR 48-80%) and 75-92 per cent (CR 15-51%) were reported respectively. Median survival time was 14-28 months and 9-13 months in LD and ED respectively[14].

The studies of 50 mg/day of oral etoposide, 21 consecutive days in combination with cisplatin 100 mg/m^2 intravenously given on day 1 in extensive stage SCLC had similar efficacy as standard regimen. Patrick et al and Schiller et al[15] reported very good results. Overall response rates were 82 per cent (CR 9%) and 80 per cent (CR 15%) respectively. Median duration of response from both studies was 7 months. Median survival times were 9.9 and 8.5 months respectively.

Our data had shown the same overall response rate as standard regimen and the two previous studies for extensive stage, but lower response was observed in limited stage. It may be from incomplete investigation for staging of limited stage in our study. About the toxicity there was significant myelosuppression. Three cases died because of febrile neutropenia and 10.7 per cent of all patients developed grade 3 and 4 neutropenia. Non hematologic toxicity was mild. Most of the patients experienced mild to moderate mucositis. All cases had total alopecia and hyper-

pigmentation of skin. Mild to moderate nausea and vomiting was reported in 80 per cent of the patients.

Recently, a randomized phase III study compared the schedule dependency of 21 day oral *versus* 3 day intravenously in combination with i.v. cisplatin in extensive stage small cell lung cancer was completed[16]. The study demonstrated that both schedules did not demonstrate any differences in the treatment outcome with respect to tumor response and survival in the small cell lung cancer patients. However, a significant greater rate of severe or life threatening hematologic toxicity was noted on the 21-day oral etoposide treatment schedule[15,16]. This CALGB study[16] concluded that 3 to 5 days administration of oral etoposide may be better than 21 days. Future trials to clarify the schedule of oral etoposide and intravenous cisplatin are needed to improve efficacy and maintain the presumed synergy between both agents.

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การศึกษาเบื้องต้นของผลการรักษามะเร็งปอดชนิดเซลล์เล็กด้วยยา Cisplatin ทางหลอดเลือดดำ ร่วมกับการรับประทานยา etoposide

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ได้ทำการศึกษาผู้ป่วยมะเร็งปอดชนิดเซลล์เล็ก (small cell) 23 ราย โดยให้ Cisplatin 100 มิลลิกรัมต่อพื้นที่ผิวหนึ่งตารางเมตรทางเส้นเลือดดำ นาน 2 ชั่วโมง ในวันแรกและให้ยา etoposide ขนาด 25 มิลลิกรัมต่อ caplet รับประทานวันละ 2 ครั้ง ติดต่อกันนาน 21 วัน (โดยให้ทั้งหมด 6 course แต่ละ course ห่างกัน 28 วัน) ผู้ป่วยถูกตัดออกจากการประเมินผลเฉพาะการตอบสนองของยา 4 ราย เนื่องจากตายภายในช่วงต้นของการรักษา (3 ใน 4 รายตายจากภาวะ febrile neutropenia) อายุเฉลี่ยของผู้ป่วยที่ศึกษา 59 ปี (ค่าเฉลี่ย 45–76 ปี) เป็นเพศหญิง 5 ราย เพศชาย 18 ราย ค่าเฉลี่ยของ Karnofsky performance status 70% (ค่าเฉลี่ย 50–90%) ระยะของโรค 5 รายอยู่ในระยะ extensive disease 8 ราย อยู่ในระยะ limited disease ผู้ป่วย extensive disease 5 ราย มีการตอบสนองชนิด complete response 1 ราย (20%) ตอบสนองแบบ partial response 3 ราย (60%) ส่วนผู้ป่วย limited disease มีการตอบสนองชนิด complete และ partial response 1 (7.1%) และ 11 ราย (78.6%) ตามลำดับ ผลข้างเคียงทางระบบเลือดที่รุนแรงจนถึงแก่ชีวิต 3 ราย (febrile neutropenia) 9 ราย (10.7%) เม็ดโลหิตขาวนิวโตรฟิลต่ำเกรด 3 และ 4 ภาวะโลหิตจางและเกร็ดเลือดต่ำเกรด 3 และ 4 เกิดในผู้ป่วย 28.6 และ 8.3% ตามลำดับ ค่ามัธยฐานของการรอดชีวิตของผู้ป่วยทั้งหมดนาน 7 เดือน

จากผลของการวิจัยนี้พบว่าการให้เคมีบำบัดด้วย Cisplatin ทางหลอดเลือดดำร่วมกับรับประทาน etoposide เป็นเวลานานๆ สามารถนำมาใช้รักษามะเร็งปอดชนิดเซลล์เล็กด้วยการตอบสนองที่ให้ผลดี แต่มีผลข้างเคียงรุนแรงมาก จึงควรพิจารณาใช้ยาดังกล่าวด้วยความระมัดระวังอย่างสูง อีกทั้งน่าจะมีการศึกษาเพิ่มเติมเกี่ยวกับระยะเวลาของการให้ยา etoposide ชนิดรับประทานด้วย

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