Phase II Study of Ifosfamide, Carboplatin, Etoposide and GM-CSF in Small Cell Lung Cancer

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Abstract

Twenty patients with small cell lung cancer (SCLC) were entered to the study. Fourteen cases were male and six cases were female. Twelve cases were extensive disease, eight cases were limited disease. Median age was 60 years (range=40-72 years), median performance status was 70 per cent (range=60-80%). All patients were treated with combination chemotherapy consisting of ifosfamide 5 g/m^2 intravenous infusion over 4 hours with mesna uroprotection, carboplatin 300 mg/m^2 intravenous infusion over 2 hours on day 1, and etoposide 120 mg/m^2 intravenous infusion over 4 hours on day 1-3. Chemotherapy was re-cycled every 28 days. Assessment of hematologic toxicity (CBC) was performed two times per week. If there was grade 3 or 4 neutropenia on any cycle of chemotherapy, GM-CSF was administered for febrile neutropenia and on the next cycle it was administered prophylactically on day 4-14.

Results : Seventeen cases were evaluable for response and toxicity (three cases were in-evaluable due to loss to follow-up after the first cycle of chemotherapy). Fourteen cases (five limited disease, nine extensive disease) achieved partial response (82.5%). Two cases had stable disease, one case died on day 7. One year survival was 23.5 per cent. Seventy and a half percent grade 3 and 4 neutropenia was seen during the first cycle. One patient had febrile neutropenia. After being prophylactically treated with GM-CSF, grade 3 and 4 neutropenia was reduced from 70.5 per cent to 56.2 per cent, 46.7 per cent, 63.6 per cent, 42.8 per cent and 0 per cent in cycle 2-6 respectively. Major toxicity of GM-CSF consisted of transient chest distress, chills, sweating and hypotension which subsided in 5-10 minutes. No fever or skin rash was observed.

Conclusion : Combination of ifosfamide, carboplatin and etoposide (ICE) is an active regimen for small cell lung cancer. However, because of its severe myelosuppression, this regimen needs hematopoietic growth factor support, and GM-CSF was used in this study. The administration of GM-CSF rendered ICE chemotherapy to be given safely.

Key word : Small Cell Lung Cancer, Chemotherapy, GM-CSF

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Chemotherapy has been a major advance in the treatment of small cell lung cancer (SCLC). It has not only resulted in high objective (75-95%) and complete (20-40%) response rates but also and mainly in significantly prolonged survival. Five-year overall survival is about 5 per cent and there are 10 times more long-term survivors in patients with limited disease (LD) than in those with extensive disease (ED). Today, results might be improved by new active drugs, development of effective consolidation and/or maintenance treatment, use of more intensive regimens, administration of alternating or sequential combination chemotherapy, adjuvant thoracic irradiation and/or surgery, and/or effective prevention of central nervous system relapses.

Latest results using combination chemotherapy including three active drugs i.e. ifosfamide, etoposide and carboplatin (ICE) regimen was reported to be very active especially for the 2 years survival of > 30 per cent[1,2]. However, the incidence of leukopenia (grade 3 and 4) was quite high (nearly 100%).

In order to optimize the toxicity of chemotherapy, the hematopoietic growth factors, mainly GM-CSF and G-CSF[3] were introduced into clinical practice. These substances have been extensively studied during the last ten years[4-6]. G-CSF (granulocyte-colony stimulating factor) preferentially stimulates neutrophil production and has been shown to reduce the duration of neutopenia following chemotherapy. GM-CSF (granulocyte-macrophage colony stimulating factor) stimulates neutrophil, monocyte and eosinophil production and function. It is associated with more diverse hematological and clinical effects, including augmenting mechanisms of host defense[7].

In SCLC, both G-CSF[8,9] and GM-CSF [10,11] have been shown able to reduce the duration of neutropenia induced by chemotherapy. The above considerations lead us to initiate the Phase II study of ICE with GM-CSF in Thai patients with SCLC.

MATERIAL AND METHOD

Patients with histological or cytological diagnosis of small cell lung cancer were entered to the study. These patients should have an evaluable or measurable lesion with normal hematologic parameters (neutrophil count ≥ 3,000/mm^3, platelets count ≥ 100,000/mm^3), normal renal function (serum creatinine ≤ 1.5 mg/ml) and serum bilirubin ≤ 1.5 mg/ml.

Baseline staging work-up consisted of chest X-ray and/or computed tomography (CT) of the chest and liver ultrasound or CT of the liver and bone scan.

After complete history, physical examination and staging work up, patients were treated with ICE regimen which consisted of ifosfamide 5 g/m^2 intravenous infusion over 4 hours with mesna uroprotection on day 1, carboplatin 300 mg/m^2 intravenous infusion over 2 hours on day 1 and etoposide 120 mg/m^2/day intravenous infusion on day 1-3. Chemotherapy was recycled every 28 days. Complete blood count and platelets count were examined on day 1 and 4 of each week. If patients had febrile neutropenia GM-CSF (leucomax®) 5 μg/kg/day was administered subcutaneously daily until white blood count returned to ≥ 10,000/mm^3. If patients had grade 3 or 4 neutropenia, then GM-CSF 5 μg/kg/day was given subcutaneously for prophylaxis on the next cycle starting day on 4-14. Adverse effects of chemotherapy and GM-CSF were closely monitored.

Thoracic radiation was administered to all limited disease (LD) patients after complete treatment with chemotherapy. Whole brain irradiation was allowed for LD patients who had complete response to chemotherapy.

RESULTS

Seventeen patients were evaluable for response and toxicity (three cases were in-evaluable due to loss to follow-up after the first cycle of

Table 1. Patients characteristics.

Enter		20	cases
Evaluable		17	cases
In-evaluable		3	cases
Age	Median	60	yrs.
	range	40-72	yrs.
Sex	M:F	14 : 6	
PS	Median	70	% -
	Range	60-80	%
Stage	Extensive : Limited	12:8	
Extensive stage			
	Bone metastases	8*	cases
	Liver metastases	4*	cases
	Adrenal metastases	2	cases
	(Bone & liver metastases*	2	cases)

Table 2. Response.

	Total No.	Resp. Duration (mos.) range	median	Survival (mos.) range	median	1yr. survival
PR	14	1-6	3	2+-20+	6+	3 (21.4%)
SD	2	-	-	2+,31+	-	1 (50%)
ED	1	-	-	7 Days.		

PR = partial response, SD = stable disease, ED = early death

Tabel 3. Hematologic toxicity.

Total No.	Cycle	Anemia gr 3,4		Leukopenia gr 3,4		Thrombocytopenia gr 3,4		GM-CSF Therapeutic	Prophylaxis
		No	%	No	%	No	%		
17	1	3	17.6	12	70.5	4	23.5	1	-
16	2	8	50	9	56.2	5	31.2	-	13
15	3	6	40	7	46.7	6	40	-	11
11	4	9	81.8	7	63.6	6	54.5	-	6
7	5	3	42.8	3	42.8	1	14.2	-	6
5	6	3	60	-	-	2	40	-	4

chemotherapy) (Table 1). Fourteen patients (five limited disease, nine extensive disease) achieved partial response (82.5%). Two patients had stable disease, one case died on day 7. One year survival was 23.5 per cent. Seventy and a half percent grade 3 and 4 neutropenia was seen during the first cycle. One patient had febrile neutropenia (Table 2). After prophylactically treated with GM-CSF, neutropenia was reduced to 56.2 per cent, 46.7 per cent, 63.6 per cent, 42.8 per cent and 0 per cent in cycle 2-6 respectively (Table 3).

Toxicity of GM-CSF : Three patients had first dose reaction after receiving a subcutaneous injection of GM-CSF, the reaction was mainly transient chest distress, chills, sweating and hypotension which subsided within 5-10 minutes. No evidence of fever or skin rash was seen.

DISCUSSION

Several chemotherapeutic agents i.e cyclophosphamide, ifosfamide, cisplatin, doxorubicin, vincristine and etoposide are active drugs for SCLC. Ifosfamide at a high dose is a very active single agent drug for SCLC but is associated with severe myelotoxicity[12]. Carboplatin has advantages over cisplatin in respect of its toxicity profile particularly emetogenicity and renal dysfunction [13]. Etoposide is widely used to treat SCLC. It is used in multiple drug regimens, either given as three intravenous doses as in the widely used etoposide/cisplatin regimen[14], or as an intravenous dose followed by a short oral course, e.g. the ECMV regimen[15] or the VICE regimen[12]. In this study, ICE regimen (ifosfamide, carboplatin, etoposide) was administered to patients with SCLC. GM-CSF was used in order to maintain dose intensity of the ICE regimen.

Because of the problems of haematological toxicity, GM-CSF was administered to one patient for febrile neutropenia on the first cycle of treatment. On subsequent cycles of chemotherapy, GM-CSF was administered to most of the patients prophylactically. The incidence of grade 3 and 4 neutropenia was decreased after receiving GM-CSF and there was no febrile neutropenia. Three patients had allergic reaction to GM-CSF which consisted of transient chest distress, chills, sweating and hypotension which subsided within 5-10 minutes. No

other side effects from GM-CSF were noted. The ICE regimen reported here had a response rate of 82.5 per cent. Compared to other reports, i.e. VICE, Prendeville et al[12] who reported a response rate of 81 per cent in 85 patients. For the PE regimen, a similar response rate of 88 per cent has been quoted[14]. The one-year survival with ICE reported here was 23.5 per cent, which was lower than the other two reports. This may reflect the small number of patients treated and the high amount of extensive disease.

Conclusion : Combination of ifosfamide, carboplatin and etoposide (ICE) is an active regimen for small cell lung cancer. However, because of its severe myelosuppression, this regimen needs hematopoietic growth factor support and GM-CSF was used in this study. The administration of GM-CSF rendered ICE chemotherapy to be given safely. Whether the ICE regimen should considered to be standard treatment or not, warrants further comparative study.

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ผลการรักษามะเร็งปอดชนิดเซลล์เล็กด้วยยา Ifosfamide, Carboplatin และ Etoposide ร่วมกับ GM-CSF

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ผู้ป่วยมะเร็งปอดชนิดเซลล์เล็กจำนวน 20 รายได้รับการรักษาผู้ป่วย 14 รายเป็นหญิงและ 6 รายเป็นชาย ผู้ป่วย 12 รายเป็นโรคระยะ extensive disease และ 8 รายเป็น limited disease ค่าเฉลี่ยของอายุผู้ป่วยเท่ากับ 60 ปี (ช่วงอายุ 40–72 ปี) ผู้ป่วยได้รับยาเคมีบำบัดซึ่งประกอบด้วย ifosfamide 5 กรัม/ม^2 หยดเข้าหลอดเลือดดำภายใน 4 ชั่วโมงร่วมกับ mesna เพื่อป้องกันผลข้างเคียงต่อกระเพาะปัสสาวะ ยา carboplatin 300 มก/ม^{2}หยดเข้าหลอดเลือดดำภายใน 2 ชั่วโมง และ etoposide 120 มก/ม^2/วัน หยดเข้าหลอดเลือดดำภายใน 4 ชั่วโมงติดต่อกัน 3 วัน ผู้ป่วยจะได้รับยาเคมีบำบัดทุก 28 วัน ตรวจเม็ดเลือดอาทิตย์ละ 2 ครั้ง ยา GM-CSF จะถูกนำมาใช้ในกรณีของ febrile neutropenia ในระหว่างการรักษาด้วยยาชุดแรกและใช้เป็นการป้องกันสำหรับการรักษาด้วยยาเคมีบำบัดชุดต่อไปถ้าเม็ดเลือดขาวต่ำ grade 3–4 ในการรักษาด้วยยาเคมีบำบัดชุดก่อน โดยจะให้ GM-CSF ขนาด 5 ไมโครกรัมต่อกิโลกรัมวันที่ 4–14 ของยาชุดนั้น

ผลการรักษาผู้ป่วย 14 ราย จากจำนวน 17 รายซึ่งสามารถประเมินผลได้มีการตอบสนองต่อการรักษาแบบ partial response (PR) ร้อยละ 82.5 ผู้ป่วย 1 รายถึงแก่กรรมในสัปดาห์แรก ผู้ป่วย 2 รายไม่พบการเปลี่ยนแปลงของก้อนมะเร็ง อัตราการรอดชีวิตที่ 1 ปีเท่ากับร้อยละ 23.5 ผลข้างเคียงจากการให้ยาชุดที่หนึ่งพบการลดต่ำของเม็ดเลือดขาว grade 3 และ 4 เท่ากับร้อยละ 70.5 ซึ่งผู้ป่วย 1 รายเกิด febrile neutropenia หลังจากให้ GM-CSF เพื่อป้องกันแล้ว พบว่าอัตราของการเกิดเม็ดเลือดขาวต่ำ grade 3 และ 4 ลดลงจาก 70.5% เป็น 56.2%, 46.7%, 63.6%, 48.2% และ 0% ในการรักษาชุดที่ 2–6 ตามลำดับ ผลข้างเคียงที่สำคัญจาก GM-CSF คืออาการแน่นอก ความดันโลหิตต่ำลง หนาวสั่น และเหงื่อออก ซึ่งอาการดังกล่าวจะคงอยู่เพียงช่วงเวลาสั้นๆ และหายไปเองภายใน 5–10 นาที

สรุป ยาเคมีบำบัดชุดดังกล่าวใช้ได้ผลดีในการรักษามะเร็งปอดชนิดเซลล์เล็ก เนื่องจากผลข้างเคียงในแง่การกดไขกระดูกรุนแรง จึงจำเป็นต้องให้ยากระตุ้นเม็ดเลือดร่วมกันเพื่อลดผลข้างเคียงของยาเคมีบำบัด

คำสำคัญ : มะเร็งปอดชนิดเซลล์เล็ก, ยาเคมีบำบัด, GM-CSF

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