Dose Escalation Study of Carboplatin with Fixed-Dose Etoposide Plus Granulocyte-Colony Stimulating Factor in Patients with Small Cell Lung Carcinoma

A Study of the Lung Cancer Study Group of West Japan

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BACKGROUND. We performed a Phase I-II trial to determine the maximum tolerated dose of carboplatin (CBDCA) with a fixed dose of VP-16 and granulocyte-colony stimulating factor (G-CSF) in small cell lung cancer (SCLC) patients.

METHODS. Treatment consisted of a starting dose of CBDCA, 400 mg/m^2 (i.v., Day 1); VP-16, 100 mg/m^2 (i.v., Days 1–3), and G-CSF, 2 μg/kg (s.c., Days 4–17) every 4 weeks for four cycles. The dose of CBDCA was escalated in increments of 50 mg/m^2 until Grade IV toxicity on the World Health Organization scale developed in two-thirds or more of the patients.

RESULTS. Seventy-five previously untreated patients with pathology confirmed SCLC were entered into the trial. Seventy-one patients were eligible and 70 patients were evaluated for response. Forty-five patients had limited disease (LD) and 26 had extensive disease (ED). The response rate of the 70 patients who could be evaluated was 81%, with 23% attaining a complete response (CR) and 58% attaining a partial response (PR). The response rate was 80% in LD patients (CR, 23%; PR, 57%) and 85% in ED patients (CR, 23%; PR, 62%). The major dose-limiting toxicity was thrombocytopenia. Nephrotoxicity, neurotoxicity, and ototoxicity were uncommon. The doses of CBDCA that resulted in unacceptable thrombocytopenia were 700 mg/m^2 in patients younger than 70 years and 500 mg/m^2 in patients older than 70 years. Overall median survival time (MST) was 9 months. MST of LD patients and ED patients were 11 months and 7 months, respectively. The dose-limiting toxicity of CBDCA with a fixed dose of VP-16 and using G-CSF as bone marrow rescue was age-related thrombocytopenia. The maximum tolerated dose of CBDCA was 650 mg/m^2 if patients were younger than 70 years and 450 mg/m^2 if they were 70 years or older.

CONCLUSIONS. When we retrospectively compared our results with those using standard chemotherapy regimens, we saw no therapeutic benefit from increasing planned doses of CBDCA up to 700 mg/m^2 in combination with G-CSF in patients with SCLC. ***Cancer* 1996;77:63–70.** © *1996 American Cancer Society.*

KEYWORDS: dose escalation study, carboplatin, etoposide, granulocyte-colony stimulating factor (G-CSF), small cell lung cancer, maximum tolerated dose, relative dose intensity.

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The treatment of patients with small cell lung carcinoma (SCLC) has undergone significant changes during the last two decades with the advent of effective anticancer agents and correct integration of radiotherapy and chemotherapy. Response rates of 90% (60% complete response) for limited disease (LD) and 70% (30% complete response) for extensive disease (ED) have been achieved, and median survival time (MST) of ED patients and LD patients are 10–12 months and 14–18 months, respectively.[1] In spite of such high response rates most patients relapse and die of their disease within 2 or 3 years, and survival beyond 5 years occurs only in 3–8% of patients overall and 7% of LD patients.

Clearly, novel approaches to the treatment of SCLC are necessary to make a significant impact on survival. One such approach is the use of dose-intensive chemotherapy combined with autologous bone marrow transplantation (ABMT) or peripheral blood stem cell transfusion (PBSCT). However, this new treatment modality for SCLC remains experimental and can only be administered at specialized institutions.[2,3] In addition, mobilization of peripheral blood progenitor cells and their collection is time consuming, costly, and associated with some morbidity. Another approach is dose-intensive chemotherapy with granulocyte-colony stimulating factor (G-CSF) or granulocyte-macrophage CSF (GM-CSF) support. These CSFs are well known agents that are capable of reducing the incidence, duration, and severity of chemotherapy-induced leukopenia.[4,5] This approach is an attractive alternative if toxicity can be minimized and significant dose escalation can be achieved, as this therapy can be more easily administered on a community basis.

Carboplatin (CBDCA) is a clinically interesting second-generation platinum compound: it is less nephrotoxic and neurotoxic than cisplatin. Both CBDCA and VP-16 are active single agents for the treatment of SCLC, with overall response rates of more than 40% in previously untreated patients.[6–8] An experimental model using an ovarian carcinoma xenograft demonstrated that carboplatin has a dose relationship in its antitumor activity.[9] There is also some evidence that this combination has an additive antitumor effect in human small cell lung cancer cell lines.[10] Furthermore, in Phase II and III trials, CBDCA/VP-16 combination therapy has been shown to produce results equivalent to the cisplatin/VP-16 combination that is presently one of the most effective regimens for SCLC.[11–13]

We have combined these two promising agents to conduct a Phase I-II study using dose-escalated CBDCA and G-CSF in previously untreated patients with SCLC. The purpose of this study is primarily to determine the maximum tolerated dose (MTD) of CBDCA in the CBDCA/etoposide regimen when used with G-CSF support, and secondarily to describe and quantify clinical toxicities of the combination and to obtain preliminary evidence of therapeutic activity of the regimen in patients with SCLC.

MATERIALS AND METHODS

Eligibility, Staging, and Restaging Procedures

Patients with histologically or cytologically proven SCLC were enrolled. All patients had measurable or evaluable disease. Eligibility requirements included Stage II–IV disease, no prior therapy, maximum age of 79 years, no other concurrent active malignancies, no other serious diseases, a life expectancy of more than 3 months, and a good performance status (Eastern Cooperative Oncology Group scale, 0–2). Laboratory requirements were as follows: leukocyte count $\geqq 4000/mm^3$; platelet count $\geqq 100{,}000/mm^3$; bilirubin $\leqq 1.5$ mg/dL; transaminase $\leqq 2\times$ the upper limit of normal; creatinine $\leqq 1.5$ mg/dL; creatinine clearance $\geqq 60$ ml/min. Written informed consent was given prior to entry onto the study.

The pretreatment evaluation consisted of a complete history and physical examination, electrocardiogram, and laboratory workup (complete blood count with differential and platelet count, electrolytes, chemistry profile, prothrombin time, and partial thromboplastin time). The staging procedures included chest X-ray, bone scan, computed tomography (CT) scan of the brain and chest, and abdominal ultrasonography or CT scan of the abdomen. Bone marrow examinations were not routinely performed. Restaging was performed after four courses of chemotherapy. Limited disease was defined as tumor confined to one hemithorax but including mediastinal involvement and bilateral supraclavicular lymph nodes. Extensive disease denoted any involvement beyond these confines, including pleural effusion.

Treatment Regimens

Chemotherapy consisted of starting doses of CBDCA 400 mg/m^2 i.v. on Day 1 and VP-16 100 mg/m^2 i.v. on Days 1, 2, and 3, and G-CSF 2 $\mu g/kg$ subcutaneously on Day 4–17. The dose of VP-16 was fixed at 100 mg/m^2. The dose of CBDCA was escalated in increments of 50 mg/m^2 according to toxicity criteria. The chemotherapy cycle was given every 4 weeks to a total of four cycles. Treatment with G-CSF was discontinued if the leukocyte count (or neutrophil count) was greater than $10 \times 10^3/mm^3$ (neutrophil count $\geqq 5 \times 10^3/mm^3$). Patients with LD who had completed four cycles of chemotherapy were given radiotherapy to the prechemotherapy tumor volume at a total dose of more than 40 Gy in daily fractions, with a daily dose of 2 Gy, 5 times a week. Patients who responded after four cycles of chemotherapy [complete response (CR) and good partial response (PR)] were eligible to receive prophylactic cranial irradiation at a dose of 24 Gy in 12 daily fractions over 3 weeks.

Toxicity and Evaluation of Response

Toxicity was scored using World Health Organization criteria. A minimum of three patients were treated at each dose level. To determine the MTD of this combination, toxicity was assessed by one of the following events: (1) Grade 4 thrombocytopenia for 1 day or Grade 4 leukopenia for 4 days or more, (2) Grade 2 renal or liver dysfunction, (3) any other nonhematologic, nonhepatic, and nonrenal Grade 3 toxicities excluding alopecia. If any of the side effects developed in one or less of the three patients, the dose level was increased to the next step. If any of the side effects developed in two or more of the three patients, the dose level was expanded to six patients. If any of the side effects developed in two or less of the six patients, the dose level was increased to the next step. The MTD was defined as the dose level at which the next higher dose level produced one of the three side effects in two-thirds or more of the patients. Patients were enrolled and treated at a lower dose level until the toxicity of the next higher dose level was fully evaluated. CBDCA and VP-16 doses were reduced by 25% if Grade 4 leukopenia developed for 4 days and more, or if Grade 4 thrombocytopenia developed for 1 day. Further chemotherapy was terminated if Grade 3 liver dysfunction or renal dysfunction developed during the treatment, or if the next cycle of chemotherapy was delayed 2 weeks more than the expected date. The criteria for proceeding to the next cycle of treatment were recovery of bone marrow function (leukocyte count $\geqq 3000$ mm^3, or neutrophil count $\geqq 1000$ mm^3), normal renal function, and recovery of hepatic toxicity to Grade 1. During the course of the study, a high incidence of severe hematologic toxicities was observed in patients older than 70 years at a dose of 500 mg/m^2. We thus made a minor protocol change to conduct the trial further: dose levels greater than 500 mg/m^2 were limited to patients younger than 70 years of age.

Response to chemotherapy was assessed by clinical examination, chest radiographs, and repeated CT scans, abdominal ultrasonography, and bronchoscopy where necessary. Tumor volume was defined as the sum of the product of the two largest perpendicular dimensions of all measurable lesions. Complete response was defined as complete disappearance of all objective clinical evidence of disease. Partial response was defined as a decrease in tumor volume by more than 50%. Good PR was defined as a decrease in tumor volume by more than 90%. Response had to be maintained for 4 weeks with no new lesions appearing. Strict extramural review for response was performed at the Evaluation Committee of the Lung Cancer Study Group-West Japan.

Statistical Methods

Survival was calculated from the first day of protocol treatment until death or last patient contact. Survival was estimated by the Kaplan–Meier method. Differences of subgroups in survival were compared using the log rank test and generalized Wilcoxon test.

TABLE 1
Patient Characteristics

Entered	75
Eligible	71
Median age (range)	63 (49–79)
Male	58
Female	13
Age	
<70 yr	57
≥70 yr	14
Performance status (ECOG)	
0–1	49
2	22
Stage	
Limited disease	44
Extensive disease	27
Prior therapy	
Yes	0
No	71

ECOG: Eastern Cooperative Oncology Group.

RESULTS

Patient Characteristics

Between August 1991 and March 1993, 75 patients with pathologically proven SCLC were entered onto the trial. Four patients were later found to be ineligible for this study: one patient had double primary cancers (SCLC and hepatoma); one patient was diagnosed as having non-small cell lung cancer instead of SCLC; one patient had concurrent pulmonary infarction; one patient, who had previously undergone surgery, had recurrent SCLC. The patient characteristics of 71 eligible patients are summarized in Table 1. Median age was 63 years (range, 49–79 years). Fifty-eight patients were men and 13 patients were women. Fifty-seven patients were younger than 70 years and 14 patients were older than 70 years. Two-thirds of the patients had a performance status of 0 or 1. Forty-four patients had limited disease and 27 had extensive disease. One patient enrolled in the trial had had mastectomy for breast cancer 10 years ago, but did not have recurrence and had received neither chemotherapy nor radiotherapy. All other patients had had no previous treatment.

Toxicity and Maximum Tolerated Dose Determination

All 71 eligible patients were assessed for toxicity. No treatment-related deaths were observed. The major toxicity was hematologic. As shown in Table 2, four of five patients (80%) older than 70 years developed Grade 4 thrombocytopenia (platelet count $<2.5 \times 10^4$/mm^3) at a

TABLE 2
Thrombocytopenia, Leukocytopenia, and Anemia in Patients Who Developed WHO Grade 4 Toxicity

	Dose Level of CBDCA (mg/m^2)						
	400	450	500	550	600	650	700
Age <70 yr							
No. of patients	5	10	9	12	9	9	3
Median platelet count (× 10^4/mm^3)	8.9	7.8	3.3	4.4	2.9	2.6	1.2
WHO toxicity Grade 4 (%)	0 (0)	1 (10)	4 (44)	4 (33)	4 (44)	3 (33)	3 (100)
Median leukocyte count	3900	4160	2700	2500	2800	3700	600
WHO toxicity Grade 4 (%)	0 (0)	1 (10)	2 (22)	0 (0)	1 (11)	0 (0)	2 (67)
Median hemoglobin (g/dL)	9.7	8.6	9.0	8.1	7.9	8.6	7.0
WHO toxicity Grade 4 (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	1 (33)
Age ≧70 yr							
No. of patients	1	8	5				
Median platelet count (× 10^4/mm^3)	2.5	2.8	1.7				
WHO toxicity Grade 4 (%)	0 (0)	4 (50)	4 (80)				
Median leukocyte count	1200	3645	800				
WHO toxicity Grade 4 (%)	0 (0)	0 (10)	3 (22)				
Median hemoglogin (g/dL)	8.9	8.5	7.1				
WHO toxicity Grade 4 (%)	0 (0)	0 (0)	0 (0)				

CBDCA, carboplatin; WHO, world health organization; WHO toxicity scale: Grade 4 thrombocytopenia = platelet count <2.5 × 10^4/mm^3; Grade 4 leukopenia = leukocyte count <1000/mm^3; Grade 4 anemia = hemoglobin <6.5 g/dL.

dose level of 500 mg/m^2. Three of five patients (60%) of the same age group developed Grade 4 leukopenia (leukocyte count <1000/mm^3). On the other hand, the dose-limiting toxicity (DLT) was not reached in patients younger than 70 years. We made a protocol change based on these acquired data and conducted the trial further. Dose levels greater than 500 mg/m^2 were limited to patients younger than 70 years of age since a high incidence of severe hematologic toxicities was observed in patients older than 70 years at a dose of 500 mg/m^2. At a dose level of 700 mg/m^2 all of three patients younger than 70 years of age developed Grade 4 thrombocytopenia, and two of three patients (60%) of the same age group developed Grade 4 leukopenia. The dose-limiting toxicity of CBDCA was reached at a dose level of 700 mg/m^2 in patients younger than 70 years, and no more patients were entered onto the trial. As initially defined, the MTD was 650 mg/m^2 if patients were younger than 70 years old and 450 mg/m^2 if they were older than 70. The other toxicities (summarized in Table 3) were generally mild and well tolerated. More importantly, no treatment-related death or neutropenic infection was observed.

Dose reductions were required at each step in more than half of the patients who received more than one cycle (Table 4). Most of the dose reduction was due to Grade 4 thrombocytopenia. The median cycle of chemotherapy at each dose level was as follows: four cycles at a dose of 400 mg/m^2, 3.5 cycles at a dose of 450 mg/m^2, 4 cycles at a dose of 500 mg/m^2, 4 cycles at a dose of 550 mg/m^2, 4 cycles at a dose of 600 mg/m^2, 4 cycles at a dose of 650 mg/m^2, and 3 cycles at a dose of 700 mg/m^2. No serious renal or hepatic toxicities were seen. Some degree of nausea or vomiting at any time during treatment occurred. No patients experienced ototoxicity. Twenty-eight of 44 patients with limited disease (64%) received thoracic radiotherapy after chemotherapy. The median dose of radiotherapy was 60 Gy.

Response Rate and Survival

The overall response rate was 81% (95% confidence interval, 72–90%), with 16 CR (23%) and 41 PR (58%) (Tables 5 and 6). The response rate was 80% in LD patients (CR, 23%; PR, 57%) and 85% in ED patients (CR, 23%; PR, 62%). The median follow-up duration of 71 eligible patients was 24 months. Overall MST was 9 months (95% confidence interval, 8–11 months). The MST of LD and ED patients were 11 and 7 months, respectively (Fig. 1). There was no statistical difference in survival between these two groups ($P > 0.05$).

DISCUSSION

The single agents CBDCA and VP-16 are highly active for the treatment of SCLC and their DLTs are mainly hematologic. We hoped that G-CSF might increase the dose intensity of CBDCA by reducing myelosuppression and thus enhancing the response rate and improving survival in patients with SCLC, even though limited effects on thrombocytopoiesis have been reported.[4,5] The need for this approach is driven by increasing evidence that dose and dose intensity (dose per unit time) of administered

TABLE 3
Side Effects (Nonhematologic)

	Dose level of CBDCA (mg/m^2)						
	400	450	500	550	600	650	700
No. of patients	6	18	14	12	9	9	3
No. of patients developing WHO toxicity							
Grade 3–4 (%)	3 (50)	4 (22)	14 (100)	10 (83)	8 (89)	8 (89)	3 (100)
BUN, creatinine	0	0	0	0	0	0	0
GOT, GPT	0	1	0	1	0	0	0
Nausea, vomiting	1	1	1	2	1	0	0
Diarrhea	0	0	0	1	0	0	0
Anorexia	1	0	4	0	0	0	0
General malaise	1	2	4	1	0	0	0
Fever	0	0	1	0	0	0	0
Hair loss	0	0	4	5	7	8	3
Hearing loss	0	0	0	0	0	0	0

CBDCA: carboplatin; WHO: World Health Organization; BUN: blood urea nitrogen; GOT: glutamate oxaloucetate transaminase; GPT: glutamate-pyruvate transaminase.

TABLE 4
Dose Reduction at Each Step (One Through Four Cycles of Chemotherapy)

	Dose level of CBDCA (mg/m^2)						
	400	450	500	550	600	650	700
No. of patients	6	18	14	12	9	9	3
Dose reduction							
Yes (%)	3 (50)	10 (56)	8 (57)	6 (50)	5 (56)	7 (78)	2 (67)
No	3	8	6	6	4	2	1

CBDCA: carboplatin.

TABLE 5
Response (No. of Patients)

CBDCA (mg/mm^2)	CR	PR	NC	PD	NE	CR rate (%)	RR (%)
400	0	5	0	1	0	0	83
450	4	11	2	1	0	22	83
500	4	5	5	0	0	29	64
550	3	8	1	0	0	25	92
600	2	5	1	0	0	25	88
650	3	5	1	0	0	33	89
700	0	2	0	0	1	0	67
Overall	16	41	10	2	1	23	81

CBDCA: carboplatin; CR: complete response; PR: partial response; NC: no change; PD: progression of disease; NE: not evaluated; RR: response rate.

anticancer agents may determine the effectiveness of cancer chemotherapeutic regimens.[14,15]

Recently three dose-escalating studies of CBDCA and VP-16 for SCLC have been reported.[16–18] The dose of VP-16 was fixed, and no G-CSF or hematopoietic marrow support was used. The present trial is the first dose escalation study of CBDCA with the primary end point of determining the MTD of CBDCA, administered with a fixed dose of VP-16 and G-CSF support. The major dose-limiting toxicity of the regimen that we selected in this trial

TABLE 6
Relationship Between Delivered Dose and CR Rate

Step	Planned dose of CBDCA (mg/m²/week)	Delivered dose of CBDCA (mg/m²/week; 1–2 cycles)	CR rate (%)
1	100	95.8	0
2	112.5	108.5	22
3	125	110.1	29
4	137.5	131.4	25
5	150	135.5	25
6	162.5	158.4	33
7	175	131.3	0

CR: complete response; CBDCA: carboplatin.

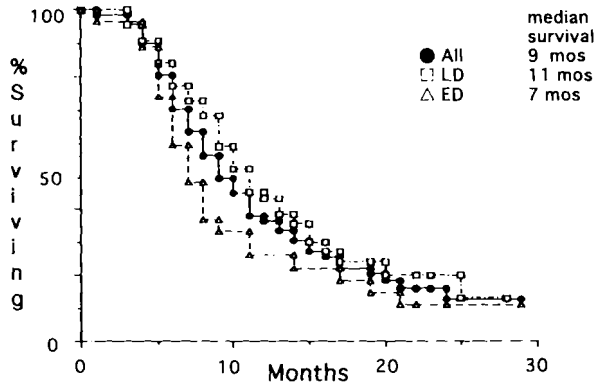

FIGURE 1. Survival curve of all small cell lung cancer patients, limited disease (LD) patients, and extensive disease (ED) patients. ●, all patients; □, LD patients; △, ED patients. Median survival times: all patients, 9 months; LD patients, 11 months; ED patients, 7 months.

was bone marrow toxicity, especially thrombocytopenia, which was anticipated from the beginning of the study. At an interim analysis it became clear that 80% of patients older than 70 years developed Grade 4 thrombocytopenia (platelet count $<2.5 \times 10^4/mm^3$) at a dose of 500 mg/m² of CBDCA. This dose level was thus considered unacceptable for patients older than 70 years. As already stated, we made a minor protocol change after accrual of 14 patients older than 70 years old. Dose levels greater than 500 mg/m² were limited to patients younger than 70 years of age since a high incidence of severe hematologic toxicities was observed in patients older than 70 years at a dose of 500 mg/m². In a Phase I trial by Liippo et al.,[17] in which CBDCA was given to previously untreated patients with a dose of 100 mg/m² VP-16 on Days 1–3 without G-CSF and the criteria of unacceptable toxicity were Grade 4 leukopenia and thrombocytopenia, the authors reported that the MTD of CBDCA was 500 mg/m². They also reported that there was a significant ($P = 0.003$) correlation between the platelet nadir during any given treatment cycle and initial creatinine clearance (≧0.9 ml/s/1.73 m²). In view of the potential thrombocytopenia induced by CBDCA, which could not be changed with G-CSF, we selected only patients with a serum creatinine clearance above 60 ml/min.

On the other hand, in a Phase I trial of CBDCA and VP-16 without G-CSF by Tueni et al.,[19] in which the criterion of intolerable toxicity was Grade 3-4 bone marrow suppression and in which most of the patients had been treated previously, the MTD of CBDCA was reported to be 350 mg/m² on Day 1 with 100 mg/m² VP-16 given on Days 1–3. In another Phase I trial of the same combination, previously untreated ED SCLC patients were treated with VP-16 200 mg/m²/day on Days 1–3 and CBDCA doses of 50, 100, or 125 mg/m²/day on Days 1–3 without marrow support.[18] Among the 10 eligible patients treated with 125 mg/m²/day of CBDCA, Grade 4 thrombocytopenia developed in 4 patients, and there was one treatment-related death. These authors thus considered this dose of CBDCA to be the MTD. From the trials described above, we may conclude that the MTD of CBDCA when used with a standard dose of VP-16 and no marrow support has been between 350 mg/m² and 500 mg/m². In the current study, we demonstrated that the MTD of CBDCA was reached at a dose of 650 mg/m² in previously untreated SCLC patients younger than 70 years, and 450 mg/m² in such patients older than 70.

In general, the patients tolerated the treatment well: gastrointestinal symptoms were minimal, and no serious renal toxicity, ototoxicity, or infection developed. Most importantly, no treatment-related death was observed. The CBDCA/VP-16 combination seems to be less toxic than the cisplatin/VP-16 combination, which is one of the most effective first-line combinations for the treatment of SCLC.[11,12] Recently, in a randomized trial, it was demonstrated that the CBDCA/VP-16 regimen caused significantly less nausea, vomiting, nephrotoxicity, and neurotoxicity compared with the cisplatin/VP-16 regimen and that both combinations were equally effective.[16] Presently we might consider the CBDCA/VP-16 regimen superior to the cisplatin/VP-16 regimen for the treatment of SCLC in light of toxicity, although further randomized trials should be conducted to confirm this advantage.

To prevent the potentially life-threatening myelotoxicity of cytotoxic chemotherapy, dose reductions were often made. The main reason for dose reduction was thrombocytopenia, and more than half of the patients required dose modification at each dose level. Therefore the dose-limiting factor of increasing dose intensity was thrombocytopenia. As a result of such planned dose reduction, we could not achieve the planned dose intensity of CBDCA. For instance, the actual delivered dose of CBDCA through one to two cycles at a dose of 650 mg/m² (step 6) was 158.4 mg/m²/week instead of the planned

dose, 162.5 mg/m^2/week. Although patients could receive platelets transfusions several times to overcome Grade 4 thrombocytopenia, such rescue brings about an increased risk of transfusion-related hepatitis and other untoward effects. Therefore methods other than G-CSF administration are apparently necessary for maintaining platelet numbers above life-threatening levels and achieving planned dose intensity, since G-CSF has not been reported to promote megakaryocytopoiesis.[4] For that purpose we will have to adopt bone marrow reconstituting methods such as ABMT or PBSCT, or combine G-CSF with other cytokines such as interleukin-3, which has proved to have some ability to increase platelet levels.[20] More recently, thrombopoietin has been purified, cloned, and shown to increase levels of platelets when injected into animals.[21-24] In the future, optimal doses of these cytokines combined with G-CSF may allow chemotherapy dose escalation and increasing dose intensity, and may hopefully improve the cure and survival rates of patients with SCLC.

The overall response rate in patients treated with our regimen was 81%, with a 23% CR rate. The response rate was 80% in LD patients (CR, 23%; PR, 57%) and 85% in ED patients (CR, 23%; PR, 62%). No correlation was found between the response rate and actual delivered dose. The relatively low delivered dose was mainly due to the 25% dose reduction of CBDCA and VP-16 made in subsequent chemotherapy cycles, which was undertaken because of Grade 4 myelosuppression, especially thrombocytopenia. The previous studies using standard doses of these two agents without G-CSF reported that objective responses were observed in 77–86% of patients with LD (CR, 29–40%) and 58–88% of patients with ED (CR, 9–17%).[11-13,16,18] When compared with these studies, the current regimen was at least equivalent in its response rate.

Despite the high activity and low incidence of serious toxicity of the combination, we were not able to attain long term survival for either LD or ED patients. The MST of LD and ED patients were 11 and 7 months, respectively. On the other hand, the MST reported by some investigators who treated ED patients with the same combination ranged from 8 to 12 months.[12,13,16,18] In all of those trials treatment was administered for up to a total of five to eight cycles without G-CSF or GM-CSF. There are several reasons for this result. First, the CR rate was between 0% and 33% throughout all dose levels in our trial. The overall CR rate was 23% in both LD and ED patients. A high CR rate might be a prerequisite for obtaining longer response duration and survival time. Second, as Smith et al.[11] indicated, a 4-week interval between treatments might be too long for a cancer like SCLC with a rapid growth rate. Third, it may be that four courses of chemotherapy were insufficient, although recent randomized studies have suggested that, as in most other cancers potentially curable with chemotherapy, maintenance chemotherapy plays a small role in SCLC in terms of survival.[25-27] Finally, chest irradiation was administered to only two-thirds of LD patients. All responding patients should have received thoracic radiotherapy since it has been clearly demonstrated in two recent meta-analyses that chemotherapy and radiotherapy combined bring about longer survival than chemotherapy alone in limited stage SCLC.[28,29]

Numerous prognostic factors have been identified in patients receiving conventional chemotherapy for SCLC.[30-32] Among them disease extent was by far the most important favorable factor, but we could not find a statistically meaningful difference in survival between LD and ED patients (MST of LD, 11 months; MST of ED, 7 months). Possibly there were not enough patients to detect statistical differences in each subgroup, or all LD patients may not have received thoracic radiotherapy, or they may have received radiotherapy too late. In regard to late radiotherapy, Murray et al.[33] recently demonstrated in a randomized trial that the early administration of thoracic irradiation in the combined modality therapy of limited stage SCLC was superior to late or consolidative irradiation. In any case, all eligible patients with limited stage SCLC should receive thoracic irradiation to achieve longer survival.

In conclusion, the DLT of CBDCA with a fixed dose of VP-16 and G-CSF as bone marrow rescue was age-related thrombocytopenia. The MTD of CBDCA in this regimen was reached at a dose of 650 mg/m^2 in SCLC patients younger than 70 years of age and 450 mg/m^2 in patients older than 70. When we retrospectively compared our results with those found using standard regimens such as VP-16 and cisplatin,[1] we could not find a therapeutic benefit from increasing planned doses of CBDCA up to 700 mg/m^2 in combination with G-CSF in patients with SCLC.

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