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ORIGINAL ARTICLE

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Dose-intensive chemotherapy in extensive-stage small-cell lung cancer

Abstract The importance of the dose intensity of chemotherapy in achieving maximal therapeutic effect has recently been reported for several chemosensitive malignant diseases, with Murray et al. reporting that intensive weekly chemotherapy using the cisplatin, vincristine, doxorubicin, and etoposide (CODE) regimen in small-cell lung cancer (SCLC) is very effective. However, leukopenia is the major obstacle to delivering the planned dose in intensive regimens. Therefore, we investigated whether recombinant human granulocyte colony-stimulating factor (rhG-CSF) could allow full drug doses to be given as scheduled, thereby improving the final outcome. Extensive-stage (ES) SCLC patients were randomized to receive either CODE alone or CODE with rhG-CSF, with the CODE regimen consisting of cisplatin given i.v. at 25 mg/m^2 weekly for 9 weeks; vincristine given i.v. at 1 mg/m^2 during weeks 1, 2, 4, 6, and 8; and doxorubicin given i.v. at 40 mg/m^2 and etoposide given i.v. at 80 mg/m^2 for 3 days during weeks 1, 3, 5, 7, and 9. rhG-CSF at 50 μg/m^2 was given s.c. on the days on which cytotoxic drugs were not given. From May 1989 to September 1991, 64 patients were enrolled in the study, of whom 63 were analyzable (31 for CODE alone and 32 for CODE with rhG-CSF). No difference in any of the patients' characteristics except gender was found between the two groups. The complete response (CR) rate was 34% in the CODE with rhG-CSF group and 23% in the CODE alone group; the median survival was 59 and 32 weeks, respectively, in these groups (P = 0.004). Therefore CODE with rhG-CSF improved the survival of ES SCLC patients. On the basis of these results a phase III study to determine whether CODE with rhG-CSF would increase survival as compared to the standard regimen in ES SCLC was designed by the Japan Clinical Oncology Group.

Key words Extensive-stage small-cell lung cancer · Dose intensity · CODE chemotherapy · rhG-CSF

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Introduction

Although combination chemotherapy for small-cell lung cancer (SCLC) has improved survival, such improvements are limited in patients with extensive disease. Survival achieved with conventional chemotherapy for extensive-stage SCLC (ES SCLC) has plateaued at 8–9 months [1], and the cure rate remains extremely low. The importance of the dose intensity of chemotherapy in achieving the maximal therapeutic effect has been reported for chemosensitive tumors [5], with Murray et al. [11] reporting that intensive weekly chemotherapy using the cisplatin, vincristine, doxorubicin, and etoposide (CODE) regimen in SCLC is very effective. However, leukopenia is the major toxicity preventing the delivery of the scheduled dose in intensive regimens. It has been reported that recombinant human granulocyte colony-stimulating factor (rhG-CSF) can reduce the degree, duration, and complications of neutropenia induced by cytotoxic chemotherapy for SCLC [3, 4, 12]. Therefore, we investigated whether rhG-CSF could allow

Table 1 Patients' characteristics (*NS* Not significant)

Characteristic	Number of patients		Probability
	CODE+rhG-CSF	CODE alone	
Eligible	32	32	
Median age in years (range)	61 (44–73)	61 (42–73)	NS
M:F (%)	25:7 (78:22)	31:1 (97:3)	0.023
Performance status (%):			
0, 1	19 (59)	15 (52)	NS
2	13 (41)	17 (48)	
Metastatic site (%):			
Liver	7 (22)	13 (41)	NS
Bone	10 (31)	5 (16)	NS
Bone marrow	3 (9)	1 (3)	NS
Brain	2 (6)	6 (19)	NS
Lung	7 (22)	6 (19)	NS
Pleura	5 (16)	7 (22)	NS
Other	4 (13)	7 (22)	NS

full drug doses to be given as scheduled to patients with ES SCLC, thereby improving the final outcome [6, 7, 9]. On the basis of the results of this study the Japan Clinical Oncology Group (JCOG) initiated a phase III study to determine whether CODE with rhG-CSF would increase survival as compared to the standard regimen [8].

Patients and methods

The criteria for entry included histological or cytological evidence of SCLC; ES disease, including ipsilateral pleural effusion, measurable or evaluable disease; no prior therapy; a life expectancy of >8 weeks; a performance status of 0–2 (Eastern Cooperative Oncology Group scale); an age of 18–75 years; adequate bone marrow reserve; normal hepatic and renal function; no active concomitant malignant disease; and written informed consent of the patient. Clinical features at diagnosis, staging procedures, and criteria for assessing the response to treatment have been described elsewhere [6, 9].

From May 1989 to September 1991, 64 consecutive patients with ES SCLC were enrolled in the study. Patients were randomly assigned to receive CODE alone or with rhG-CSF support. CODE chemotherapy was similar to that described by Murray et al. [11], with the regimen consisting of cisplatin given at 25 mg/m^2 weekly for 9 weeks; vincristine given at 1 mg/m^2 during weeks 1, 2, 4, 6, and 8; and doxorubicin given at 40 mg/m^2 and etoposide 80 mg/m^2 for 3 days during weeks 1, 3, 5, 7, and 9. rhG-CSF at 50 μg/m^2 was given by s.c. injection daily except on treatment days. Treatment was delayed for $\geq$1 week when total leukocyte counts were $<1\times10^3$/μl or platelet counts were $<30\times10^3$/μl. When counts recovered, treatment was restarted using the full drug dose.

Results

In all, 64 patients were enrolled and all were eligible. The patients' characteristics according to treatment group are given in Table 1 [6, 7, 9]. Age and performance status were well matched between the groups, although there were more women in the rhG-CSF group and hepatic metastases were more frequent in the control group. One patient committed suicide before the beginning of treatment. Therefore, 63 patients, 32 in the rhG-CSF group and 31 in the control group, were evaluable for response, toxicity, and survival.

Figure 1 shows the changes observed in mean neutrophil counts during CODE therapy. Absolute neutrophil counts measured in patients treated with rhG-CSF were higher than those determined in patients in the control group throughout the treatment period. Table 2 shows the incidence of febrile episodes in neutropenic patients; significantly fewer febrile patients were receiving rhG-CSF (44% versus 77%; $P<0.01$). Toxicities other than leukopenia have been described elsewhere [6].

The cumulative percentage of the planned dose received by patients in each group is shown in Table 3. The percentages of the scheduled cisplatin, doxorubicin, and etoposide doses delivered were significantly higher in patients treated with rhG-CSF than in control patients. The use of rhG-CSF thus allowed improved delivery of the CODE regimen.

Table 4 shows the tumor response to CODE therapy. The complete response (CR) rate was 34% in patients treated

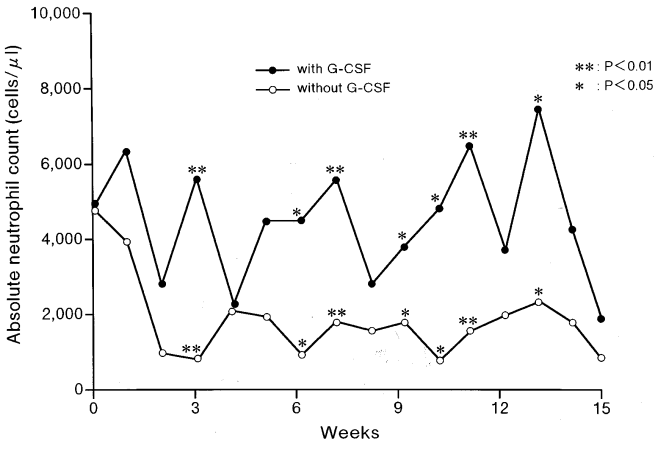

Fig. 1 Changes in mean neutrophil counts observed during CODE therapy with (●) or without (○) rhG-CSF. *$P<0.05$; $P<0.01$

Table 2 Incidence of neutropenic fever of ≥38 °C (*NS* Not significant, *ANC* absolute neutrophil count)

Parameter	CODE+rhG-CSF (n = 32)	CODE alone (n = 31)	P
Number of febrile patients(%)	14 (44)	24 (77)	<0.01
Mean duration of neutropenic fever (days)	3.4	4.3	NS
Mean duration of ANC <500/μl	9.1	24.7	<0.01

Table 3 Delivered dose intensity (*DI* Dose intensity)

Drug	Delivered DI/scheduled DI		
	CODE+rhG-CSF (n = 32)	CODE alone (n = 31)	P
Cisplatin	0.836	0.716	0.02
Vincristine	0.839	0.750	0.06
Doxorubicin	0.824	0.730	0.04
Etoposide	0.812	0.684	0.02
Mean	0.828	0.720	

Table 4 Response to therapy (*PR* Partial response, *NC* no change, *PD* progressive disease, *NE* not evaluable)

Response	Number of patients responding (%)		
	CODE+rhG-CSF (n = 32)	CODE alone (n = 31)	P
CR	11 (34)	7 (23)	
PR	20 (63)	19 (61)	0.07
NC	0	2 (6)	
PD	0	1 (4)	
NE	1 (3)	2 (6)	
CR+PR	31 (96)	26 (84)	0.10

with rhG-CSF and 23% in control patients; the overall response rate was 96% and 84%, respectively. No significant difference in the CR rate or overall response rate was found between the two groups.

The median follow-up of living patients was 42.3 months. At the time of this analysis, 24 patients in the rhG-CSF group and 21 in the control group had died of SCLC; a further 2 and 5 patients, respectively, had died of causes unrelated to the disease. The 45-week median survival rate recorded for all patients is greater than that reported in the literature [2]. The median survival recorded after the rhG-CSF group was 59 weeks as compared with 32 weeks for the control group. The 1-, 2-, and 3-year actuarial survival noted for patients treated with rhG-CSF were 59.4%, 31.3%, and 9.4% as compared with 22.6%, 6.5%, and 3.2%, respectively, for control patients. The survival advantage for patients treated with CODE with rhG-CSF was statistically significant. Multivariate analysis according to prognostic factors confirms that treatment with rhG-CSF is the only variable that significantly affects patient survival [7].

Discussion

This trial has demonstrated that the use of rhG-CSF in the CODE regimen is associated with an increase in delivered dose intensity. In addition, CODE plus rhG-CSF is associated with a 27-week prolongation of median survival time and an approximately 5-fold increase in the 2-year survival rate (31.3% versus 6.5%) as compared with the CODE-only group. The median survival of 32 weeks recorded for patients who received CODE alone is comparable to that reported for ES SCLC patients [2].

This is the first randomized study of chemotherapy with rhG-CSF in SCLC patients to show that rhG-CSF administration significantly prolongs survival by allowing the cytotoxic drug dose intensity to be increased. In contrast, Miles et al. [10] reported that in their randomized trial of weekly alternating chemotherapy with or without rhGCSF in SCLC patients, rhG-CSF administration did not allow a significant increase in received dose intensity. In their trial, cycle delays due to leukopenia were similar in both arms and nonhematologic toxicities, such as increased creatinine concentration, also prevented increases in received dose intensity. Therefore, rhG-CSF may not be suitable for regimens in which myelosuppressive drugs are given weekly. Since the CODE regimen designed by Murray et al. [11] alternates cycles of myelosuppressive and nonmyelosuppressive drugs, it may be more suitable for use with rhG-CSF to alleviate chemotherapy-induced neutropenia.

Conclusions

Our results demonstrate that in patients with ES SCLC, CODE with rhG-CSF prolongs survival as compared to CODE alone. The results of a phase III JCOG trial will be reported in the near future.

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