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ORIGINAL ARTICLE

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Phase II study of recombinant human interleukin 3 administration following carboplatin and etoposide chemotherapy in small-cell lung cancer patients

Abstract Recombinant human interleukin 3 (rhIL-3) has been suggested to be a useful agent for the treatment of chemotherapy-induced thrombocytopenia. For evaluation of this possibility, rhIL-3 was given subcutaneously for 10 days to patients with small-cell lung cancer (SCLC). Chemotherapy consisted of carboplatin (CBDCA) given at 400 mg/m^2 to previously untreated patients or at 350 mg/m^2 to previously treated patients on day 1 and etoposide (VP-16) given at 100 mg/m^2 on days 1–3 every 4 weeks. If the platelet count nadir was $<75{,}000/\mu l$ in the control cycle of chemotherapy, patients were randomly assigned for the next cycle to rhIL-3 given at 5 or 10 μg/kg per day on days 4–13. A total of 41 patients (32 previously untreated patients and 9 previously treated patients) were enrolled in the study. The platelet count nadir in the cycles including rhIL-3 was significantly higher at both dose levels ($P<0.01$) than in the control cycle. The duration of thrombocytopenia ($<75{,}000/\mu l$) and the mean time from the 1st day of chemotherapy to thrombocyte recovery ($>100{,}000/\mu l$) in the rhIL-3 cycle were significantly shorter than those in the control cycle ($P<0.01$). The neutrophil count nadir and the duration of neutropenia ($<1{,}000/\mu l$) were also significantly improved in the rhIL-3 cycle ($P<0.05$). The major side effects were fever (80.5%), headache (24.3%), and fatigue (14.6%). All side effects were tolerable and of less than grade II. There was no difference in the efficacy of the two dose levels, but the 5-μg/kg dose appeared to be better tolerated than the 10-μg/kg dose. We conclude that rhIL-3 administration following chemotherapy consisting of CBDCA and VP-16 reduces the incidence and severity of chemotherapy-induced thrombocytopenia and neutropenia with an acceptable adverse-events profile.

Key words Recombinant human interleukin 3 (rhIL-3) · Thrombocytopenia · Chemotherapy · Small-cell lung cancer

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Introduction

Small-cell lung cancer (SCLC) is a chemosensitive solid tumor; systemic chemotherapy improves the survival of SCLC patients. To improve the outcome of this disease further, many ongoing clinical trials are examining regimens such as the combination of chemotherapy and thoracic irradiation and dose-intensive chemotherapy. However, increasing the dose of chemotherapeutic agents is frequently limited by myelosuppression. To overcome this myelotoxicity, several hematopoietic growth factors, including granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage (GM)-CSF, have been developed. These CSFs have already demonstrated their ability to reduce chemotherapy-induced neutropenia and to increase the chemotherapy dose and frequency of on-schedule administration [1, 4, 6, 19]; however, chemotherapy-induced thrombocytopenia is not reduced by G-CSF or GM-CSF.

Interleukin 3 (IL-3) is a glycoprotein with a molecular weight of 25 kDa. It is mainly produced by activated T-lymphocytes and promotes the proliferation and differentiation of myeloid progenitors of neutrophils, macrophages, eosinophils, basophils, megakaryocytes, and erythrocytes [15, 23, 25]. The gene encoding human IL-3 has been cloned [30], and recombinant human IL-3 (rhIL-3) is now available for therapeutic administration [16]. In preclinical studies in a primate model, rhIL-3 administration following cyclophosphamide or 5-fluorouracil chemotherapy has been shown to hasten the recovery of neutrophil and platelet counts [11]. Multilineage stimulatory effects on hematopoiesis were observed in patients with advanced malignancies, myelodysplastic syndromes, and aplastic anemia [7–9, 14]. A number of clinical trials involving rhIL-3 administration to patients receiving chemotherapy have demonstrated its hematopoietic effects and toxicity. Subcutaneous infusion of rhIL-3 therapy is well tolerated, and toxicity is mild at a dose of ≤10 μg/kg per day; the maximum tolerated dose is around 15 μg/kg per day and the dose-limiting toxicity is headache [2]. Additional side effects include fever, flu-like symptoms, myalgias, and skin rash, among others. Multilineage hematopoiesis was demonstrated at a dose of ≥5 μg/kg per day [2, 20]. However, little is known about the optimal dose and hematopoietic effects, especially on thrombopoiesis, of rhIL-3.

In the present study, rhIL-3 was given at two potential optimal doses (5 and 10 μg/kg per day). The objective of this study was to evaluate the safety and efficacy of rhIL-3 given following carboplatin and etoposide chemotherapy in patients with SCLC.

Patients and methods

Patient selection

Patients presenting with histologically or cytologically confirmed, previously untreated SCLC, or tumor relapse or progressive disease after first-line chemotherapy were eligible for this study. The interval between the most recent chemotherapy and the start of the trial had to be ≥4 weeks. Patients receiving a weekly chemotherapy regimen were excluded. Additional entry criteria were as follows: an age between 15 and 74 years; a World Health Organization (WHO) performance status of ≤2 [29]; a leukocyte count of ≥4,000/μl; a platelet count of ≥100,000/μl; a hemoglobin concentration of ≥9.0 g/dl; and creatinine clearance of ≥60 ml/min. Patients with severe heart, lung, liver, or kidney impairment were excluded, as were patients with prior thoracic or pelvic irradiation, a history of serious allergic reactions, or bone marrow metastasis. All patients gave written informed consent and the protocols were approved by the institutional review board for human experimentation.

rhIL-3 and chemotherapy

Escherichia coli-derived nonglycosylated rhIL-3 with a specific activity of $2-10\times10^6$ U/mg protein was provided by Sandoz Pharmaceuticals (Tokyo, Japan) as a lyophilized powder in vials of 275, 550, and 825 μg. The drug was reconstituted with 1.1 ml of sterile water prior to administration as a daily subcutaneous injection.

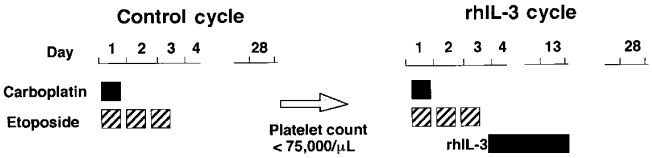

Fig. 1 Diagram of the protocol schedule

Previously untreated patients received chemotherapy consisting of carboplatin given at 400 mg/m² on day 1 and etoposide given at 100 mg/m² on days 1, 2, and 3; this regimen was repeated every 3 or 4 weeks. Patients who had relapsed or progressed after initial chemotherapy received the same chemotherapeutic agents, but the dose of carboplatin was reduced to 350 mg/m².

Study design

The treatment schedule is shown in Fig. 1. Patients who fulfilled the eligibility criteria were provisionally enrolled into the study. The first treatment cycle was the control cycle. Patients who experienced platelet nadir counts of <75,000/μl in this cycle were entered into the study. The next treatment cycle was an rhIL-3 cycle; carboplatin and etoposide chemotherapy given in this cycle was the same as that used in the control cycle. rhIL-3 was injected subcutaneously for 10 days, on days 4–13; patients were randomized to receive either 5 or 10 μg/kg per day and were stratified according to the platelet nadir counts measured during the control cycle (<50,000/μl or ≥50,000/μl). Chemotherapy was repeated every 3 to 4 weeks for four to six cycles unless patients demonstrated disease progression or undue toxicity. Patients with limited disease received thoracic radiotherapy after four cycles of chemotherapy.

All patients were hospitalized during the study. Pretreatment study investigations included a history and physical examination; chest radiography; electrocardiography; a complete staging evaluation, including computed tomographic or magnetic resonance imaging scans of the brain, chest, and abdomen; a nuclear medicine bone scan; and bone marrow aspiration. Blood cell counts, including differential counts, body temperature (measured axillary), blood pressure, and pulse were measured before the study and three times weekly during treatment. Liver and renal function tests, serum electrolytes, total protein, albumin, C-reactive protein, urinalysis, prothrombin time, fibrinogen, and fibrinogen degradation products were determined before the study and once weekly during treatment.

Side-effect evaluation

All side effects were scored according to WHO criteria [29]. Patients were removed from the study when tumor progression or nonhematologic WHO grade III or IV toxicity (except nausea, vomiting, or alopecia) occurred. Blood transfusions were given if the platelet count decreased to <25,000/μl and/or if a bleeding tendency was observed. G-CSF was given if the neutrophil count decreased to <500/μl.

Definition of tumor response

A complete response was defined as the complete disappearance of all measurable and assessable disease for at least 4 weeks. A partial response was defined as a ≥50% decrease in the sum of the products of the two largest perpendicular diameters of all measurable tumors that lasted for ≥4 weeks and the absence of any new lesions. Progressive disease was defined as the development of new lesions or an increase in the sum of the products of the two largest perpendicular diameters of all measurable tumors by ≥25%.

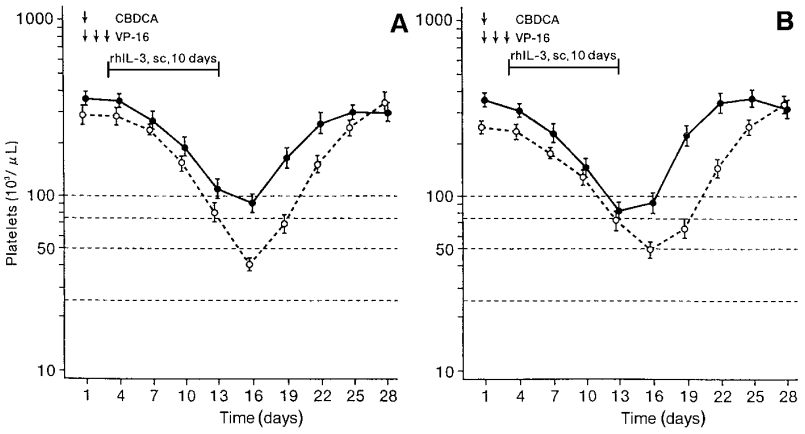

Fig. 2 A, B Platelet counts obtained during the control (white circles) and rhIL-3 cycles (black circles) with rhIL-3 at **A** 5 μg/kg per day and **B** 10 μg/kg per day. (*CBCDA* Carboplatin, *VP-16* etoposide). Each point represents the mean value ±SE.

Statistical analysis

The one-sample Wilcoxon test and the McNemar test were used for statistical analysis. A P value of <0.05 was considered significant.

Results

Patients' characteristics

Between January and December 1994, 41 patients were enrolled into this study. The characteristics of these patients are listed in Table l. In all, 20 patients were randomized to rhIL-3 at 5 μg/kg and 21 patients were randomized to 10 μg/kg. There was no significant difference between the characteristics of the patients in the two groups. Nine patients were excluded from the rhIL-3 efficacy evaluation because one patient lacked a complete set of blood cell counts and rhIL-3 administration was discontinued within 6 days in eight patients. At an rhIL-3 dose of 5 μg/kg per day, administration was discontinued in two patients: one patient refused further treatment on day 1 due to chills and fever (37.2 °C); the other patient received rhIL-3 for 2 days and then refused treatment due to fever (37.5 °C), headache, and fatigue. At the dose of 10 μg/kg per day, administration was discontinued in six patients: in four patients, IL-3 was given only once; in one patient, only twice; and in one patient, on only 5 days. The reasons why patients could not continue rhIL-3 treatment were fever, headache, and fatigue. Therefore, 32 patients were assessable for rhIL-3 efficacy; however, the tolerability of rhIL-3 and the response to chemotherapy were assessable in all 41 patients.

Table 1 Patients' characteristics

Characteristic	rhIL-3 dose (μg/kg per day)		Total
	5	10	
Number of patients	20	21	41
Gender (M:F)	16:4	20:1	36:5
Age (years, median [range])	67.5 (39–76)	65 (58–74)	65 (39–76)
Clinical stage (LD:ED)	12:8	12:9	24:17
Performance status (WHO):			
0	6	7	13
1	9	12	21
2	4	1	5
3	1	1	2
Previous treatment:			
Untreated	15	17	32
Treated	5	4	9

(*LD* Limited disease, *ED* extensive disease)

Hematologic effects

The effects of rhIL-3 on thrombocytopenia are shown in Fig. 2 and Table 2. At both doses, the platelet count nadir and recovery were improved as compared with those seen in the control cycle. There were statistically significant differences in mean nadir platelet counts between the control cycle and the rhIL-3 cycle at both doses ($P<0.01$). There were also statistically significant differences in the mean duration of thrombocytopenia, the days on which platelet counts were $<75{,}000/\mu l$ ($P<0.01$ or 0.001), and the time from the start of chemotherapy until thrombocyte recovery to $\geq 100{,}000/\mu l$ ($P<0.01$ or $P<0.001$). The numbers of patients receiving platelet transfusions were not significantly improved in the rhIL-3 cycle. There was no statistically significant difference in the efficacy of rhIL-3 treatment on thrombocytopenia between the two doses.

Table 3 shows the effects of rhIL-3 on neutropenia. rhIL-3 significantly improved nadir neutrophil counts ($P<0.01$ or $P<0.05$) and the duration of neutropenia, the number of days on which neutrophil counts were $<1{,}000/\mu l$ ($P<0.01$ or $P<0.05$). There was a statistically significant difference in the time to neutrophil recovery, i.e., counts of $\geq 2{,}000/\mu l$ at an rhIL-3 dose of 5 μg/kg per day only. rhIL-3 also reduced the number of patients requiring G-CSF support.

Table 2 Effects of rhIL-3 on thrombocytopenia[a]

Parameter	rhIL-3 dose (μg/kg per day)							
	5				10			
	Control	rhIL-3	*n*	*P*[b]	Control	rhIL-3	*n*	*P*[b]
Platelet nadir (× 10^3/μl)	37 ±3	68 ±10	18	<0.01	42 ±4	66 ±8	14	<0.01
Time at platelet count <75,000/μl (days)	5.6±0.7	1.3± 0.5	10	<0.01	6.0±0.8	1.5±0.5	11	<0.001
Time to platelet recovery to ≥75,000/μl (days)	2.8±0.4	0.6± 0.2	10	<0.01	3.3±0.5	0.6±0.3	11	<0.001
Time to platelet recovery to >100,000/μl (days)	19.8±0.5	11.4± 2.5	10	<0.01	19.7±0.5	13.9±1.5	11	<0.001
Number of platelet transfusions	6	3		0.257[c]	2	2		1.0[c]

[a] All data represent mean values ±SE
[b] Calculated using the one-sample Wilcoxon test
[c] Calculated using the McNemar test

Table 3 Effects of rhIL-3 on neutropenia[a]

Parameter	rhIL-3 dose (μg/kg per day)							
	5				10			
	Control	rhIL-3	*n*	*P*[b]	Control	rhIL-3	*n*	*P*[b]
Neutrophil nadir (μl)	465 ±83.7	824.2±109.3	18	<0.01	415 ±63.5	764.3±106	14	<0.05
Time at neutrophil count <1000/μl (days)	6.1± 0.9	1.6± 0.5	18	<0.01	6.1± 0.9	2.6± 1.0	12	<0.05
Time to neutrophil recovery to ≥2000/μl (days)	5.8± 1.5	3.2± 0.5	11	<0.05	4.6± 1.2	5.8± 1.4	11	0.577
G-CSF support (number of occasions)	10	5		<0.05[c]	10	2		<0.01[c]

[a] All data represent mean values ±SE
[b] Calculated using the one-sample Wilcoxon test
[c] Calculated using the McNemar test

Side effects

All 41 patients were assessable for side-effects analysis (Table 4). Fever was the most commonly observed adverse event in this study. Grade I or II fever occurred in 33 of 41 patients, and the incidence of grade II fever was related to the rhIL-3 dose (Table 4). Temperature usually increased during the first 24 h of rhIL-3 administration, and fever disappeared before the next injection. Other major side effects were headache (24.3%) and fatigue (14.6%). Fever and headache responded well to nonsteroidal antiinflammatory drugs such as acetaminophen. All adverse events were of grade I or II.

At an rhIL-3 dose of 5 μg/kg per day, 23 grade I and 14 grade II side effects occurred. In contrast, at the dose of 10 μg/kg per day, 18 grade I and 22 grade II side effects occurred. Thus there appeared to be an increase in the severity of adverse events in patients receiving rhIL-3 10 μg/kg per day.

Table 5 shows the laboratory abnormalities. Eosinophilia was observed in 16 of 41 patients (39%). At an rhIL-3 dose of 5 μg/kg per day, 7 patients had eosinophilia of 500–1,000/μl, whereas at a dose of 10 μg/kg per day, 5

Table 4 Side effects

Symptom	rhII-3 dose (μg/kg per day)				Total (%)
	5 (*n* = 20)		10 (*n* = 21)		
	Grade I	Grade II	Grade I	Grade II	
Fever	11	5	5	12	33 (80.5)
Headache	2	3	2	3	10 (24.3)
Fatigue	0	1	2	3	6 (14.6)
Warmth	2	1	2	0	5 (9.8)
Anorexia	0	0	2	1	3 (7.3)
Chills	2	0	0	1	3 (7.3)
Pruritus	2	1	0	0	3 (7.3)
Erythema	0	0	2	0	2 (4.9)
Tachycardia	2	0	0	0	2 (4.9)
Bloodshot eyes	1	1	0	0	2 (4.9)
Nausea/vomiting	0	0	0	2	2 (4.9)
Other	1	2	3	0	6 (6.5)
Totals	23	14	18	22	77

Table 5 Laboratory abnormalities (*CRP* C-reactive protein)

Abnormality	rhIL-3 dose (μg/kg per day)		
	5 (n = 20)	10 (n = 21)	Total (%)
Eosinophilia >500/μl	7	9	16 (39.0)
Increased CRP	3	2	5 (12.1)
Decreased total protein	0	3	3 (7.3)
Decreased albumin	0	2	2 (4.9)
Increased fibrinogen	1	1	2 (4.9)
Decreased total cholesterol	0	1	1 (2.4)
Proteinuria	0	1	1 (2.4)
Microscopic hematuria	0	1	1 (2.4)
Urine sediment abnormality	1	0	1 (2.4)
Totals	12	20	32

and 4 patients had eosinophilia of 500–1,000/μl and ≥1,000/μl, respectively. Thus, this abnormality was rhIL-3 dose-dependent. No patient experienced liver dysfunction. However, there were 12 laboratory abnormalities in patients receiving rhIL-3 at 5 μg/kg per day and 20 in patients receiving 10 μg/kg per day. Similarly to side effects, there was a tendency for the number of patients who experienced laboratory abnormalities to increase at an rhIL-3 dose of 10 μg/kg per day.

Response to chemotherapy

At the 350-mg/m^2 carboplatin dose, which was given to previously treated patients, 5 achieved a partial response and 1 showed progressive disease (Table 6). At the 400-mg/m^2 dose, which was given to previously untreated patients, 9 showed a complete response; 22, a partial response; 3, no change; and 1, progressive disease (Table 6). In these two groups the complete response and response rates were 0 and 25.7% and 83.3% and 88.6%, respectively. The overall complete response rate was 22.0% (95% confidence interval 9.3–34.7%) and the overall response rate was 87.8% (95% confidence interval 77.8–97.8%).

Discussion

The present study showed that rhIL-3 administration following carboplatin and etoposide chemotherapy in SCLC patients reduced the severity of chemotherapy-induced thrombocytopenia and neutropenia with acceptable adverse events. rhIL-3 significantly improved mean nadir platelet counts from grade III to grade II toxicity at both dose levels (Table 2, Fig. 2). The mean nadir neutrophil counts were also ameliorated from grade IV to grade III toxicity (Table 3). Recovery from thrombocytopenia and neutropenia was significantly improved by rhIL-3 administration.

D'Hondt et al. [6] have reported a rhIL-3 dose-dependent increase in platelet and neutrophil recovery for patients treated with 7.5 and 10 μg/kg per day. Postmus et al. [20] have also demonstrated that rhIL-3 given at 8 μg/kg per day increases platelet counts; however, they did not demonstrate a significant improvement in nadir platelet and neutrophil counts, and Biesma et al. [2] failed to demonstrate a rhIL-3 dose-related effect on platelets and leukocytes. The reasons why we observed an improvement in nadir platelet and neutrophil counts were considered to be the study inclusion criteria and the frequent blood sampling done during episodes of thrombocytopenia and neutropenia.

One of the inclusion criteria for the patients in this phase II study was that the nadir platelet counts in the control cycle had to be <75,000/μl. In all, 57 patients were provisionally enrolled into the study; of these, 4 (7.0%) were excluded due to nadir platelet counts of >75,000/μl during the control cycle. This criterion was not adopted in other trials [2, 6, 20, 26–28]. Such selection of patients was considered important to the design in this study, and we have adopted this criterion in a placebo-controlled phase III study now being conducted in Japan. In this study all patients were admitted to hospital during the study. This allowed frequent blood sampling and accurate estimation of nadir platelet and neutrophil counts.

On the basis of the efficacy and side effects observed in this study, we have recommended that the rhIL-3 dose for phase III studies and future clinical use be 5 μg/kg per day for 10 days. Veldhuis et al. [28] have also reported that rhIL-3 at 5 μg/kg per day is an optimal dose in the carboplatin and cyclophosphamide regimen, and D'Hondt et al. [6] observed hematopoietic effects at doses of ≥2.5 μg/kg per day and did not encounter the maximum tolerated dose until 10 μg/kg per day. Speyer et al. [26] recommended a dose of 250 or 500 mg/m^2 given subcutaneously for 5 days; these doses are approximately equivalent to 2–5 μg/kg per day.

No significant difference between the number of platelet transfusions given in the control versus rhIL-3 cycles was observed. Therefore, it may be difficult to decrease the

Table 6 Response to carboplatin and etoposide (*CR* Complete response, *PR* partial response, *NC* no change, *PD* progressive disease)

Carboplatin dose (mg/m^2)	Number of patients				CR rate (%)	Response rate (%)
	CR	PR	NC	PD		
350	0	5	0	1	0	83.3
400	9	22	3	1	25.7	88.6
Totals	9	27	3	2	22.0[a]	87.8[b]

[a] 95% confidence interval 9.3–34.7%
[b] 95% confidence interval 77.8–97.8%

number of platelet transfusions required during rhIL-3 treatment. In our protocol, platelet transfusions were permitted if the platelet count was $<25{,}000/\mu l$ and/or if a bleeding tendency was observed. However, the timing of platelet transfusion varies with the attending physician and the frequency of blood sampling. Thus, it would appear difficult to make the number of platelet transfusions a target parameter for rhIL-3 studies. Finally, it should be clarified in future phase III studies as to whether chemotherapy with rhIL-3 support can improve SCLC patient survival.

The adverse events observed in the present study were fever, headache, fatigue, and warmth (Table 4). These side effects are similar to those reported previously [2, 5, 6, 10, 20, 27]. The incidence of fever was often dose-related in these studies, as it was in the present study, and headache became the dose-limiting toxic side effect in rhIL-3 dose-escalation studies [2, 20]. However, headache was not accompanied by signs of meningeal irritation, such as neck rigidity, as previously described [7–9, 20].

In this study, eight patients refused to continue rhIL-3 administration due to side effects, mainly fever and headache. Previous work has shown that rhIL-3 may be involved at various levels of allergic inflammation [13, 17, 21]. Furthermore, rhIL-3 has been shown to induce enhanced basophil and eosinophil formation [18] and a morphologic change in eosinophils characteristic for activation [22]. We also observed a dose-dependent increase in the absolute number of eosinophils; however, basophil numbers did not increase during rhIL-3 treatment [20].

Many combination chemotherapies are used in the treatment of SCLC patients. A cooperative study performed by the West Japan Lung Cancer Study Group has investigated the combination of carboplatin and etoposide with G-CSF support [12], and objective responses were seen in 81% (complete response 23%, partial response 58%) of patients. Other trials using this regimen obtained response and survival data similar to those obtained using a cisplatin and etoposide regimen [3, 24]. We used the carboplatin and etoposide combination as the standard regimen for SCLC and achieved similar responses in the present study. The major dose-limiting toxic side effect of this combination is myelosuppression; the dose of carboplatin as monotherapy is limited by thrombocytopenia and the combination produces both neutropenia and thrombocytopenia. Therefore, this combination is well suited for evaluation of the effects of rhIL-3 on myelosuppression after chemotherapy.

In conclusion, subcutaneous rhIL-3 administration to SCLC patients following carboplatin and etoposide combination chemotherapy ameliorates the incidence and severity of chemotherapy-induced thrombocytopenia and neutropenia with an acceptable adverse-events profile.

Appendix

The following investigators and institutions participated in this study: Takehito Nakabayashi, M.D., Sapporo National Hospital, Sapporo; Yushi Nakai, M.D., Sendai Kosei Hospital, Sendai; Yuzo Kurita, M.D., Niigata Cancer Center Hospital, Niigata; Shuichi Yoneda, M.D., Saitama Cancer Center, Saitama; Shoji Kudoh, Nippon Medical School, Tokyo; Keisuke Toyama, M.D., Tokyo Medical College, Tokyo; Yutaka Ariyoshi, M.D., Aichi Cancer Center, Nagoya; Hidehiko Saito, M.D., Nagoya University, Nagoya; Toshiyuki Sawa, M.D., Gifu Municipal Hospital, Gifu; Kiyoyuki Furuse, M.D., National Kinki-Chuo Hospital, Osaka; Masahiro Fukuoka, M.D., Osaka City General Hospital, Osaka; Minoru Takada, M.D., Osaka Prefectural Habikino Hospital, Osaka; Naotsugu Kurihara, M.D., Osaka City University, Osaka; Harumichi Ikegami, M.D., The Center for Adult Disease, Osaka; Shigenori Nakajima, M.D., Kinki University, Osaka; Kazuya Higashino, M.D., Hyogo College of Medicine, Nishinomiya; Nobuyuki Katagami, M.D., Kobe City General Hospital, Kobe; Jiro Takahara, M.D., Kagawa Medical School, Takamatsu; Tadashi Kamei, M.D., Kagawa Prefectural Center Hospital, Takamatsu; Shin-ei Ryu, M.D., Shimonoseki Kosei Hospital, Shimonoseki; and Hidehiko Yamamoto, M.D., Aso Iizuka Hospital, Iizuka.

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