A randomized phase III trial of postoperative adjuvant therapy for completely resected stage IA-IIIA lung cancer using an anti-angiogenetic agent: irsogladine maleate

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Aim. Although angiogenesis plays an important role in the invasion and metastasis of solid tumors, very few anti-angiogenetic drugs have been developed. Reexamining the anti-angiogenetic effects of existing drugs such as Thalidomide is another possible strategy for drug discovery. Irsogladine maleate (IM) is a drug invented to treat gastric ulcers; however, several reports have shown that IM also exerts anti-angiogenetic effects *in vitro*, *in vivo* and in humans. In order to elucidate whether treatment with IM would improve the prognoses of patients with resected lung cancer, we conducted a randomized trial.
Methods. In the control group, uracil-tegafur (250 mg/m²/day) was administered for two years to patients with resected stage IB - IIIA lung cancer, and no adjuvant therapy was administered to those with stage IA disease. In the study group, IM (4 mg/body/day) was additionally administered for two years.
Results. No significant differences were observed in the major prognostic factors among 305 eligible patients between the study and control groups. Adverse effects were minimal. The overall survival of the patients in the study and control groups were not statistically different. When the analysis was stratified by regimen, among the patients with resected stage IA disease, disease-specific survival in the study group was slightly higher than that in the control group; however, the difference was not significant (p=0.07).
Conclusion. Although it could not be proven that IM improves the prognoses of resected

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lung cancer patients, IM might have some effect on resected stage IA disease, and another trial should be conducted.

The prognosis of resected non-small cell lung cancer remains poor. The 5-year survival rate of patients even with resected stage I disease is 60-80%, and that of patients with resected stage III disease is only 20-40%.[1, 2] In order to improve the prognosis of such patients, many clinical trials of postoperative adjuvant therapy have been conducted. Although postoperative irradiation has not been proven to improve the survival of patients, some randomized trials have recently revealed that adjuvant chemotherapy improves the prognosis of resected lung cancer patients.[3-7] However, most of these trials were limited to patients with resected stage II - III disease,[3, 4] and there are no effective regimens for patients with resected stage I disease, except some reports of uracil-tegafur.[5, 6]

Recently, new strategies of anti-cancer therapy have been developed. One strategy includes molecular-targeting therapy, such

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as gefitinib for pulmonary adenocarcinoma patients with EGFR mutations. Another strategy involves inhibition of tumor angiogenesis. Angiogenesis plays an important role in growth, invasion and metastasis of solid tumors.[8-10] Although many novel anti-angiogenetic agents have been invented and examined, most have failed to show anti-neoplastic effectiveness as well as acceptable adverse effects in humans. When this study began, there were no anti-angiogenetic drugs usable in humans. On the other hand, several reports have suggested that some existing drugs used to treat other diseases also exert anti-angiogenetic effects.[11, 12] These drugs are usually safe and inexpensive, and utilizing these effects is another possible therapeutic modality of anti-angiongnesis.

Irsogladine maleate (IM) is a drug originally invented to treat gastric ulcers due to its protective effects on the gastric mucosa.[13, 14] However, it has also been reported that IM exerts anti-angiogenetic effects *in vitro*,[15, 16] *in vivo*[15-17] and in humans.[18] IM is a very safe drug with few adverse effects, as proven by a large amount of experience for use as an anti-ulceral drug. A very safe drug with anti-angiogenetic effects is regarded to be suitable for study in an adjuvant trial including resected stage I lung cancer patients.

In this study, we evaluated whether the two-year administration of oral IM improves the prognoses of patients with completely resected non-small cell lung cancer.

Materials and methods

Study design

This study was a prospective multi-center randomized phase III parallel study conducted by the Japanese Northern East Area Thoracic Surgery Study Group (JNETS) to assess whether the additional oral administration of an anti-angiogenetic agent (IM) for two years can improve the prognoses of patients with completely resected stage IA-IIIA non-small cell lung cancer. This study was

approved by the Institutional Review Board of Tohoku University in December 2000 and was registered on the University Hospital Medical Information Network Clinical Trial Registration, Japan (UMIN-CTR: registration number: UMIN000005901). Details are available at the following address: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000006978&language=J.

Eligibility criteria and randomization

The eligibility criteria of the study were as follows:
1. histologically confirmed non-small cell lung cancer;
2. completely resected by lobectomy, bilobectomy or pneumonectomy with hilar and mediastinal nodal dissection;
3. pathological stage IA, IB, IIA, IIB or IIIA disease (TNM classification ver. 6);
4. age between 25 and 74 years;
5. performance status (ECOG criteria) 0 or 1 with adequate organ function;
6. without any previous cancer within five years;
7. without any prior chemotherapy or radiotherapy;
8. without prior administration of anti-angiogenetic drugs.

Within two to eight weeks after surgery, written informed consent was obtained from each participant. The participants were registered and randomized at the Central Management Center with random assignment (1:1) stratified by gender, age, pathological stage and hospital.

Treatment and follow-up

Among the participants with pathological stage IA disease, those assigned to the control group (Group B) were administered neither IM nor uracil-tegafur and were instead followed, whereas those assigned to the study group (Group A) were administered IM (4 mg/body/day) for two years. Among the participants with pathological stage IB-IIIA disease, those assigned to the control group (Group D) were admin-

istered uracil-tegafur (250 mg/m²/day) for two years, whereas those assigned to the study group (Group C) were administered uracil-tegafur (250 mg/m²/day) and IM (4 mg/body/day) for two years. The patient follow-up was performed by the regional hospitals until five years after surgery. The causes of death were determined by the Data and Safety Monitoring Committee of JNETS after reviewing the patients' medical records if necessary. Therapy-related deaths were regarded as deaths from lung cancer.

Endpoints and statistical analysis

The primary endpoint was overall survival, defined as the time from surgery until death from any cause. The secondary endpoints were disease-specific survival and disease-free survival.

We assumed that two years of administration of IM would prolong survival up to 50%. The predicted 5-year survival rate in the control group was estimated to be 50%. With an alpha error of 5% and a power of 80%, the sample size was calculated as 294 cases for both groups.

Categorical variables were compared using either chi square test, Fisher's exact probability test or G test (William's correction). Average values were compared using Student's *t*-test. The survival rates were calculated using Kaplan-Meier method. Differences in the survival curves were evaluated with log rank test. A multivariate analysis was performed using Cox's proportional hazard model. P values of less than 0.05 were regarded as statistically significant. The calculations were conducted using Sigmaplot 12 (Systat Software Inc., San Jose, CA).

Results

Between May 2001 and December 2006, 307 patients from 12 hospitals affiliated with JNETS were registered. Two cases were excluded from the analysis because their pathological reports were corrected later by the pathologists of the regional hospitals and the patients were defined as ineligible. The remaining 305 eligible patients were analyzed (Figure 1).

Characteristics of the patients and follow-up

The characteristics of the patients are shown in Table I. There were no statistically significant differences in major prognostic factors between the study group and the control group.

As of August 1, 2012, three (1%) and 11 patients (3.6%) were lost to follow-up within three and five years, respectively. The median follow-up period of the living patients was 1,889 days. Forty-two patients died of lung cancer and 16 patients died of other causes. The causes of the 16 deaths other than lung cancer included five malignant tumors of other organs (rectal carcinoma, hepatocellular carcinoma, bladder carcinoma, carcinoma of the trachea, malignant tumor of the facial muscle), accident by earthquake, suicide, cerebral infarction, cerebral hemorrhage, renal failure, hepatitis, myelodysplastic syndrome, amyotrophic lateral sclerosis, interstitial pneumonia, bacterial pneumonia and benign disease (details unknown).

Compliance

Of the 305 eligible patients, nine (3%) did not receive allocated intervention. The reasons not to receive intervention included patient refusal and the occurrence of other diseases before the first administration of allocated therapy. Two hundred and thirty-two patients (76.1%) received at least 80% of the scheduled treatments. The reasons to quit administration are shown in Figure 1.

Protocol violation

Although the protocol indicated that additional anti-cancer therapy should be avoided before recurrence or other metachronous cancers were apparent, five patients (1.7%) were treated with anti-cancer drugs without histologically or graphically firm evidence. Among these five cases, tu-
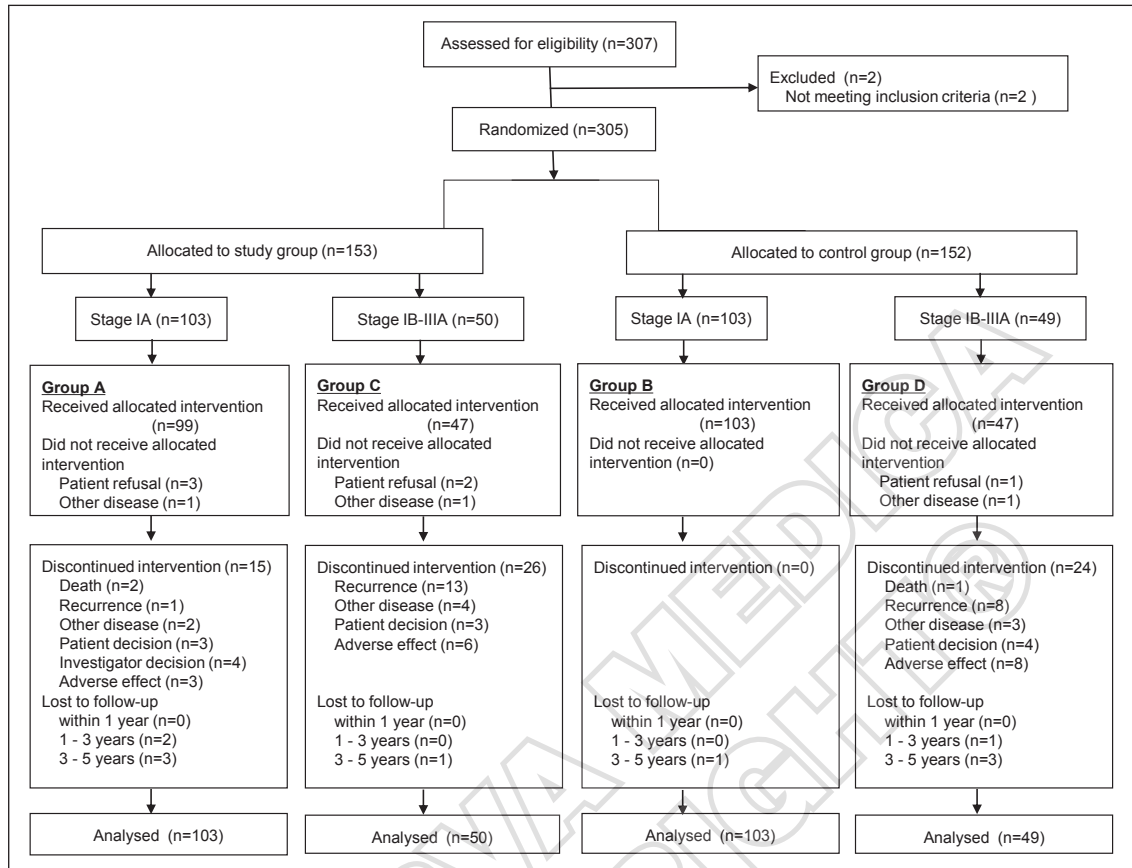
Figure 1.—CONSORT (Consolidated Standards of Reporting Trials) diagram. The disposition of all participants is shown.

mor markers were increased in two, pleural effusion was increased in one and the patients requested administration in two. One patient had been assigned to the study group, and the remaining four patients had been assigned to the control group.

Adverse effects

The number of patients suffering adverse effects of NCI-CTC (version 2.0) Grade 2 or higher is shown in Table II. Almost all of the adverse effects were classified as Grade 2, and none were life-threatening.

Survival

The overall and disease-specific survival rates of the patients according to clin-

icopathological factors, combining both groups (the study group and the control group), are shown in Table III. The overall 5-year survival rate of all 305 patients was 82.0% and the disease-specific survival rate was 87%. The prognoses of the female patients were significantly better than those of the male patients. According to pathological stage, the survival rate of the patients with resected pathological stage IA disease was highest and that of the patients with resected stage IB disease was the second highest. The overall survival rate of the younger patients was significantly higher than that of the older patients, whereas the disease-specific survival rates of the two groups were not statistically different. The prognoses of the patients with adenocarcinoma were sig-

TABLE I.—*Characteristics of the patients.*

	Study Group (A+C)	Control Group (B+D)	P value
Gender			>0.1
Female	71	71	
Male	82	81	
Age	63.7±8.1	63.4±8.5	>0.1
69 or under	114	114	
70 or over	39	38	
Pathological T factor			>0.1
pT1	114	112	
pT2	38	39	
pT3	1	1	
Pathological N factor			>0.1
pN0	130	129	
pN1	16	15	
pN2	7	8	
Pathological stage			>0.1
IA	103	104	
IB	26	25	
IIA	10	6	
IIB	7	9	
IIIA	7	8	
Histological type			>0.1
Adenocarcinoma	131	125	
Non-adenocarcinoma.	22	27	
Operative procedure			>0.1
Lobectomy	151	147	
Bilobectomy	2	2	
Pneumonectomy	0	3	
Perioperative blood transfusion			>0.1
Yes	2	1	
No	151	151	

TABLE II.—*Number of patients suffering adverse effects according to the assigned group.*

Grade	A Group (N.=99)*			B Group (N.=103) *			C Group (N.=47) *			D Group (N.=47) *		
	2	3	4	2	3	4	2	3	4	2	3	4
Hemoglobin	4											
White blood cell	2			3			2			3		
Platelet		1										
Albumin	2											
Total bilirubin	2						3			6	1	
AST	1			3	1					1		
ALT	4			6						4		
Creatinine	1											
Nausea and vomiting										1		
Anorexia	2						5			2		
Diarrhea	1									1		
Oral mucositis							1					
Rush							1					
Sense of smell										1		
Weight loss							2					

*: Patients who were not administered the assigned therapy were excluded from this analysis.

TABLE III.—*Five-year survival rates of all eligible patients in this study according to the clinicopathological factors.*

	Number	Overall 5-year survival rate	P value	Disease-specific 5-year survival rate	P value
All cases	305	82.0%		87.0%	
Gender			<0.001		0.014
Male	163	73.6%		82.0%	
Female	142	91.5%		92.2%	
Pathological stage			<0.001		<0.001
IA	207	89.7%		95.0%	
IB	51	79.7%		83.3%	
IIA	16	37.5%		41.3%	
IIB	16	62.5%		66.7%	
IIIA	15	46.7%		51.9%	
Age			0.002		>0.1
69 or under	228	85.8%		87.9%	
70 or over	77	70.6%		84.1%	
Histology			<0.001		0.003
Adenocarcinoma	256	85.0%		89.1%	
Non-adenocarcinoma	49	66.7%		75.5%	
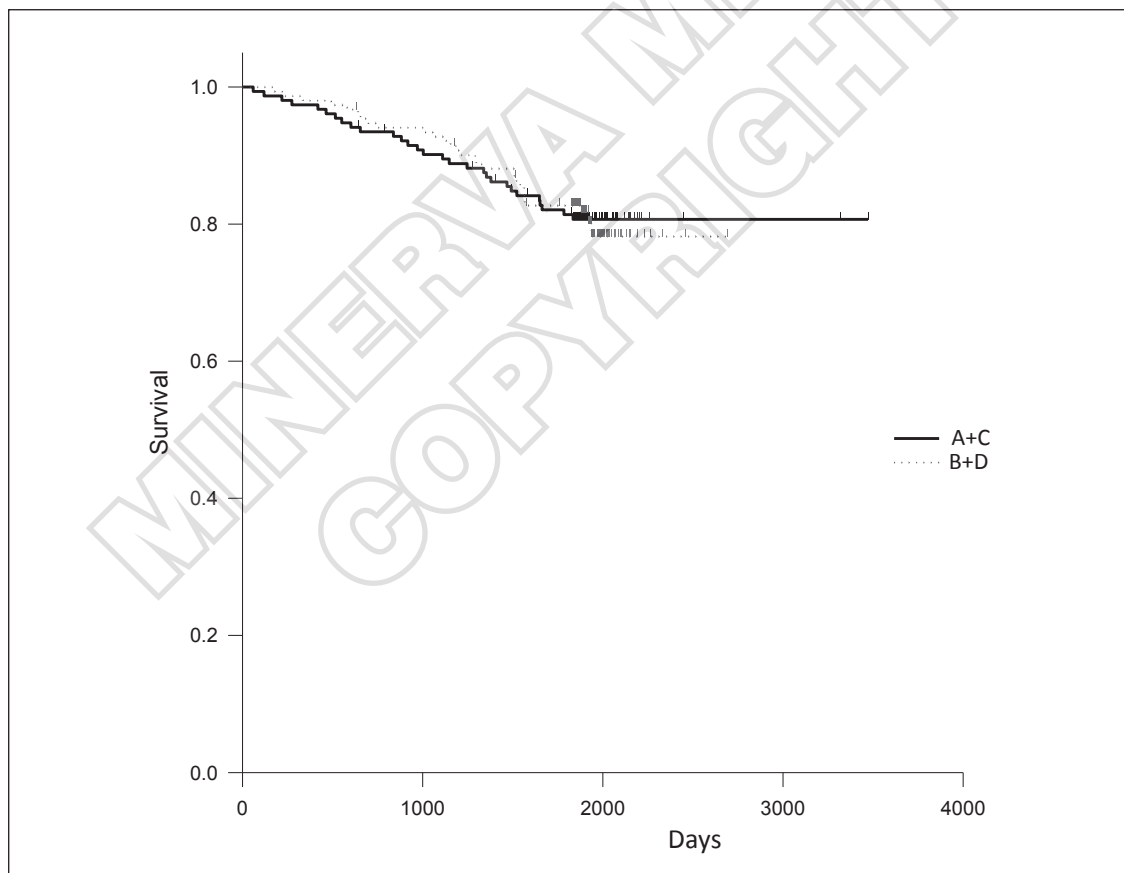
Figure 2.—The overall survival curves of the patients according to the assigned group are shown. There were no significant differences in overall survival between the patients in the study and control groups.

nificantly better than those of the patients with non-adenocarcinoma.

The survival curves of the patients according to assigned group are shown in Figure 2. The overall 5-year survival rates of the patients in the study and control groups were 82.4% and 82.7%, respectively, which were not statistically different (P>0.1). Neither the disease-specific survival nor the disease-free survival was statistically different between the two groups (disease-specific 5-year survival rate: 86.8% *vs.* 87.1%, disease-free 5-year survival rate: 73.6% *vs.* 75.6%).

In order to adjust the influence of several factors which affected the prognoses, a multivariate analysis using Cox proportional hazard model was also performed. Gender, age, histology (adenocarcinoma/non-adenocarcinoma), pathological stage (IA/IB/IIA+IIB+IIIA) and group (study group/control group) were selected as covariates in the Cox proportional hazard model. Although the pathological stage, gender and age were found to affect survival, group did not affect survival significantly.

In the protocol of this study, the administered regimens were different between the patients with resected pathological stage IA disease (Groups A and Group B) and those with stage IB - IIIA disease (Groups C and Group D). Therefore, an analysis stratified by regimen was also conducted.

Among the patients with resected pathological stage IA disease, the disease-specific survival of the patients in Group A was slightly higher than that of the patients in Group B; however, the difference was not statistically significant (5-year survival rate: 96.9% vs. 93.1%, P=0.07; Figure 3). In con-
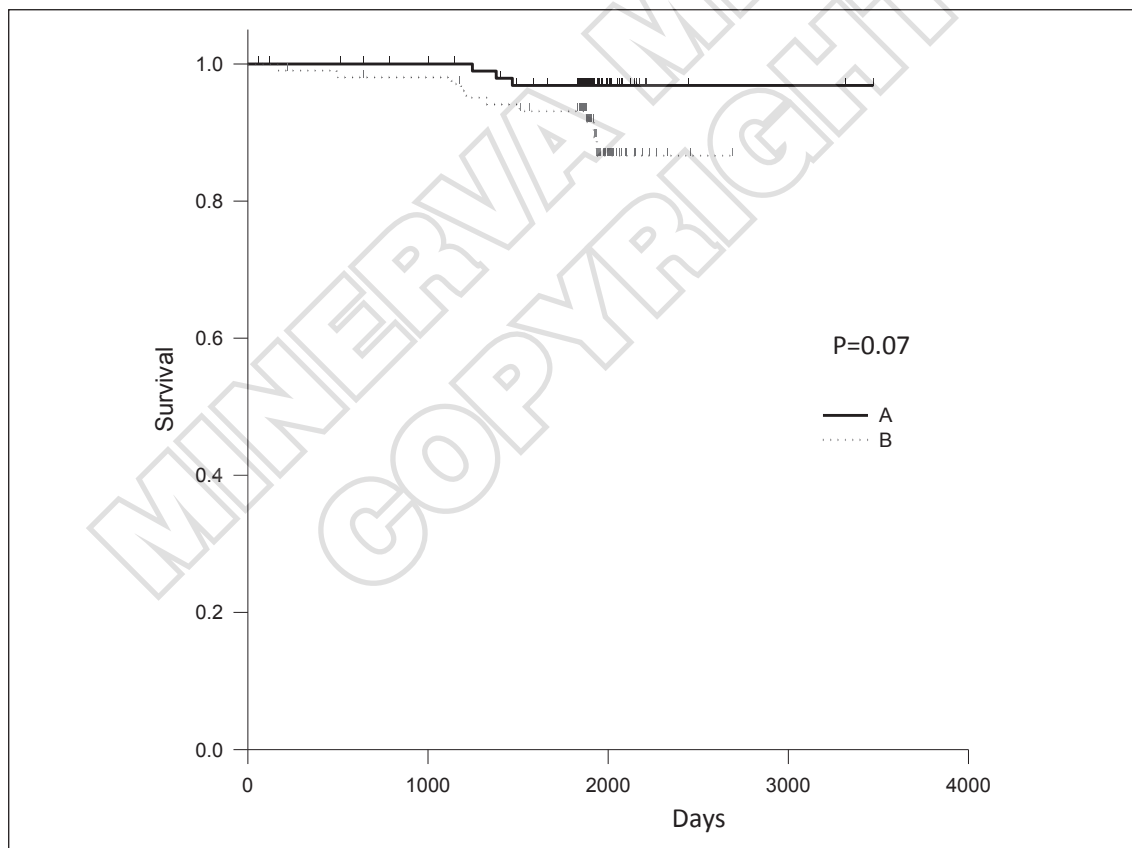

Figure 3.—The disease-specific survival curves of the resected stage IA lung cancer patients according to the assigned group are shown. The disease-specific survival of the patients in Group A was slightly higher than that of the patients in Group B; however, the difference was not statistically significant (P=0.07).

trast, neither the overall survival nor the disease-free survival was different. Using the Cox model (covariates: gender, age, histology, group) with the data of the resected pathological stage IA patients, the p value of group was found to be the smallest (P=0.08) among the covariates, whereas the p values of gender, age and histology were each over 0.1. Among the patients with resected pathological stage IB-IIIA disease, the survival of the patients in Group C and Group D were not statistically different.

Discussion

Angiogenesis plays an important role in many kinds of diseases, including diabetic retinopathy and rheumatoid arthritis.[8, 9] Angiogenesis in solid tumor tissues is also closely correlated with the growth, invasion and metastasis of the tumors.[10] Recently, many novel anti-angiogenetic agents have been invented; however, most have not been proven to be both effective and safe in humans. Bevacizumab [19] and aflibercept [20] are the few exceptions and are presently used in humans. However, both of these drugs are associated with serious adverse effects such as massive hemoptysis and gastrointestinal perforation. Furthermore, these newly invented drugs are extraordinarily expensive, and there are concerns regarding the cost-benefit balance.

On the other hand, some investigators have noticed anti-angiogenetic effects among existing drugs used to treat other diseases. Thalidomide is a well-known sleeping pill that exhibits teratogenesis; however, it has recently been revealed to exert anti-angiogenetic effects and it is used to treat multiple myeloma as an anti-neoplastic agent.[11] Some macrolides are also known to exert anti-angiogenetic effects.[12] These kinds of drugs are safer and less expensive than newly invented drugs, and re-examining the anti-angiogenetic effects of existing drugs is another possible strategy for drug discovery.

Irsogladine maleate (IM) is a drug developed in Japan, and is used to treat gastric ul-

cers due to its protective effects on the gastric mucosa,[13, 14] by suppression of the large opening gaps between epithelial cells in the gastric mucosa. It has been noticed that suppressing the gaps between epithelial cells is related to anti-angiogenic effects. Therefore, several investigators have attempted to evaluate the anti-angiogenetic effects of IM. Consequently, IM has been revealed to exert selectively inhibiting effects against the growth of cells and tubular morphogenesis in human endothelial cells *in vitro*.[16] In addition, several reports from Japan and other countries have revealed that IM exerts a suppressive effect against increases in tumor volume, neovascularization and capillary networks in mice.[15-17] Furthermore, focusing on the anti-angiogenetic effects in humans, the results of a small randomized trial indicated that IM significantly inhibits the progress of human diabetic retinopathy.[18] It is evident that IM exerts anti-angiogenetic effects in humans, and a long period of clinical use indicates that the drug is very safe with few adverse effects. Therefore, we planned the present randomized trial.

Although several trials are currently ongoing, this report is the first to evaluate the effects of adjuvant therapy in completely resected lung cancer patients using an anti-angiogenetic agent. The results of this study show that administration of IM for two years is safe, although it is not able to improve the prognoses of all patients with resected lung cancer. However, among the patients with resected pathological stage IA disease, the disease-specific survival of the patients in Group A (the administration of IM for two years) was slightly higher than that of the patients in Group B (no adjuvant therapy); but the difference was not statistically significant (p=0.07). This tendency did not present in overall survival because there were more deceased patients who died from other diseases in Group A than in Group B. Although statistical significance was not observed, there was a possibility that IM would have shown effects to improve the prognoses of the patients with resected stage IA lung cancer if this randomized trial had been limited to patients

with stage IA disease and the sample size had been adequately large for such trial. To elucidate whether this assumption is correct, another trial should thus be conducted.

Based on the results of our study, the effects of IM might differ between the patients with resected stage IA lung cancer and those with more advanced cancer. Although the mechanisms underlying the anti-angiogenetic effects observed in solid tumors are not fully understood, such phenomena have been reported in previous investigations.[21]

In analyzing the results of this randomized trial, one of the most important issues is whether or not the trial was appropriately conducted. In this study, random assignment was performed with stratification by gender, age, pathological stage and hospital, and there were no deviations in the background characteristics of the patients between the study group and the control group. Compliance was over 75%, and the number of patients lost to follow-up was minimal. These facts indicate that the trial was conducted appropriately.

There are several issues to be discussed in this study. First, although the standard therapy for completely resected stage IA patients is currently regarded as no adjuvant therapy, such patients were enrolled in this study. The 5-year survival rates of these patients have been reported to be approximately 80%,[1, 2] which is not adequately high. We therefore concluded that novel trials aiming to improve the prognoses of these patients should be planned if any anti-neoplastic drugs without serious adverse effects can be identified or developed. IM was regarded as suitable for such an investigation.

Second, in this study, the regimen of adjuvant therapy used in the control group for patients with stage IB disease was uracil-tegafur. Although uracil-tegafur cannot be administered in most Western countries, it is a standard adjuvant regimen for resected stage IB lung cancer patients in Japan, as several randomized trials have revealed improvements in the prognoses of such patients.[5, 6]

Third, the regimen for patients with stage II - III disease also included oral administration of uracil-tegafur. The current standard regimen of adjuvant therapy for such patients is platinum doublet. However, it was uncertain which drug was best when we started this trial, and several regimens including platinum doublet [22, 23] and uracil-tegafur [5] have been reported to be promising. Although the accrual of our study finished in 2006, several reports of randomized trials of adjuvant therapy for lung cancer which revealed positive results were published in 2005-2006,[3, 4, 24] and a pooled analysis conducted by the LACE collaborative group, in which the efficacy of platinum doublet for adjuvant therapy was fully established, was published in 2008.[25]

Fourth, phase III study usually follow phase I/II study, however, the present study did not have such study. The reason for omitting the phase I/II study was as follows: when we started the trial, IM had been clinically used without serious side effects for many patients with gastric ulcers all over Japan for more than seven years. The side effects and the adequate dose of IM had already been established. Therefore, we considered that phase I/II trials for IM were unnecessary.

Fifth, although we estimated the assumed 5-year survival rate of the patients in the control group to be approximately 50%, the actual observed survival rate was over 80%. The most important reason for this difference is that the majority of patients had pathological stage IA disease in this trial. If the predicted 5-year survival rate in the control group had been estimated to be 80%, the sample size would have been calculated as 726 cases for both groups. When another randomized trial only for resected stage IA lung cancer is planned, that number of patients will be mandatory.

Conclusions

The present study is not only one of the rare adjuvant trials including resected stage IA lung cancer patients, but it is also the first report of an adjuvant trial using

an anti-angiogenetic agent. Although the adverse effects caused by the administration of IM were minimal, IM therapy did not bring about any improvements in the prognosis. However, IM might exert some effects in pathological stage IA disease only. At present, there are no clinical trials evaluating the effects of postoperative adjuvant therapy in pathological stage IA lung cancer patients, although the 5-year survival rate of 80% remains inadequate. One of the reasons for not conducting such trials is that the adverse effects of anti-cancer agents might cause more harm than benefit in these patients. In such situations, clinical trials of adjuvant therapy focusing on the anti-angiogenetic effects of existing drugs, including IM, that are very safe and less expensive, is another possible strategy for improving the prognoses of patients, and other trials are therefore awaited.

Riassunto

Uno studio randomizzato di fase III con terapia post-operatoria adiuvante per il cancro polmonare di fase IA-IIIA completamente resecato utilizzando un agente angiogenico: irsogladina maleato

Obiettivo. Nonostante l'angiogenesi rivesta un ruolo importante nell'invasione e nella metastatizzazione dei tumori solidi, sono stati sviluppati un numero molto limitato di medicinali antiangiogenici. Un riesame degli effetti antiangiogenici dei medicinali esistenti, come talidomide, è un'altra possibile strategia per la scoperta e lo sviluppo di nuovi farmaci. Irsogladina maleato (IM) è un medicinale creato per trattare le ulcere gastriche; tuttavia, numerose segnalazioni hanno mostrato che IM esercita anche effetti antiangiogenici *in vitro, in vivo* e negli esseri umani. Al fine di chiarire se il trattamento con IM migliori la prognosi dei pazienti con carcinoma polmonare resecato, abbiamo condotto uno studio randomizzato controllato.

Metodi. Nel gruppo di controllo, uracile-tegafur (250 mg/m²/giorno) è stato somministrato per due anni in pazienti con carcinoma polmonare in stadio IB-IIIA resecato, con nessuna terapia adiuvante somministrata ai soggetti nello stadio IA. Nel gruppo sperimentale, IM (4 mg/kg p.c./giorno) è stata somministrata per ulteriori due anni.

Risultati. Non sono state osservate differenze significative nei principali fattori prognostici tra i 305 pazienti eleggibili del gruppo sperimentale e del gruppo di controllo. Gli effetti indesiderati erano minimi. La sopravvivenza complessiva dei pazienti nel gruppo sperimentale e in quello di controllo non mostrava differenze statisticamente significative. Quando l0analisi è stata stratificata per regime, tra i pazienti con malattia in stadio IA resecata, la sopravvivenza specifica alla malattia nel gruppo sperimentale era leggermente superiore rispetto al gruppo di controllo; tuttavia, la differenza non era statisticamente significativa (P=0,07).

Conclusioni. Sebbene non sia stato possibile dimostrare che IM migliori la prognosi dei pazienti con carcinoma polmonare resecato, IM potrebbe avere alcuni effetti sulla malattia in stadio IA resecata; pertanto, è necessario condurre ulteriori studi al riguardo.

PAROLE CHIAVE: Polmoni, neoplasie - Chemioterapia, adiuvante - Angiogenesi, inibitori - Trial randomizzati controllati.

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