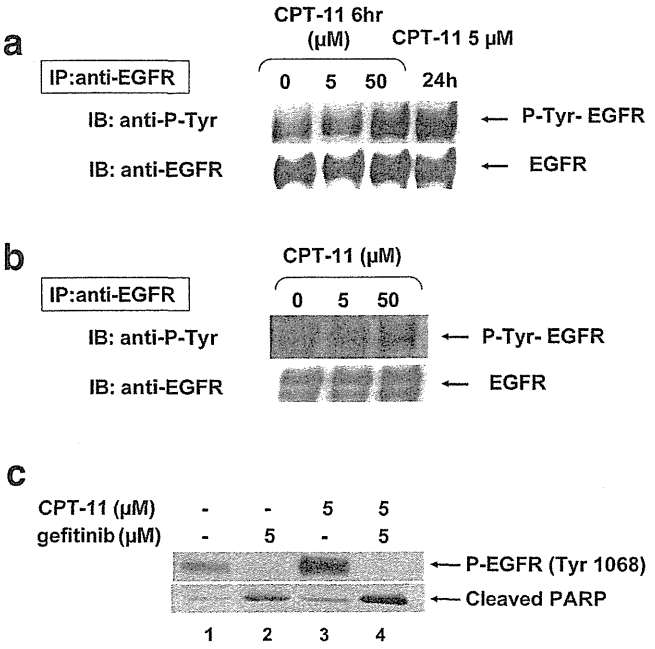

FIGURE 5 – The effect of CPT-11 on EGFR phosphorylation in WiDR cells. Lovo (*a*) and WiDR (*b*) cells (5×10^6) were treated with 5 or 50 μM CPT-11 for 6 hr. Additionally Lovo cells were treated with 5 μM CPT-11 for 24 hr. The 1,500 μg of total cell lysate was immunoprecipitated with an anti-EGFR antibody. Tyrosine-phosphorylated EGFR was determined with an anti-phosphotyrosine antibody and the membranes were reblotted by anti-EGFR antibody. (*c*) Lovo cells were treated with gefitinib or CPT-11 alone (lane 2 and 3) and in combination (lane 4) for 24 hr. A 20 μg of protein of each sample was analyzed by Western blotting using antiphospo-EGFR (Tyr 1068) and cleaved PARP antibody.

drugs. These results suggest that this regimen is intensive but can be tolerated, at least in mice.

The *in vitro* and *in vivo* experiments in our study demonstrated the synergistic potential of gefitinib – CPT-11 combination. We previously reported that topoisomerase I up-regulation by counter-part drugs was a possible mechanism for the synergy in an CPT-11 containing regimen.[23] On the other hand, the synergistic potential of gefitinib with topotecan, cisplatin, paclitaxel or radiation has been reported.[18,24–28] To elucidate the biochemical mechanism underlying the synergistic interaction between the gefitinib and CPT-11, the effect of CPT-11 on EGFR-phosphorylation was examined (Fig. 5). Increased phosphorylation of EGFR was observed after exposure to CPT-11 in dose and time-dependent manner in WiDR and Lovo cells. Since EGFR expression and phosphorylation were the major determining factors for sensitivity of the cells to gefitinib-induced growth-inhibition,[14] biochemical modulation of EGFR by CPT-11 might be responsible for the synergistic interaction between gefitinib and CPT-11. EGFR is induced and activated by cellular stress, such as oxidative stress and UV irradiation.[29–34] Ohmori *et al.*[22] demonstrated that increased autophosphorylation of EGFR was obtained in cisplatin-exposure in human lung cancer cells. A number of reports suggest that EGFR promotes cell survival through the activation of the ERK or the AKT pathway.[31,32] EGFR activation induced by these cellular stress may play a survival response against apoptosis.[31,32] In the present study, PARP activation by gefitinib was markedly enhanced by combination with CPT-11 at 5 μM exposure, which is comparable with IC_{50} value of CPT-11 in Lovo cells, although no PARP activation was observed by monotherapy of CPT-11. On the other hand, gefitinib does not modify the expression and the activation of topoisoerase I (data not shown). These result suggest that the inhibitory effect of gefitinib on the activated survival signal transduction induced by CPT-11 lead to synergistic effect. The findings of the present study suggest that biological modulation by various anticancer agents including DNA damaging agents will contribute to the synergistic effects of these anticancer agents and gefitinib in EGFR expressing tumor and support clinical evaluation of gefitinib in combination with DNA-targeting agents, especially CPT-11, in the treatment of colorectal cancers.

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Pilot Study of Concurrent Etoposide and Cisplatin Plus Accelerated Hyperfractionated Thoracic Radiotherapy Followed by Irinotecan and Cisplatin for Limited-Stage Small Cell Lung Cancer: Japan Clinical Oncology Group 9903

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Abstract

Purpose: Irinotecan and cisplatin (IP) significantly improved survival compared with etoposide and cisplatin (EP), in patients with extensive-stage small cell lung cancer (SCLC) in a previous Japan Clinical Oncology Group (JCOG) randomized trial. JCOG9903 was conducted to evaluate the safety of sequentially given IP following concurrent EP plus twice-daily thoracic irradiation (TRT) for the treatment of limited-stage SCLC (LSCLC).

Experimental Design: Between October 1999 and July 2000, 31 patients were accrued from 10 institutions. Thirty patients were assessable for toxicity, response, and survival. Treatment consisted of etoposide 100 mg/m^2 on days 1 to 3, cisplatin 80 mg/m^2 on day 1, and concurrent twice-dailyTRTof 45 Gy beginning on day 2. The IP regimen started on day 29 and consisted of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on day 1, with three 28-day cycles.

Results: There were no treatment-related deaths. The response rate was 97% (complete response, 37%; partial response, 60%). Median overall survival was 20.2 months; 1-, 2-, and 3-year survival rates were 76%, 41%, and 38%, respectively. Of the 24 patients who started the IP regimen, 22 received two or more cycles. Hematologic toxicities of grade 3 or 4 included neutropenia (67%), anemia (50%), and thrombocytopenia (4%). Nonhematologic toxicities of grade 3 or 4 included diarrhea (8%), vomiting (8%), and febrile neutropenia (8%). Of the 20 patients with recurrence, none had local recurrence alone and only two had both local and distant metastasis as the initial sites of disease progression.

Conclusions: IP following concurrent EP plus twice-dailyTRT is safe with acceptable toxicities. A randomized phase III trial comparing EP with IP following EP plus concurrentTRT for LSCLC is ongoing (JCOG0202).

Despite efforts to curb smoking, lung cancer remains the leading cause of cancer deaths in many industrialized countries. Small cell lung cancer (SCLC) accounts for about 15% of all lung cancer histology. Whereas combination chemotherapy is the cornerstone of SCLC treatment, meta-analyses showed that adding thoracic radiotherapy to combination chemotherapy significantly improves the survival of patients with limited-stage SCLC (LSCLC; i.e., disease confined to the hemithorax; refs. 1, 2). Several randomized trials have shown that early use of concurrent thoracic radiotherapy is superior to sequential or late use when etoposide and platinum are employed as combination chemotherapy (3–5). An intergroup phase III study showed accelerated hyperfractionated radiotherapy with etoposide and cisplatin (EP) to be superior to standard fractionation, with 5-year survival rates of 26% and 16%, respectively (6). Although substantial progress has been made during the past two decades, many LSCLC patients experience tumor recurrence and succumb to the disease, indicating the need for improved LSCLC therapy.

The Japan Clinical Oncology Group (JCOG) previously conducted a randomized phase III trial comparing irinotecan and cisplatin (IP) with EP in patients with extensive-stage SCLC. The response rate and overall median survival were significantly better for IP (i.e., 84.4% and 12.8 months with IP versus 67.5% and 9.4 months with EP, respectively). The 2-year

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Note: Portions of this study were presented at the 39th Annual Meeting of the American Society of Clinical Oncology, May 31 to June 3, 2003, Chicago, Illinois.

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survival rates were 19.5% for IP and 5.2% for EP (7). These encouraging results prompted us to explore the use of IP in LSCLC. We therefore undertook a pilot study to evaluate the safety of IP following concurrent EP plus twice-daily thoracic irradiation (TRT) for LSCLC.

Experimental design

Eligibility criteria. Patients with histologically or cytologically documented LSCLC, defined as disease confined to one hemithorax including bilateral supraclavicular nodes, were enrolled in this study. Additional eligibility criteria consisted of measurable or assessable disease, age <75 years, Eastern Cooperative Oncology Group performance status of 0 to 2, no previous treatment, leukocyte count $\geq 4{,}000/mm^3$, platelet count $\geq 10^5/mm^3$, hemoglobin ≥ 9.5 g/d, serum creatinine ≤ 1.5 mg/d, creatinine clearance ≥ 60 mL/min, serum bilirubin ≤ 1.5 mg/d, serum transaminase $\leq 2 \times$ ULN, and $PaO_2 \geq 70$ mm Hg. Exclusion criteria included active infection, uncontrolled heart disease or a history of myocardial infarction within the previous 3 months, interstitial pneumonia/active lung fibrosis on chest X-ray, peripheral neuropathy, malignant pleural or pericardial effusion, diarrhea, intestinal obstruction or paralysis, and active concomitant malignancy. The TRT portal should be no more than half of the hemithorax. No prior chemotherapy or radiotherapy was permitted. Pregnant or lactating women were excluded. Before enrollment in the study, each patient provided a complete medical history and underwent physical examination, blood cell count determinations, arterial blood gas, biochemical laboratory examinations, chest X-ray, electrocardiogram, chest computed tomographic scan, and whole-brain computed tomographic or magnetic resonance imaging, abdominal ultrasound and/or computed tomographic, and isotope bone scans. Blood cell counts, differential white counts, and other laboratory data were obtained weekly during each course of chemotherapy. All patients were reassessed at the end of treatment in the same manner as at the time of enrollment.

Treatment plan. Induction chemotherapy consisted of cisplatin 80 mg/m^2 on day 1 and etoposide 100 mg/m^2 on days 1 to 3. TRT was begun on day 2 of the induction chemotherapy and given twice daily (1.5 Gy per fraction, with ≥ 6 hours between fractions) and directed to the primary tumor for a total dose of 45 Gy in 3 weeks. The initial field included the primary disease site with a 1.5-cm margin around the mass, the ipsilateral hilum, the entire width of the mediastinum, and the supraclavicular lymph nodes (only if there was nodal tumor involvement). TRT was done with linear accelerators and the energy was 6 to 10 MV photons. After the administration of 30 to 36 Gy, the radiation field was reduced around the primary tumor and involved lymph nodes using parallel opposed oblique fields to limit the dose to the spinal cord and protect the uninvolved lung field. Following chemoradiotherapy, patients were treated with three cycles of IP. The IP regimen started on day 29 and consisted of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on day 1, with three 28-day cycles. If the leukocyte count decreased to $<3{,}000/mm^3$ or the platelet count fell below $100{,}000/mm^3$ on the first day of IP, chemotherapy was withhold until the counts recovered to $\geq 3{,}000/mm^3$ and $\geq 100{,}000/mm^3$, respectively. Administration of irinotecan was skipped on day 8 and/or 15 if the leukocyte count was $\leq 2{,}000/mm^3$, the platelet count was $\leq 50{,}000/mm^3$, or there was any diarrhea regardless of grade, or a fever of $\geq 37.5°C$. The dose of irinotecan in subsequent cycles was reduced by 10 mg/m^2 from the planned dose if grade 4 hematologic toxic effects or grade 2 or 3 diarrhea developed. Administration of granulocyte colony-stimulating factor was prohibited on the days of chemotherapy or radiotherapy. Primary prophylactic granulocyte colony-stimulating factor was not given. For patients who had developed grade 4 neutropenia during the previous cycles of chemotherapy, secondary prophylactic granulocyte colony-stimulating factor administration was allowed. Prophylactic antibiotics were not given.

Treatment was discontinued in patients with grade 4 nonhematologic toxicity. Prophylactic cranial irradiation (25 Gy in 10 fractions) was conducted for patients showing a complete response or near complete response defined as a reduction of >90% in the sum of the products of the greatest perpendicular dimensions of bidimensional lesions. Tumor responses were assessed radiographically. Standard WHO response criteria (8) were used, and all responses were confirmed ≥ 28 days after initial documentation of the response. JCOG criteria were used to assess toxicity (9). JCOG criteria are similar to those of the National Cancer Institute Common Toxicity Criteria (10). Esophageal toxicity was graded as follows: grade 3, moderate to severe ulceration and edema, cannot eat, requires narcotic drugs; grade 4, serious ulceration and edema, resulting in complete obstruction or perforation.

Statistical consideration. The primary objective of this study was to evaluate the safety and feasibility of sequential administration of IP following EP plus concurrent twice-daily TRT. Simon's optimal two-stage design was used to determine the sample size and decision criteria (11). The regimen would be considered feasible if two cycles or more of IP were completed without grade 4 nonhematologic toxicity or treatment related death in at least 90% of patients and not feasible if the completion rate was $\leq 70\%$. The required number of patients was estimated to be 27, with $\alpha = 0.05$ and $\beta = 0.80$. We determined the planned sample size for the study to be 30 patients accrued over 12 months, with 36 months of additional follow-up.

Time-to-progression was calculated from the date of entry into study until the date of documented progression or death (in the absence of progression). Survival was calculated from the protocol treatment start date until the date of death. Both intervals were determined by the Kaplan-Meier method.

The protocol was approved by the Clinical Trial Review Committee of JCOG and the Institutional Review Board of the participating institutions. All patients provided written informed consent.

Results

Patient characteristics. Between October 1999 and July 2000, 31 patients were accrued from 10 institutions. Patient characteristics are detailed in Table 1. Although eligible, no patients with a performance status of 2 were actually enrolled in this trial. Thirty-one patients ultimately participated. One patient did not receive the protocol treatment because of a problem with the radiation equipment in the institution providing treatment. Thus, this patient was not evaluable.

Adherence to treatment plan. All patients completed concurrent chemoradiotherapy. Six patients did not receive the IP regimen, because of disease progression, septic shock

Table 1. Patient characteristics

Patient registered	31
Assessable	30
Not assessable (not treated)	1
Median age (range)	64 (43-74)
Gender	
Male	27
Female	4
Performance status 0/1	8/23

during chemoradiotherapy, renal dysfunction, or leukocytopenia, and two refused IP. Of the 24 patients given the IP regimen, 22 received two cycles or more of IP. The reasons for terminating IP before the second treatment cycle were grade 4 diarrhea in one patient and refusal, not significant toxicity, in one patient. Of the 22 patients who received two cycles or more of IP, nine received the original planned dose. In five patients, dose reductions in the second cycle of IP were necessary, 11 patients skipped day 8 and/or 15 irinotecan, and one patient had a minor protocol violation. Fifteen patients required that the second cycle of IP be delayed for 1 to 14 days. Of 17 patients (58%) who received the entire treatment, the median time delay from the planned protocol was 4 days (range, 0-21 days). Six patients were able to start the third cycle of IP without delay, relative to the first cycle of IP.

Toxicity. Toxicities associated with concurrent chemoradiotherapy are summarized in Table 2. The major toxicity was neutropenia. One patient had febrile neutropenia and septic shock. The same patient experienced grade 3 fatigue and anterior chest pain. IP was well tolerated (Table 3), despite diarrhea, vomiting, and hematologic toxicities. One patient, who had grade 2 nausea/vomiting, refused further treatment after the first cycle of IP. Another patient, who refused days 8 and 15 irinotecan during the second cycle, had grade 2 diarrhea and nausea/vomiting. No grade 3 or 4 pulmonary toxicity was observed. There were no treatment-related deaths.

Table 2. Major toxicities concurrent EP/TRT (n = 30)

Toxicity	Grade 3, no. patients (%)	Grade 4, no. patients (%)
Hematologic		
Anemia	0	0
Leucopenia	13 (43)	15 (50)
Neutropenia	9 (30)	19 (63)
Thrombocytopenia	2 (7)	1 (3)
Nonhematologic		
Esophagitis	2 (7)	0
Infection	1 (3)	0
Hypotension*	0	1 (3)
Fatigue*	1 (3)	0
Anterior chest pain*	1 (3)	0
Febrile neutropenia	2 (7)	

*These events occurred in the same patient.

Table 3. Major toxicities irinotecan and cisplatin (IP), (n = 24)

Toxicity	Grade 2, no. patients (%)	Grade 3, no. patients (%)	Grade 4, no. patients (%)
Hematologic			
Anemia	6 (25)	12 (50)	0
Leucopenia	6 (25)	12 (50)	5 (21)
Neutropenia	5 (21)	12 (50)	5 (21)
Thrombocytopenia	5 (21)	1 (4)	0
Nonhematologic			
Diarrhea	4 (17)	1 (4)	1 (4)
Vomiting	3 (13)	2 (8)	0
Febrile neutropenia	—	2 (8)	0
Fever	2 (8)	0	0
Infection	4 (17)	0	0

Neither grade 2, or more severe, late radiation toxicities nor radiation recall reactions were reported.

Response and survival. The overall response rate was 97% (complete response, 37%; partial response, 60%). Overall and progression-free survivals are depicted in Figs. 1 and 2 The median follow-up time of all patients was 20 months and that for surviving patients 40 months. The median progression-free survival was 9 months, and the median overall survival was 20 months. The 24- and 36-month overall survivals were 41% and 38%, the 24- and 36- month progression-free survivals 30% and 26%, respectively.

Pattern of relapse. First sites of disease progression are presented in Table 4. Of the 18 patients who have died to date, all died of progressive disease. Surprisingly, no patient showed relapse solely at the local-regional site (within TRT field). Only two patients had both local and distant involvement. There were 11 patients whose initial site of relapse was the brain. Of these, six had relapses solely in the brain. Whereas two patients had complete response and received prophylactic cranial irradiation, four had partial remission and did not receive prophylactic cranial irradiation.

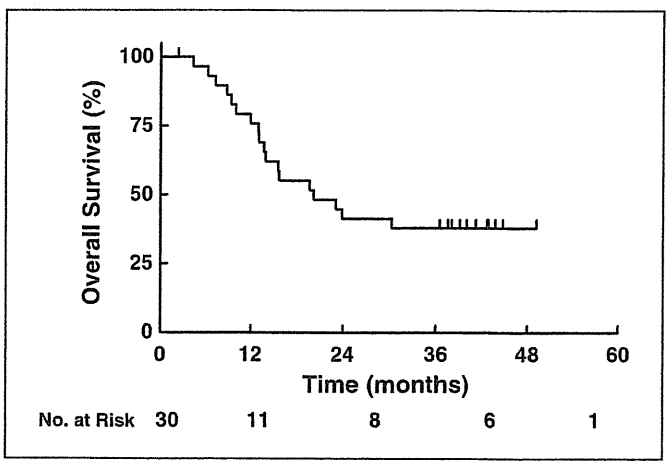

Fig. 1. Overall survival.

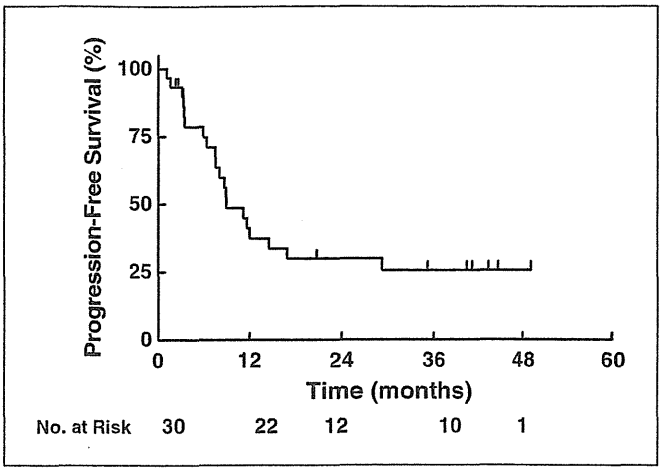

Fig. 2. Progression-free survival.

Other relapse sites included the liver in four patients, bone in three, pleural effusion in three, and supraclavicular lymph nodes in two.

Discussion

Irinotecan is one of the most active agents against SCLC (12). A phase II study of irinotecan and cisplatin yielded a response rate of 86% and median survival of 13.2 months in patients with extensive SCLC (13). A phase III study confirmed excellent results and showed IP to be more effective than etoposide and cisplatin in extensive SCLC (7). Three confirmatory trials, comparing IP with EP for extensive SCLC are ongoing in Europe and the United States. Although dose-finding studies to explore integrating irinotecan into the early concurrent phase of chemoradiation for LSCLC are also currently being conducted by the Radiation Therapy Oncology Group and other U.S. groups. The dose-finding JCOG study of concurrent use of IP with TRT in stage III non-small cell lung cancer showed that the full dose of irinotecan could not be given due to neutropenia, diarrhea, and pulmonary toxicity (14). Thus, we employed IP as a sequential treatment following EP plus concurrent TRT.

The present trial showed IP following concurrent EP plus twice-daily TRT to be safe, with acceptable toxicities. Hematologic toxicities and diarrhea, while on the IP regimen following concurrent chemoradiotherapy, are similar to those of a previous phase III trial conducted by JCOG (JCOG9503; ref. 7). Neither grade 3 or 4 pulmonary toxicity nor treatment related deaths were observed. The West Japan Thoracic Oncology Group conducted a similar phase II study of EP plus twice-daily TRT followed by IP for LSCLC (15). Promising response (88%) and 2-year survival (51%) rates were reported, with acceptable toxicities.

Table 4. Sites of first failure (n = 20)

Site	No. patient (%)
Isolated local-regional failure	0 (0)
Local-regional and distant	2 (10)
Distant	18 (90)
Brain only	6 (30)
Other sites of failure*	12 (60)

*Recurrence at sites other than the primary tumor or brain only.

Local failure is an important problem in the treatment of LSCLC. Turrisi et al. showed the rate of local failure to be reduced in the twice-daily TRT plus EP group as compared with the once-daily TRT plus EP group: the rate was 52% in the group receiving once-daily therapy and 36% in that receiving twice-daily therapy (6). Eighteen percent of patients who received EP plus concurrent twice-daily TRT had first progression within the thorax in the previous JCOG phase III trial (5). It is noteworthy that no patient relapsed solely at the local-regional site and only two patients had both local and distant involvement in the present trial. There may be an interaction between TRT and IP even given sequentially. Another possibility relates to recent improvements in radiotherapeutic techniques with better imaging of the target volume by chest computed tomographic. This possibility should be assessed in a future randomized trial.

It is important to integrate new active anticancer agents to the combined modality treatments for LSCLC. Irinotecan has been clearly shown to have clinical activity in a randomized trial, against extensive-stage SCLC. Several other new agents including targeted therapies have failed to show clinical activity against SCLC. Based on these considerations, we conducted a randomized phase III trial comparing EP with IP following EP plus concurrent TRT for the treatment of LSCLC (JCOG0202). In the JCOG0202, eligible patients were randomized after the completion of induction chemoradiotherapy. Although feasibility may be a limitation of the present study, improvements are anticipated with appropriate use of granulocyte colony-stimulating factor, antibiotics, and patient education.

In summary, irinotecan and cisplatin following EP plus concurrent twice-daily TRT is a safe and active regimen for LSCLC. The observed low rate of local recurrence is encouraging. A randomized phase III trial comparing EP with IP following EP plus concurrent TRT for the treatment of LSCLC is currently under way.

Acknowledgments

We thank F. Koh and N. Tamura for data management and Drs. S. Niho and K. Yoh for support in the data analysis.

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Phase 1 Clinical Trials in Oncology

TO THE EDITOR: Horstmann et al. (March 3 issue)[1] assume that a tumor response is of benefit to subjects in phase 1 oncology trials. This assumption is not valid. A complete or partial tumor response in a phase 1 trial is a surrogate end point, which for most agents has not been linked to a clinically meaningful outcome, such as improved survival.[2]

Informing subjects that they have a 10.6 percent chance of a tumor response is potentially misleading unless accompanied by an explicit discussion of clinical end points and whether any connection exists between a tumor response and clinical end points.[3] This discussion should include an explanation that a tumor response is not a cure or a life extender.

Kurzrock and Benjamin's editorial[4] serves only to increase the misrepresentation of phase 1 research.[5] It is important to know that phase 1 research is essential for the development of future treatments. But it is simply misleading to treat an improvement in the rate of tumor response as an increase in the likelihood of direct clinical benefit to subjects.

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TO THE EDITOR: The article by Horstmann et al. and the accompanying editorial indicate rates of clinical benefit higher than those reported in previous meta-analyses. Horng et al.,[1] in a critique of informed consent in phase 1 oncology trials, decried the frequent lack of an explicit statement that efficacy was not to be expected. However, in addition to evidence presented by Horstmann et al., recent phase 1 trials with established drugs have often resulted in high response rates. Among nine trials involving patients with refractory non–small-cell lung cancer that were presented at the meeting of the American Society of Clinical Oncology in May 2002, the reported response rate was 41 percent (range, 0 to 57 percent) in 150 patients, with one drug-related death recorded. Prior estimates of the risks and benefits of phase 1 oncology trials need updating, and insistence on not conveying therapeutic intent in the informed-consent process in all instances is misplaced.

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1. Horng S, Emanuel EJ, Wilfond B, Rackoff J, Martz K, Grady C. Descriptions of benefits and risks in consent forms for phase 1 oncology trials. N Engl J Med 2002;347:2134-40.

TO THE EDITOR: In their review of 460 phase 1 oncology trials sponsored by the Cancer Therapy Evaluation Program between 1991 and 2002, Horstmann et al. report that the overall toxicity-related death rate was 0.49 percent, which suggests that these trials are relatively safe, considering that virtually all participants have a deadly disease and have exhausted the conventional treatments.[1]

We analyzed the data from 363 trials of investigational new drugs, involving 12,395 adults with solid tumors, that were published between 1976 and

1993.[2] A total of 117 toxicity-related deaths (0.94 percent) and 33 early deaths from unknown causes (0.27 percent) were noted. In addition, 36 trials were excluded from the analysis because further clinical development of the drug was not recommended. We found that toxicity-related death occurred in 26 of 1039 patients in these trials (2.5 percent). Thus, the rate of death due to toxic events varies among phase 1 oncology trials and may be higher than suspected.

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TO THE EDITOR: Kurzrock and Benjamin argue that clinical benefit is an objective of phase 1 cancer trials, citing my article as an instance of an opposing "misconception."[1] The misconception is theirs, as is evident in authoritative definitions.[2,3] Moreover, in failing to distinguish between what phase 1 trials are specifically designed to measure (dose–toxicity profiles) and what is incidental to the design (e.g., the possibility of benefit), Kurzrock and Benjamin ignore the way in which the strictures of protocol constrain the goals of medicine. This misunderstanding, known as the "therapeutic misconception,"[4] reinforces the fiction that clinical research is an extension of clinical care, rather than a fundamentally distinct and sometimes contrary enterprise. Patients in early cohorts in these trials who receive, by design, what Kurzrock and Benjamin call "subtherapeutic" doses are not involved in a trial that aims to maximize their clinical benefit. Failure to see this as a conflict between the objectives of science and those of personal care is the reason the therapeutic misconception has been called "the most important threat to the validity of informed consent to research."[5]

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THE AUTHORS REPLY: The letters from Drs. Rothschild and King and from Dr. Muggia demonstrate the complexity of understanding "benefits" in the context of phase 1 oncology trials. As Drs. Rothschild and King suggest, tumor response, the most common measure of the effect of agents used for the treatment of cancer, is indeed a surrogate marker. Although tumor response does not necessarily correlate with clinical benefit, it is predictive of potential benefit, and there is evidence that tumor response is associated with symptom relief, improved quality of life, and increased survival.[1-4]

We agree that information provided to potential participants in phase 1 trials should be comprehensive, contextual, and clear about the uncertain or inconsistent relationship of possible tumor responses to clinically meaningful benefit.

Furthermore, it should be made clear that although some participants in phase 1 trials may benefit clinically, these trials are designed to evaluate safety, not therapeutic effect. There is a difference between the possibility of benefit from an intervention in a trial and the intent of the researchers when designing the trial. In this regard, we disagree with Dr. Muggia and maintain that consent forms should not describe the purpose or intent of phase 1 trials as therapeutic. Nonetheless, we recognize that although institutional review boards, bioethicists, and others might emphasize the intention of a trial, prospective patients may be more interested in possible benefits than in whether or not the trial is intended to be therapeutic. Our data demonstrate that sometimes there is therapeutic benefit, regardless of the intention of the research.

The statement by Drs. Sekine and Tamura that "the rate of death due to toxic events varies among phase 1 oncology trials" is consistent with the findings of our study. The data they cite emphasize two important realities that should be considered with

regard to response or toxicity rates in phase 1 trials: first, different subsets of data have strikingly different benefit and toxicity rates, and second, response and toxicity rates based on published data may be biased. Their data support the view that the details of a trial matter in interpreting the data on response and toxicity. Simply labeling a trial phase 1 is not sufficiently informative about risks and benefits; more specific details about the trial and the intervention are necessary.

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THE EDITORIALISTS REPLY: Rothschild and King's allegation that it is "misleading to treat an improvement in the rate of tumor response as an increase in the likelihood of direct clinical benefit to subjects" is at variance with our clinical experience and the oncology literature. Decades ago, Freireich et al.[1] established that improvement in survival in leukemia could be attributed directly to the duration of a response. A response to chemotherapy in randomized trials improved the quality of life despite significant side effects.[2] Differences in benefit between patients with and those without a response may be obscured, however, by an inadequate definition of a response. For example, patients with gastrointestinal stromal tumors who were treated with imatinib mesylate and who had stable disease according to the criteria of the Response Evaluation Criteria in Solid Tumors group derived a benefit that was indistinguishable from the benefit in those with a partial response.[3] Logic dictates that patients with good performance status and intact organ function — the eligibility criteria for most phase 1 studies — will not die of their cancer unless it progresses.

The perception that, in phase 1 studies, drugs are administered to patients solely to reveal drug toxicity is incorrect, since the objectives of phase 1 trials specifically include describing the response. Oncologists refer patients for phase 1 studies because they determine that participation in those studies offers their patients, whose disease has progressed after recognized therapies, their best chance of benefit. Thus, the primary concern of treating physicians and patients is efficacy. Miller's contention that the scientific restrictions of the protocols interfere with patient care is partially valid. For instance, some patients who might benefit are excluded from phase 1 trials by the eligibility criteria. Low initial doses and small dose increases, resulting from excessive caution about patient safety, can detract from benefit to patients. Nonetheless, as Horstmann et al. have demonstrated, phase 1 studies resulted in stable disease or better in up to 44.7 percent of patients, including those treated at the lower doses.

Increased time before the progression of cancer benefits patients unless the therapy has serious toxic effects. The worse "toxicity" is most often that due to progressive disease. We agree with Muggia, who demonstrates that recent phase 1 trials have higher response rates than previously reported and have extraordinarily low death rates. Although participants in any study should be informed that patients who have a response to therapy may not always benefit, it is misleading to tell patients that there is no clinical benefit from a response and that phase 1 trials have no therapeutic aim.

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Standard Thoracic Radiotherapy With or Without Concurrent Daily Low-dose Carboplatin in Elderly Patients with Locally Advanced Non-small Cell Lung Cancer: a Phase III Trial of the Japan Clinical Oncology Group (JCOG9812)

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Background: The purpose of this study was to evaluate whether radiotherapy with carboplatin would result in longer survival than radiotherapy alone in elderly patients with unresectable stage III non-small cell lung cancer (NSCLC).

Methods: Eligible patients were 71 years of age or older with unresectable stage III NSCLC. Patients were randomly assigned to the radiotherapy alone (RT) arm, irradiation with 60 Gy; or the chemoradiotherapy (CRT) arm, the same radiotherapy and additional concurrent use of carboplatin 30 mg/m^2 per fraction up to the first 20 fractions.

Results: This study was terminated early when 46 patients were registered from November 1999 to February 2001. Four patients (one in the RT arm, three in the CRT arm) were considered to have died due to treatment-related causes. The JCOG Radiotherapy Committee assessed these treatment-related deaths (TRDs) and the compliance with radiotherapy in this trial. They found that 60% of the cases corresponded to protocol deviation and 7% were protocol violation in dose constraint to the normal lung, two of whom died due to radiation pneumonitis. As to the effectiveness for the 46 patients enrolled, the median survival time was 428 days [95% confidence interval (CI) = 212–680 days] in the RT arm versus 554 days (95% CI = 331 to not estimable) in the CRT arm.

Conclusions: Due to the early termination of this study, the effectiveness of concurrent use of carboplatin remains unclear. We re-planned and started a study with an active quality control program which was developed by the JCOG Radiotherapy Committee.

Key words: non-small cell lung cancer – elderly patients – carboplatin – chemoradiotherapy

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in the USA, Europe and Japan. In Japan, the number of elderly is increasing dramatically. In 2001, the proportion of Japanese population older than 65 years was 18%; in other words, the number of people older than 65 years exceeded 22 million (1). Lung cancer death rates for men and women aged 75 or more have increased to ~531 and 138 per 100 000 population, respectively (1). To establish the effective treatment for the elderly with lung cancer has thus become of greater importance.

Until recently, the standard treatment for locally advanced non-small cell lung cancer (NSCLC) was radiotherapy alone. However, the 5-year survival rate of patients with stage III remained under 10% (2–4). To improve the survival rates, many clinical trials comparing radiotherapy with chemoradiotherapy have been conducted (5–11). A recent meta-analysis suggested that the combination of chemotherapy containing cisplatin (CDDP) and radiation could improve the survival rate compared with radiotherapy alone (12,13). However, it is still unclear whether the combined chemoradiotherapy is also suitable for elderly patients. This is partly because the elderly had been considered inappropriate as study patients.

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Almost all evidence available has thus been derived from subset analysis of trials for locally advanced NSCLC. A secondary analysis of RTOG 94-10 revealed a greater survival benefit for concurrent chemotherapy (14). Schild et al. reported no significant difference in tumor regression between younger and older patients in an NCCTG trial (15). Meanwhile, some reports on inoperable NSCLC patients indicate that chemoradiotherapy has survival benefit compared with radiotherapy, but this may not be applicable for those >70 years of age, for whom radiation alone could be most beneficial (16,17).

Therefore, we cannot treat the elderly in the same way as we can younger patients: first, as elderly patients have poorer prognosis than younger patients, they may think that their quality of life is more important than risking radical treatment. Secondly, the elderly tend to be vulnerable to intensive care and toxicities of treatment drugs (18–21). Less toxic therapy may be more effective for the elderly with NSCLC.

Some clinical trials, in which the elderly were not included, showed some efficacy of carboplatin (CBDCA), an analog of CDDP, having no nephrotoxicity, neurotoxicity or ototoxicity and being much less emesis-provoking than CDDP (22–24). Additionally, some investigators found the same radiosensitizing properties of CBDCA (25–28) as also found for CDDP. Therefore, we hypothesized CBDCA to be more acceptable in the treatment of elderly patients. A phase II study has reported the use of radiotherapy and concurrent low-dose daily CBDCA in elderly patients with locally advanced NSCLC (29). For stage III patients, the median survival time (MST) was 15.1 months. Given an MST of ~10 months by radiation alone (5,6,8,9,11,17), this combined chemoradiotherapy seemed promising. Here we performed a randomized study to determine whether this combined chemoradiotherapy has an impact on survival in elderly patients with unresectable locally advanced NSCLC compared with radiotherapy alone.

PATIENTS AND METHODS

PATIENTS

Eligibility criteria for this study were as follows: age ≥71 years; a histologically confirmed non-small cell carcinoma; unresectable disease; stage IIIA except T3N1M0 and IIIB which does not have disease extended to any contralateral hilar nodes or any supraclavicular nodes, atelectasis of the entire lung or malignant pleural effusions; measurable disease; a required radiation field of less than one half of one lung; no previous chemotherapy or radiotherapy; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; PaO_2 ≥70 torr, white blood cell count ≥4000/μl, hemoglobin level ≥9.5 g/dl, platelet count ≥100 000/μl, serum bilirubin level ≤1.5 mg/dl, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ twice the upper limit of normal, and serum creatinine level ≤ the upper limit of normal; a life expectancy of at least 3 months; and written informed consent. Exclusion criteria included patients with active infection, interstitial pneumonia or active lung fibrosis, chronic obstructive pulmonary disease (COPD) or uncontrolled heart disease, an active synchronous cancer, or a metachronous cancer within three disease-free years.

Staging was performed by chest radiograph in two directions, computed tomography (CT) scan or magnetic resonance imaging (MRI) of the head, CT scan of the chest, CT scan or ultrasound of the abdomen, and bone scintigraphy.

TREATMENT

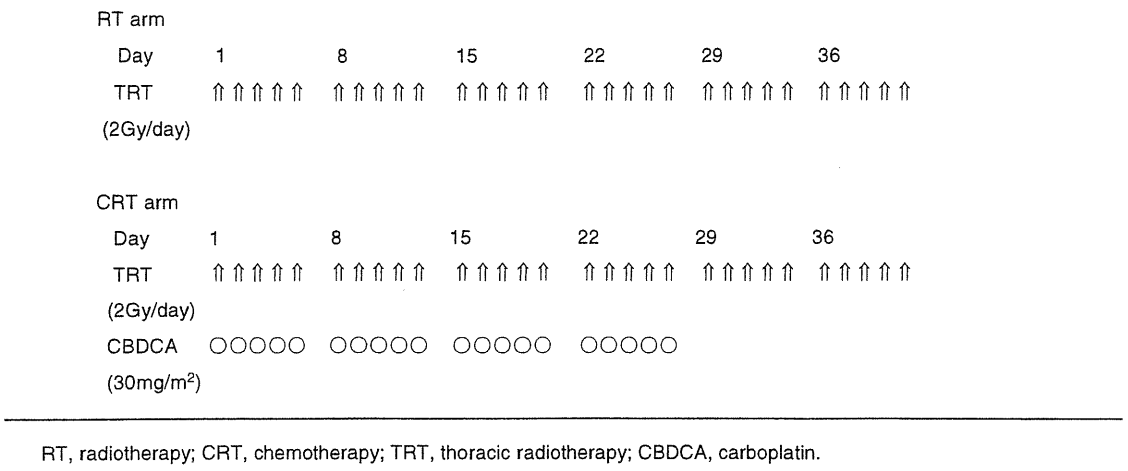
Patients were randomly assigned to the radiotherapy (RT) arm or the chemoradiotherapy (CRT) arm, by the minimization method of balancing PS (0 or 1 versus 2), stage (IIIA versus IIIB) and institution. The RT consisted of 60 Gy in 30 fractions over 6 weeks. In the CRT arm, patients received the same radiotherapy as in the RT arm and concurrent intravenous administration of CBDCA 30 mg/m^2 (30 min infusion) 1 h before every radiation treatment up to the first 20 fractions (Fig. 1).

Radiotherapy was delivered with megavoltage (6–10 MeV photons) equipment using anterior/posterior opposed fields up to 40 Gy including the primary tumor, the metastatic lymph nodes and the regional node. A booster dose of 20 Gy was given to the primary tumor and the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique fields. The clinical target volume (CTV) for the primary tumor was defined as the gross tumor volume (GTV) plus 1 cm taking account of subclinical extension. CTV and GTV for the metastatic nodes (>1 cm in shortest dimension) were the same. Regional nodes excluding contra-lateral hilar and supraclavicular nodes were included in the CTV; however, lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The planning target volumes for the primary tumor, the metastatic lymph nodes and regional nodes were determined as CTVs plus 0.5–1.0 cm margins laterally and 1.0–2.0 cm margins cranio-caudally taking account of set up variations and internal organ motion. Lung heterogeneity corrections were not used.

The criteria for stopping the treatment are pulmonary toxicities, which include the National Cancer Institute-Common Toxicity Criteria (NCI-CTC; version 2.0) grade 2 respiratory distress and <60 torr PaO_2, other than hematopoietic toxicities (leukopenia, neutropenia and thrombocytopenia) or gastrointestinal toxicities (dysphagia).

EVALUATION

To assess the rate of tumor response and toxicity, all patients received a complete blood cell count; blood chemistry, including AST, ALT, lactate dehydrogenase, bilirubin, serum creatinine, blood urea nitrogen, total protein, serum albumin, serum electrolytes and calcium; and weekly chest X-rays during the treatment period. Best overall response was evaluated as tumor response by mono- or bi-dimensional measurement in accordance with the World Health Organization (WHO) criteria (30), and toxicity was evaluated in accordance with the NCI-CTC (version 2.0).



RT, radiotherapy; CRT, chemotherapy; TRT, thoracic radiotherapy; CBDCA, carboplatin.

Figure 1. Treatment schema.

Study Design and Statistical Analysis

This trial was a multi-center randomized phase III study. The study protocol was approved by the JCOG Clinical Trials Review Committee and the institutional review board of each participating institution before the initiation of the study.

The primary end-point was overall survival, which was defined as the interval from randomization to death from any cause. Secondary end-points were response rate, which was the proportion of the patients evaluated as having a complete reponse (CR) or partial response (PR) in best overall response out of all eligible patients; progression-free survival (PFS) defined as the interval from randomization to the diagnosis of progression or death from any cause; sites of progression; and toxicity. The estimate of survival time was performed by the Kaplan–Meier method (31). The trial was designed to have an 80% power to detect 5 months difference in MST (10 months in the RT arm and 15 months in the CRT arm) with a one-sided alpha of 0.05 by log rank test (32). The planned sample size was 190 patients by Shoenfeld and Richter's methods (33) with 1.5 years follow-up after 3 years accrual.

In-house interim monitoring is performed by the JCOG Data Center to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress. The monitoring reports are submitted and reviewed by the JCOG Data and Safety Monitoring Committee (DSMC) twice yearly.

An expedited report was required by the JCOG DSMC to allow rapid identification of any life-threatening adverse events or unexpected toxicities according to the JCOG toxicity reporting system based on the ICH-E2A guidelines.

RESULTS

From November 1999 to February 2001, 46 patients were enrolled in this study: 23 in the RT arm and 23 in the CRT arm. Four treatment-related deaths (TRDs) had been reported, however, before the forty-sixth patient were assigned. Therefore, we suspended the registration and checked the details of all randomized patients to assess the safety of treatment regimens. As a result, it was revealed that three of these deaths were due to pneumonitis. The JCOG DSMC advised consultation with the JCOG Radiotherapy Committee (RC) about the radiotherapy compliance in all patients. The JCOG RC collected each patient's irradiation planning data retrospectively and found poor protocol compliance which was related to TRD. Consequently, we decided to terminate this trial in August 2001 following the recommendation of the JCOG DSMC.

PATIENTS CHARACTERISITICS

Patient characteristics are listed in Table 1. No specific characteristics of patients were found in the elderly patients with locally advanced NSCLC compared with younger patiests and the two treatment arms were well balanced with respect to age and stage.

Toxicity of Treatment

Both hematological and non-hematological toxicities during the treatment and follow-up period were assessed. Table 2 summarizes the hematological toxicity. Patients receiving CBDCA suffered from leukocytopenia, neutropenia and thrombocytopenia more than patients receiving RT alone. There was no grade 4 hematological toxicity in the RT arm. Two (8.7%) and four (17.4%) patients in the CRT arm experienced grade 4 leukocytopenia and neutropenia, respectively.

Non-hematological toxicity observed in this study is listed in Table 3. None of the patients developed grade 3 esophagitis in either treatment arm. In the RT arm, other grade 3/4 toxicities were edema, fatigue, dyspnea and pneumonitis in one patient each. In the CRT arm, other grade 3/4 toxicities were neutropenic fever, dyspnea and pneumonitis. Grade 3/4 (RTOG/EORTC Radiation Toxicity Score) of late lung toxicity was observed in two patients in the RT arm and four patients in the CRT arm. Four TRDs were observed in this study. Three of

Table 1. Patient characteristics

Characteristics	RT arm	CRT arm
No. of eligible patients	23	23
Age (years)		
Median	77	77
Range	72–84	71–83
Male/female	19/4	16/7
Type of tumor		
Adenocarcinoma	6	11
Squamous cell	16	11
Large cell	1	1
PS (ECOG)		
0	3	9
1	19	13
2	1	1
Stage of disease		
IIIA	11	12
IIIB	12	11
Weight loss		
<10%	21	23
⩾10%	2	0

RT, radiotherapy; CRT, chemoradiotherapy; PS, performance status.

Table 2. Hematological toxicity

	RT arm (n = 23)					CRT arm (n = 23)				
Grade	1	2	3	4	%grade 4	1	2	3	4	%grade 4
Leukocytes	10	2	2	0	0	3	7	11	2	8.7
Neutrophils	4	3	0	0	0	2	8	6	4	17.4
Hemoglobin	5	3	0	0	0	5	8	3	0	0
Platelets	2	0	2	0	0	4	5	8	0	0

RT, radiotherapy; CRT, chemoradiotherapy.

these patients were thought to have died as a result of pneumonitis. The details of these cases are follows. Case 1: a 78-year-old man had stage IIIA (T3N2) squamous cell carcinoma. He was treated with RT alone and died of pneumonitis at 28 days after therapy. Case 2: a 79-year-old man had stage IIIB (T4N2) adenocarcinoma. He was treated with CBDCA + RT and died of bacterial pneumonia at 37 days after therapy and had been taking steroid hormone due to radiation pneumonitis. Case 3: a 73-year-old man had stage IIIA (T3N2) squamous cell carcinoma. He was treated with CBDCA + RT and died of pneumonitis at 80 days after therapy. Case 4: a 80-year-old man had stage IIIB (T4N2) squamous cell carcinoma. He was treated with CBDCA + RT and died of pneumonitis at 54 days after therapy. Thus, three out of four TRDs were in the CRT arm and one was in the RT arm.

Table 3. Non-hematological toxicity

	RT arm (n = 23)					CRT arm (n = 23)				
Grade	1	2	3	4	% grade 4	1	2	3	4	% grade 4
Edema	0	0	0	1	4.5	0	0	0	0	0
Fatigue	1	0	0	1	4.5	7	1	0	0	0
Fever	3	0	0	0	0	1	1	0	0	0
Esophagitis	13	2	0	0	0	10	2	0	0	0
Nausea	0	0	0	–	–	2	2	0	–	–
Vomiting	0	0	0	0	0	1	0	0	0	0
Febrile neutropenia	–	–	0	0	0	–	–	1	0	0
Cough	3	1	0	–	–	6	0	0	–	–
Dyspnea	–	0	0	1	4.5	–	2	1	0	0
Pneumonitis	1	0	0	–	4.5	1	0	1	0	0
Creatinine	1	0	0	0	0	0	0	0	0	0
Hyponatremia	7	–	0	0	0	5	–	1	0	0
Heart	0	0	0	0	0	0	1	0	0	0
Lung	8	4	2	0	0	9	6	1	3	13.0

RT, radiotherapy; CRT, chemoradiotherapy.

Protocol Compliance

In the RT arm, 22 (95.6%) patients received full treatment doses. In the CRT arm, 20 (87.0%) patients completed the treatment. As to the administration of CBDCA, there were few protocol deviations.

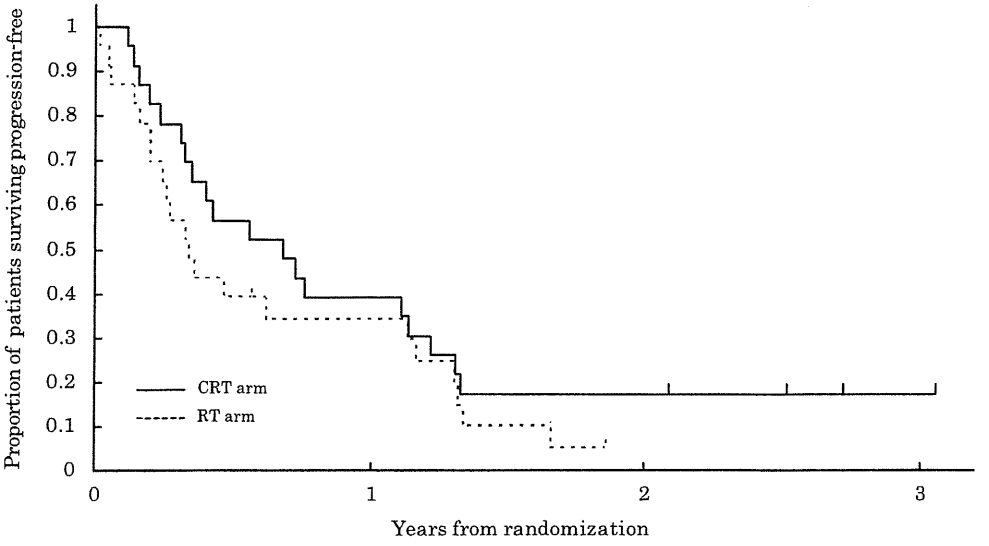
Three of the patients discontinued the protocol treatment: one was due to grade 2 eruption, one was due to cerebral infarction and one was due to insufficient recovery from leukopenia. One patient in the RT arm did not start the treatment due to local progression (Table 4).

Quality Assurance of Radiotherapy

We evaluated the quality of radiotherapy retrospectively based on the collected radiation therapy planning data. The data of 45 patients were reviewed and evaluated for the analysis. Details of this analysis have been reported by Ishikura et al. (34); three cases were revealed to be protocol violation due to normal lung volume constraint defined in the protocol. Unacceptable protocol deviations were identified as follows; 17, 15 and 31 cases on field border placement for the primary tumor, the metastatic lymph nodes and the elective nodal irradiation, respectively. Overall, 27 of 45 cases (60%) had at least one unacceptable deviation. Most cases judged to have protocol violation were primarily due to a smaller radiation field. Only 18 cases (40%) were judged to be protocol compliant.

Response and Survival

The tumor response in each arm is listed in Table 5. No patients achieved a CR in either arm. Of the 23 patients in the RT arm, 12 [52.2%, 95% confidence interval (CI) = 30.6–73.2%] achieved PR and six (26.1%) had stable disease. Of the



RT, radiotherapy; CRT, chemoradiotherapy.

Figure 2. Progression-free survival for patients treated with radiation alone or radiation with concurrent daily CBDCA.

Table 4. Protocol compliance

Pattern	RT arm (n = 23)	CRT arm (n = 23)
Complete protocol treatment	22	20
Progression/relapse*	1	0
Adverse events		
Cerebral infarction	0	1
Eruption	0	1
Leukopenia	0	1
Patient refusal	0	0
Death on protocol	0	0
Other	0	0

*Before starting the radiotherapy.
RT, radiotherapy; CRT, chemoradiotherapy.

Table 5. Response to treatment

Response	RT arm (n = 23)	CRT arm (n = 23)
Complete response	0 (0)	0 (0)
Partial response	12 (52.2)	11 (47.8)
Stable disease	6 (26.1)	7 (30.4)
Progression	4 (17.4)	4 (17.4)
Not evaluable	1 (4.4)	1 (4.4)
Objective response	52.2%	47.8%

RT, radiotherapy; CRT, chemoradiotherapy.

23 patients in the CRT arm, 11 (47.8%, 95% CI = 26.8–69.4%) achieved PR and seven (30.4%) had stable disease.

Seventeen (73.9%) patients in the RT arm and 15 (65.2%) patients in the CRT arm had died at the time of analysis. The median progression-free survival time was 122 days (95% CI = 88–413 days) on the RT arm versus 248 days (95% CI = 127–416 days) on the CRT arm (Fig. 2.). The MST was 428 days (95% CI = 212–680 days) on the RT arm versus 554 days (95% CI = 331 to not estimable) on the CRT arm (Fig. 3.). The 1-year survival rate was 60.9% (95% CI = 40.9–80.8%) on the RT arm versus 65.2% (95% CI = 45.8–84.7%) on the CRT arm.

Pattern of Progression/Relapse

The first site of disease progression or relapse is listed in Table 6. Sixteen patients in the RT arm and 13 patients in the CRT arm had relapsed or had disease progression at the time of analysis. Eight patients (out of 16, 50.0%) in the RT arm and seven patients (out of 13, 53.8%) in the CRT arm had relapse or disease progression within the radiation field whether relapse outside the radiation field occurred or not.

DISCUSSION

We conducted this randomized controlled trial to determine whether chemoradiotherapy was superior to radiotherapy alone with respect to overall survival of elderly patients with locally advanced NSCLC. The study was terminated early when 24% of the planned sample size was accrued because of a high proportion of TRDs due to radiation pneumonitis and protocol violation.

Pulmonary toxicities including radiation pneumonitis and fibrosis caused by radiation therapy are, in general, common but not severe. In this study, however, the risk of TRD was 8.7% (four out of 46) and was much higher than in other trials. For instance, Ohe et al. (35) retrospectively analyzed the incidence of TRDs in the treatment of thoracic radiotherapy and/or chemotherapy for patients with locally advanced NSCLC, and reported that seven of 448 patients (1.6%)

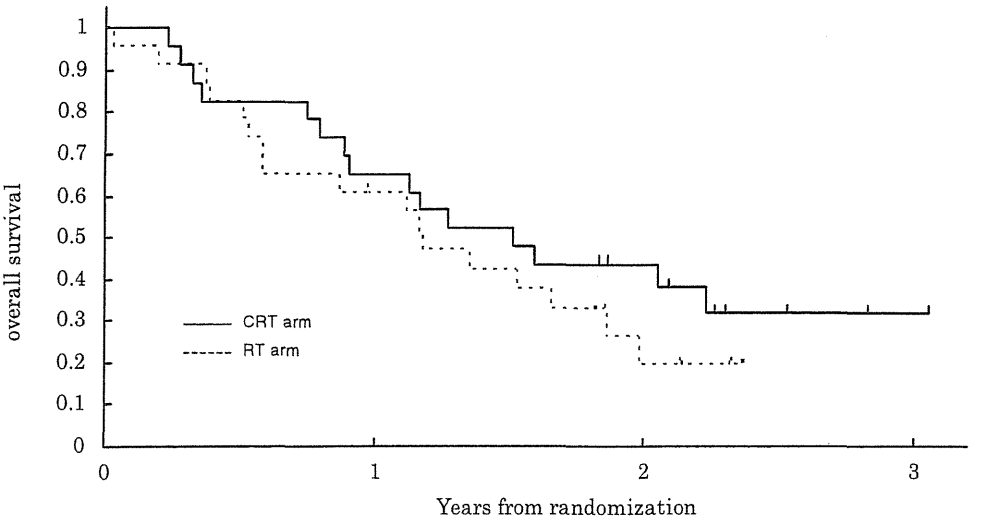


Figure 3. Overall survival for patients treated with radiation alone or radiation with concurrent daily CBDCA.

Table 6. First site of disease progression

	RT arm (n = 23)	CRT arm (n = 23)
Local	8	5
Distant	8	6
Local + distant	0	2

RT, radiotherapy; CRT, chemoradiotherapy.

died of radiation-induced pneumonitis. The high proportion of pulmonary toxicities in our trial may be due partly to the high age of the patients. Schild et al. (15) reported that they found 6% of elderly (older than 75 years) with NSCLC had grade 4 pneumonitis whereas this was the case in only 1% of younger patients ($P = 0.02$). It was controversial that the four TRDs out of 46 was sufficient reason to terminate the on-going trial; however, we thought it was serious that half of the TRDs (two out of four) were judged to be associated with protocol violation concerning the radiation field, which was to be less than half of one lung. Because the JCOG had not yet established the quality control/assurance system for radiotherapy before this trial, we concluded that we would not be able to control the risk of radiation pnuemonitis due to protocol deviation if we continued this study. What was an issue in this study was not only the high TRD rate, but also the poor protocol compliance of RT. The reasons for the poor protocol compliance are limited participation of radiation oncologists during protocol development, limited educational resources for attending radiation oncologists and no quality control program. Although the retrospective systematic review of radiation planning and protocol compliance of radiotherapy was the first experience in the JCOG, both the Lung Cancer Study Group and the entire JCOG had become aware of the importance of a quality control system for radiotherapy. The JCOG Executive Committee decided to establish the Radiation Therapy Quality Assurance Center (RTQAC) within the JCOG Data Center under the supervision of the JCOG Radiotherapy Committee. The RTQAC started the prospective quality control and quality assurance (QC/QA) program in September 2002 with a new activated phase III study for limited disease of small cell lung cancer, JCOG0202. Up to 2004, the QC/QA program has been expanded to the other group studies, such as esophageal cancer study, breast cancer study, prostate cancer study and brain tumor study. In addition, the JCOG Executive Committee mandates the QC/QA program by the RTQAC for all JCOG trials when protocol treatment includes radiation therapy.

The clinical question raised in this trial has not been answered. The data from the 46 patients enrolled were not considered to be conclusive because of the small sample size. No remarkable difference was found between the arms in terms of safety and efficacy such as tumor response, PFS and overall survival. We considered that it still remained an important clinical question to be investigated whether the daily low-dose CBDCA plus radiotherapy was effective or not. Therefore, we re-planned and started a new phase III trial (JCOG0301), in which the prospective QC/QA program by the RTQAC is added to the identical design to this JCOG9812. The protocol involves initial review of radiation planning and final review of the actual radiation record for all randomized patients. The JCOG0301 was activated in September 2003, and we have achieved very good protocol compliance upto now.

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ORIGINAL REPORT

Randomized Pharmacokinetic and Pharmacodynamic Study of Docetaxel: Dosing Based on Body-Surface Area Compared With Individualized Dosing Based on Cytochrome P450 Activity Estimated Using a Urinary Metabolite of Exogenous Cortisol

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose

Docetaxel is metabolized by cytochrome P450 (CYP3A4) enzyme, and the area under the concentration-time curve (AUC) is correlated with neutropenia. We developed a novel method for estimating the interpatient variability of CYP3A4 activity by the urinary metabolite of exogenous cortisol (6-beta-hydroxycortisol [6-β-OHF]). This study was designed to assess whether the application of our method to individualized dosing could decrease pharmacokinetic (PK) and pharmacodynamic (PD) variability compared with body-surface area (BSA) –based dosing.

Patients and Methods

Fifty-nine patients with advanced non–small-cell lung cancer were randomly assigned to either the BSA-based arm or individualized arm. In the BSA-based arm, 60 mg/m^2 of docetaxel was administered. In the individualized arm, individualized doses of docetaxel were calculated from the estimated clearance (estimated clearance = 31.177 + [7.655 × 10^{-4} × total 6-β-OHF] − [4.02 × alpha-1 acid glycoprotein] − [0.172 × AST] − [0.125 × age]) and the target AUC of 2.66 mg/L · h.

Results

In the individualized arm, individualized doses of docetaxel ranged from 37.4 to 76.4 mg/m^2 (mean, 58.1 mg/m^2). The mean AUC and standard deviation (SD) were 2.71 (range, 2.02 to 3.40 mg/L · h) and 0.40 mg/L · h in the BSA-based arm, and 2.64 (range, 2.15 to 3.07 mg/L · h) and 0.22 mg/L · h in the individualized arm, respectively. The SD of the AUC was significantly smaller in the individualized arm than in the BSA-based arm ($P < .01$). The percentage decrease in absolute neutrophil count (ANC) averaged 87.1% (range, 59.0 to 97.7%; SD, 8.7) in the BSA-based arm, and 87.4% (range, 78.0 to 97.2%; SD, 6.1) in the individualized arm, suggesting that the interpatient variability in percent decrease in ANC was slightly smaller in the individualized arm.

Conclusion

The individualized dosing method based on the total amount of urinary 6-β-OHF after cortisol administration can decrease PK variability of docetaxel.

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INTRODUCTION

Many cytotoxic drugs have narrow therapeutic windows despite having a large interpatient pharmacokinetic (PK) variability. The doses of these cytotoxic drugs are usually calculated on the basis of body-surface area (BSA). Although several physiologic functions are proportional to BSA, systemic exposure to a drug is only partially related to

this parameter.[1-3] Consequently, a large interpatient PK variability is seen when doses are based on BSA. This large interpatient PK variability can result in undertreatment with inappropriate therapeutic effects in some patients, or in overtreatment with unacceptable severe toxicities in others. Understanding interpatient PK variability is important for optimizing anticancer treatments. Factors that affect PK variability include drug absorption, metabolism, and excretion. Among these factors, drug metabolism is regarded as a major factor causing PK variability. Unfortunately, however, no simple and practical method for estimating the interpatient variability of drug metabolism is available. If drug metabolism in each patient could be predicted, individualized dosing could be performed to optimize drug exposure while minimizing unacceptable toxicity.

Docetaxel is a cytotoxic agent that promotes microtubule assembly and inhibits depolymerization to free tubulin, resulting in the blockage of the M phase of the cell cycle.[4] Docetaxel has shown promising activity against several malignancies, including non–small-cell lung cancer, and is metabolized by hepatic CYP3A4 enzyme.[5-15]

Human CYP3A4 is a major cytochrome P450 enzyme that is present abundantly in human liver microsomes and is involved in the metabolism of a large number of drugs, including anticancer drugs.[16-18] This enzyme exhibits a remarkable interpatient variation in activity as high as 20-fold, which accounts for the large interpatient differences in the disposition of drugs that are metabolized by this enzyme.[19-22] Several noninvasive in vivo probes for estimating the interpatient variability of CYP3A4 activity have been reported and include the erythromycin breath test, the urinary dapsone recovery test, measurement of midazolam clearance (CL), and measurement of the ratio of endogenous urinary 6-beta-hydroxycortisol (6-β-OHF) to free-cortisol (FC).[23-27] The erythromycin breath test and the measurement of midazolam CL are the best validated, and both have been shown to predict docetaxel CL in patients.[28,29] However, neither probe has been used in a prospective study to validate the correlations observed, or to test their utility in guiding individualized dosing.

We developed a novel method for estimating the interpatient variability of CYP3A4 activity by urinary metabolite of exogenous cortisol. The total amount of 24-hour urinary 6-β-OHF after cortisol administration (total 6-β-OHF) is significantly correlated with docetaxel CL, which is metabolized by the CYP3A4 enzyme. We also illustrate the possibility that individualized dosing to optimize drug exposure and decrease interpatient PK variability could be performed using this method.[30]

We conducted a prospective, randomized PK and pharmacodynamic (PD) study of docetaxel comparing BSA-based dosing and individualized dosing based on the interpatient variability of CYP3A4 activity, as estimated by a urinary metabolite of exogenous cortisol. The objective of this study was to assess whether the application of our method to individualized dosing could decrease PK and PD variability of docetaxel compared with BSA-based dosing.

PATIENTS AND METHODS

Patient Selection

Patients with histologically or cytologically documented advanced or metastatic non–small-cell lung cancer were eligible for this study. Other eligibility criteria included the following: age $\geq$ 20 years; Eastern Cooperative Oncology Group performance status of 0, 1, or 2; 4 weeks of rest since any previous anticancer therapy; and adequate bone marrow (absolute neutrophil count [ANC] $\geq$ 2,000/μL and platelet count $\geq$ 100,000/μL), renal (serum creatinine level $\leq$ 1.5 mg/dL), and hepatic (serum total bilirubin level $\leq$ 1.5 mg/dL, AST level $\leq$ 150 U/L, and ALT level $\leq$ 150 U/L) function. Written informed consent was obtained from all patients before enrollment onto the study.

The exclusion criteria included the following: pregnancy or lactation; concomitant radiotherapy for primary or metastatic sites; concomitant chemotherapy with any other anticancer agents; treatment with steroids or any other drugs known to induce or inhibit CYP3A4 enzyme[17]; serious pre-existing medical conditions, such as uncontrolled infections, severe heart disease, diabetes, or pleural or pericardial effusions requiring drainage; and a known history of hypersensitivity to polysorbate 80. This study was approved by the institutional review board of the National Cancer Center.

Pretreatment and Follow-Up Evaluation

On enrollment onto the study, a history and physical examination were performed, and a complete differential blood cell count (including WBC count, ANC, hemoglobin, and platelets), and a clinical chemistry analysis (including serum total protein, albumin [ALB], bilirubin, creatinine, AST, ALT, gamma-glutamyltransferase, alkaline phosphatase [ALP], and alpha-1 acid glycoprotein [AAG]) were performed. Blood cell counts and a chemistry analysis except for AAG were performed at least twice a week throughout the study. Tumor measurements were performed every two cycles, and antitumor response was assessed by WHO standard response criteria. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (version 2.0).

Study Design

This study was designed to assess whether the application of our method to individualized dosing could decrease PK and PD variability compared with BSA-based dosing. The primary end point was PK variability and the secondary end point was PD variability (ie, toxicity). In our previous study involving 29 patients who received 60 mg/m^2 of docetaxel, the area under the concentration-time curve (AUC) was calculated to be 2.66 $\pm$ 0.91 (mean $\pm$ standard deviation [SD]) mg/L $\cdot$ h.[30] We assumed that the variability of AUC, represented by the SD, could be reduced by 50% in the individualized arm compared with that in the BSA-based arm, and that AUC would be normally distributed. The required sample size was 25 patients per arm to detect this difference with a two-sided F test at α = .05 and a power of 0.914.

Patients were randomly assigned to either the BSA-based arm or individualized arm (Fig 1). In the BSA-based arm, each patient received a dose of 60 mg/m^2 of docetaxel. In the individualized arm, individualized doses of docetaxel were calculated from the estimated docetaxel CL after cortisol administration and the target AUC (described in the Docetaxel Administration section).

Cortisol Administration and Urine Collection

In the individualized arm, 300 mg of hydrocortisone (Banyu Pharmaceuticals Co, Tokyo, Japan) was diluted in 100 mL of 0.9%

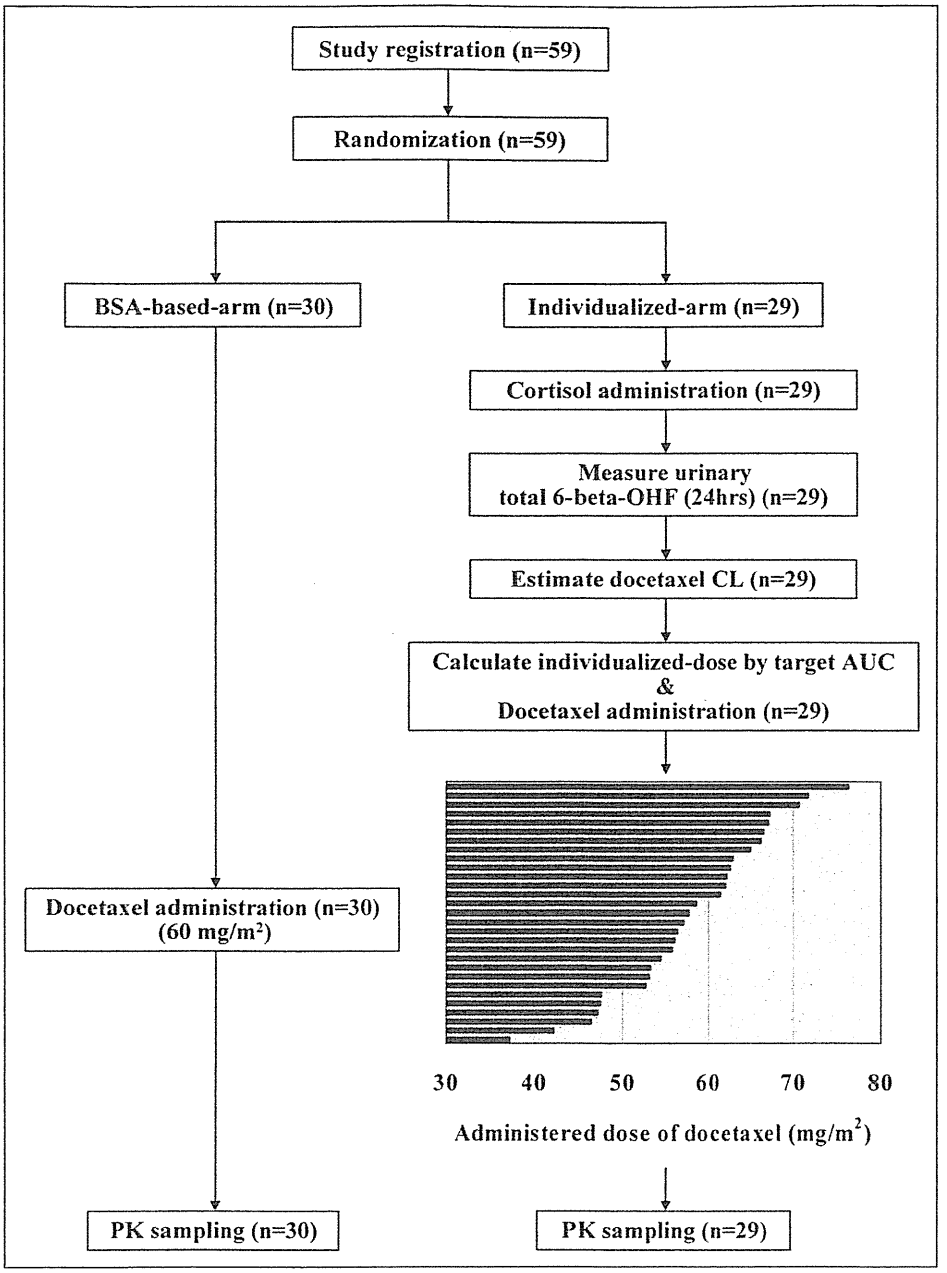

Fig 1. Study flow diagram and administered dose of docetaxel. PK, pharmacokinetic; AUC, area under the concentration-time curve; CL, clearance; 6-β-OHF, 6-beta-hydroxycortisol.

saline and administered intravenously for 30 minutes at 9 AM on day 1 in all patients to estimate the interpatient variability of CYP3A4 activity. After cortisol administration, the urine was collected for 24 hours. The total volume of the 24-hour collection was recorded, and a 5-mL aliquot was analyzed immediately.

Docetaxel Administration

Docetaxel (Taxotere; Aventis Pharm Ltd, Tokyo, Japan) was obtained commercially as a concentrated sterile solution containing 80 mg of the drug in 2 mL of polysorbate 80. In the BSA-based arm, a dose of 60 mg/m^2 of docetaxel was diluted in 250 mL of 5% glucose or 0.9% saline and administered by 1-hour intravenous infusion at 9 AM to all patients.

In the individualized arm, individualized dose of docetaxel was calculated from the estimated CL and the target AUC of 2.66 mg/L · h using the following equations:

$$\text{Estimated CL (L/h/m}^2) = 31.177 + (7.655 \times 10^{-4} \times \text{total-6-}\beta\text{-OHF [}\mu\text{g/d]}) - (4.02 \times \text{AAG [g/L]}) - (0.172 \times \text{AST [U/L]}) - (0.125 \times \text{age [years]})^{30}$$

$$\text{Individualized dose of docetaxel (mg/m}^2) = \text{estimated docetaxel CL (L/h/m}^2) \times \text{target AUC (2.66 mg/L} \cdot \text{h)}$$