Table 3. Treatment details and outcome for the study cohort

Patient	Regimen (mg/m^2)	Total no. of cycles	Dose reduction in consolidation chemotherapy	DI of P (mg/m^2/week)	RDI of P (%)	DI of E (mg/m^2/week)	RDI of E (%)	Duration of TRT (days)	V20 (%)	Response	PFS (months)	Survival time (months)
1	E(100) + P(40)[a] + TRT	2	No	5.0	25.0	37.5	50.0	23	21	CR	14.0+	14.0+
2	E(100) + P(80) + TRT	4	Yes	17.2	86.0	73.7	98.2	19	25	CR	7.3+	7.3+
3	E(100) + P(80) + TRT	4	Yes	17.8	89.1	68.7	91.6	27	35	CR	10.7+	10.7+
4	E(100) + P(80) + TRT	4	Yes	15.7	78.4	61.6	82.1	30	13	PR	9.3	22.2
5	E(100) + P(80) + TRT	2	No	9.5	47.5	35.6	47.5	29	20	PR	4.3	11.4
6	E(100) + P(80) + TRT	4	No	19.6	98.2	73.7	98.2	29	30	PR	18.2	48.1+
7	E(100) + P(80) + TRT	4	No	17.2	86.2	64.6	86.2	26	27	PR	13.1	26.1+
8	E(80)[b] + P(80) + TRT	3	Yes	11.4	56.9	39.4	52.5	30	21	PR	8.3	17.1
9	E(100) + P(60)[a] + TRT	4	Yes	14.4	71.8	61.0	81.4	30	25	CR	20.6+	20.6+
10	E(100) + P(80) + TRT	4	Yes	13.1	65.5	49.1	65.5	28	NA	PR	14.4	16.5
11	E(100) + P(80) + TRT	2	Yes	7.9	39.5	30.5	40.6	33	26	PR	3.9	14.8
12	E(100) + P(80) + TRT	2	No	9.9	49.6	37.2	49.6	29	22	CR	14.1	27.2

DI, dose intensity; P, cisplatin; RDI, relative dose intensity; E, etoposide; V20, the percentage of lung volume receiving >20 Gy; PFS, progression-free survival; CR, complete response; +, without event; PR, partial response; NA, not available.
[a]Dose reduction because of a decline in renal function.
[b]Dose reduction because of physician's decision.

Table 4. Toxicities during concurrent chemoradiotherapy

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3 or 4 (%)
Leukopenia	0	0	2	10	100
Neutropenia	0	0	0	12	100
Anemia	2	1	0	0	0
Thrombocytopenia	0	2	2	1	25
Febrile neutropenia	—	—	8	0	67
Nausea–vomiting	2	2	2	0	17
Esophagitis	1	3	0	0	0
Appetite loss	5	2	2	0	17

Table 5. Toxicities during consolidation chemotherapy

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3 or 4 (%)
Leukopenia	0	2	4	4	67
Neutropenia	0	0	2	9	92
Anemia	2	4	3	1	33
Thrombocytopenia	2	2	2	2	33
Febrile neutropenia	—	—	4	0	33
Nausea–vomiting	2	5	2	0	17
Appetite loss	4	1	1	0	8
Radiation pneumonitis	3	0	1	0	8

DISCUSSION

Two meta-analyses have shown that the combined modality of chemotherapy and TRT improves the survival of individuals with LD-SCLC in comparison with chemotherapy alone (6,7). The schedule, dose and fractionation of TRT have been extensively investigated in patients with LD-SCLC in several randomized controlled trials (8,9). On the basis of two pivotal Phase III trials (10,11), etoposide and cisplatin chemotherapy with early concurrent twice-daily TRT is currently considered the standard treatment for patients with LD-SCLC. An age-specific subset analysis of one of these Phase III trials (11), in which patients received etoposide–cisplatin with early concurrent TRT, showed that the survival outcomes for individuals aged 70 years or older were similar to those of their younger counterparts, although the elderly patients experienced greater toxicity, in particular hematologic toxicity (12). However, given that the patients in this subgroup analysis were assigned either once- or twice-daily TRT, the significance of early concurrent twice-daily TRT in the management of elderly patients with LD-SCLC has remained undefined. No specific Phase III trial of elderly patients with LD-SCLC has been reported. We therefore retrospectively analyzed the feasibility and antitumor efficacy of etoposide–cisplatin chemotherapy with early concurrent

twice-daily TRT for treatment of LD-SCLC in patients aged 70 years or older.

The median overall survival time of 24.1 months in our cohort is similar to that described for non-elderly patients with LD-SCLC in previous studies (10,11). This favorable survival outcome may be attributable to the strict selection of elderly patients in good general condition; all 12 patients in the present study had normal organ function, an Eastern Cooperative Oncology Group performance status of 0 or 1 and no severe co-morbidity. Given that the elderly are more likely to have reduced organ function as well as concomitant morbidities or medications, the general condition of elderly SCLC patients is worse than that of younger patients (1). Among LD-SCLC patients, increasing age was found to be significantly associated with a lower likelihood of receiving combined chemoradiotherapy (7). Indeed, in the present study, only 12 (48%) of the 25 identified elderly patients with LD-SCLC were treated with etoposide–cisplatin and early concurrent twice-daily TRT.

Despite the strict selection of patients, highly treatment-related toxicity was observed in our cohort. The major adverse events were hematologic toxicities, with neutropenia of Grade 4 being apparent in all patients (100%) and febrile neutropenia of Grade 3 in eight patients (67%) during the first cycle of concurrent chemoradiotherapy. The previous analysis of the outcome of elderly patients in the Phase III study in which individuals received etoposide–cisplatin chemotherapy with early concurrent once- or twice-daily TRT found statistically significant differences not only in the incidence of hematologic toxicity (Grade 4 or 5: 61% in younger patients vs. 84% in patients aged 70 years or older, $P < 0.01$) but also in that of treatment-related deaths (1% vs. 10%, respectively, $P = 0.01$) (12). Although no treatment-related deaths were observed in the present study, severe hematologic toxicity was consistent with that in this foregoing analysis (12). In addition, maintenance of the optimal dose intensity of chemotherapy was difficult in our cohort because of frequent dose reductions or treatment delays due to hematologic or infection-related toxicities. Indeed, the actual dose intensity was <70% of the planned dose intensity for both etoposide and cisplatin in the present study, a value much smaller than that for non-elderly patients in a previous Phase III study (>90% for both agents) (10). On the other hand, the toxicity of radiotherapy was acceptable in our study, with all patients completing TRT within a median of 29 days (range, 19–33). None of our patients developed radiation esophagitis of Grade 3 or higher. With regard to pulmonary complications, one patient developed radiation pneumonitis of Grade 3. A recent meta-analysis of randomized trials in which patients with LD-SCLC were treated with chemoradiotherapy reported that the time between the first day of chemotherapy and the last day of radiotherapy was an important prognostic factor for LD-SCLC, with the survival advantage being more pronounced if the TRT was completed in <30 days (13). In the present study, a shorter time to completion of TRT may also be associated with our favorable survival outcome. However, elderly patients with LD-SCLC must be carefully selected and monitored during treatment because of the increased potential for the development of treatment-related morbidity and mortality.

The optimal therapeutic strategy for elderly patients with LD-SCLC remains a matter of debate. Despite the highly treatment-related toxicity, patients in our cohort derived a survival benefit with no treatment-related deaths, suggesting that the full-dose chemoradiotherapy may represent a valid option for 'fit' elderly patients with adequate organ function. Since the general condition of elderly patients varies widely from patients to patients, prospective evaluation and definition of 'fit' elderly patients who are candidates for full-dose chemoradiotherapy are important. Research is also needed to develop modified chemoradiotherapy regimens that are less toxic for the elderly. A modified chemotherapy schedule designed to reduce toxicity for elderly patients with LD-SCLC was evaluated in a Phase II trial, with two cycles of a chemotherapy regimen (oral etoposide and carboplatin) combined with early concurrent twice-daily TRT being found to have acceptable toxicity and to produce promising results, with a 5-year survival rate of 13% (14). A recent Phase III trial specifically designed for elderly or poor-risk patients with extensive-disease SCLC found that split doses of cisplatin plus etoposide (cisplatin at 25 mg/m^2 and etoposide at 80 mg/m^2 on days 1–3) could be safely administered and were effective (15). Such split-dose chemotherapy might also be suitable for the treatment of patients with LD-SCLC. We are currently conducting a clinical trial to evaluate the feasibility of etoposide at 80 mg/m^2 and cisplatin at 25 mg/m^2 on days 1–3 with early concurrent twice-daily TRT for elderly patients with LD-SCLC.

The overall findings of the present study suggest that administration of full-dose chemotherapy and early concurrent twice-daily TRT is highly myelotoxic for elderly patients with LD-SCLC. Development and assessment of modified treatment regimens with reduced toxicity are thus warranted for such patients.

Conflict of interest statement

None declared.

References

1. Sekine I, Yamamoto N, Kunitoh H, Ohe Y, Tamura T, Kodama T, et al. Treatment of small cell lung cancer in the elderly based on a critical literature review of clinical trials. *Cancer Treat Rev* 2004;30:359–68.
2. Gridelli C, Langer C, Maione P, Rossi A, Schild SE. Lung cancer in the elderly. *J Clin Oncol* 2007;25:1898–907.
3. Morita T. A statistical study of lung cancer in the annual of pathological autopsy cases in Japan, from 1958 to 1997, with reference to time trends of lung cancer in the world. *Jpn J Cancer Res* 2002;93:15–23.
4. Socinski MA, Bogart JA. Limited-stage small-cell lung cancer: the current status of combined-modality therapy. *J Clin Oncol* 2007;25:4137–45.

5. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol* 2004;22:4626–31.
6. Pignon JP, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RL, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992;327:1618–24.
7. Ludbrook JJ, Truong PT, MacNeil MV, Lesperance M, Webber A, Joe H, et al. Do age and comorbidity impact treatment allocation and outcomes in limited stage small-cell lung cancer? A community-based population analysis. *Int J Radiat Oncol Biol Phys* 2003;55: 1321–30.
8. Bonner JA, Sloan JA, Shanahan TG, Brooks BJ, Marks RS, Krook JE, et al. Phase III comparison of twice-daily split-course irradiation versus once-daily irradiation for patients with limited stage small-cell lung carcinoma. *J Clin Oncol* 1999;17:2681–91.
9. Schild SE, Bonner JA, Shanahan TG, Brooks BJ, Marks RS, Geyer SM, et al. Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;59:943–51.
10. Turrisi AT, 3rd, Kim K, Blum R, Sause WT, Livingston RB, Komaki R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340:265–71.
11. Takada M, Fukuoka M, Kawahara M, Sugiura T, Yokoyama A, Yokota S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol* 2002;20:3054–60.
12. Yuen AR, Zou G, Turrisi AT, Sause W, Komaki R, Wagner H, et al. Similar outcome of elderly patients in intergroup trial 0096: cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. *Cancer* 2000;89:1953–60.
13. De Ruysscher D, Pijls-Johannesma M, Bentzen SM, Minken A, Wanders R, Lutgens L, et al. Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. *J Clin Oncol* 2006;24:1057–63.
14. Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. Carboplatin, etoposide, and accelerated hyperfractionated radiotherapy for elderly patients with limited small cell lung carcinoma: a phase II study. *Cancer* 1998;82:836–41.
15. Okamoto H, Watanabe K, Kunikane H, Yokoyama A, Kudoh S, Asakawa T, et al. Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. *Br J Cancer* 2007;97:162–9.

Zoledronic acid-induced regression of multiple metastases at nonskeletal sites

Bisphosphonates have been shown to reduce skeletal complications in individuals with bone metastases secondary to a wide range of solid tumors including lung, breast, and prostate cancer [1]. They are widely administered as palliative agents together with chemotherapy, hormonal therapy, or irradiation [2]. In addition, several types of cancer cells including hematologic malignancies respond to bisphosphonates *in vitro*, with such effects having been attributed, at least in part, to inhibition of the Ras-signaling pathway [3]. We now report an unusual case in which tumors in visceral organs and soft tissues responded markedly to treatment with the bisphosphonate zoledronic acid (ZA) alone, with the performance status of the patient improving in the absence of chemotherapy.

A 69-year-old man with no significant past medical history presented with pain in his left hip joint at our hospital in January 2007. X-ray examination revealed an osteosynthetic change in his left femur, and a metastatic tumor in his left thigh bone was indicated. Positron emission tomography with 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG–PET) revealed uptake of the tracer at multiple sites including the left femur, right rib, left scapula, bilateral adrenal glands, s.c. tissue of the right gluteal region, and abdominal lymph nodes (Figure 1A, left panel). Concomitant computed tomography (CT) revealed tumors of various sizes at multiple sites corresponding to those of tracer uptake, with enlargement of the left adrenal glands apparent from a diameter of 50.2 mm. Biopsy specimens were obtained from the putative tumor on the left femur and the s.c. nodule of the right buttock. On the basis of the morphological and immunohistochemical staining characteristics of the specimens, a histopathologic diagnosis of spindle cell carcinoma was made, but the primary site of the tumor was not determined. The patient's general condition was poor, and he had an Eastern Cooperative Oncology Group performance status of three at the time of diagnosis. Systemic chemotherapy was therefore not selected, and palliative care was commenced. Together with prescription of narcotics and 20 Gy of radiation

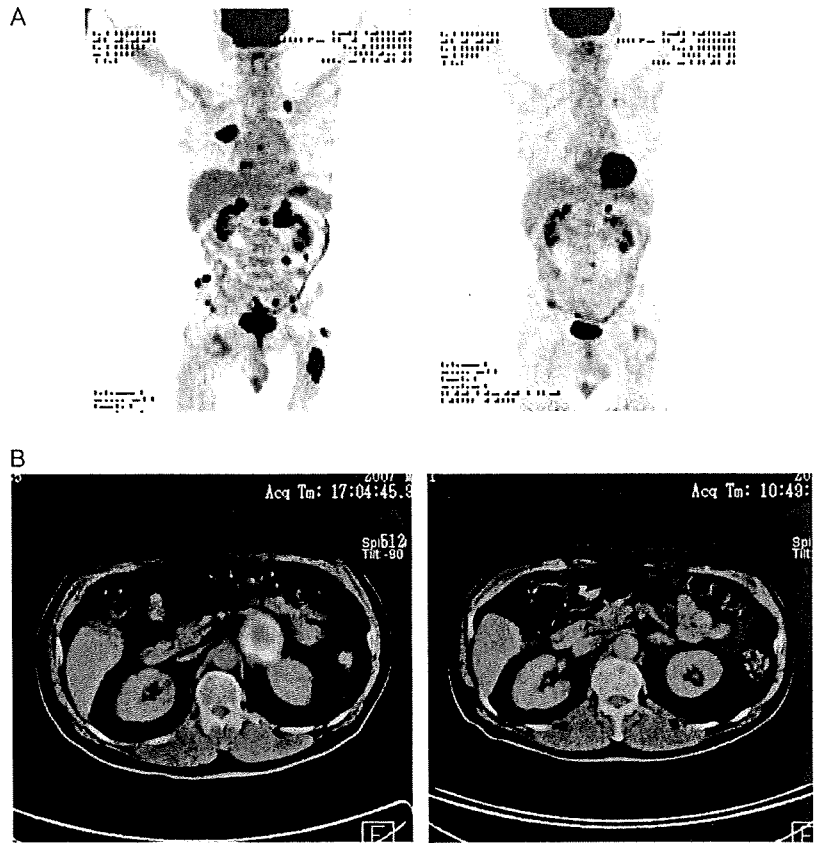

Figure 1. Positron emission tomographies with 2-[fluorine-18]fluoro-2-deoxy-D-glucose before (A, left panel) and after (A, right panel) zoledronic acid treatment, and the corresponding computed tomographies before (B, left panel) and after zoledronic acid treatment (B, right panel) are shown.

to the left femur, ZA (4 mg/body) was administered i.v. every 4 weeks to reduce bone pain. After 6 months, his general condition was dramatically improved and follow-up FDG–PET revealed decreased uptake of the tracer in metastases not only in bone including the right rib, which was not irradiated, but also in the adrenal glands, abdominal lymph nodes, and s.c. tissue of the right buttock (Figure 1A, right panel). Unexpectedly, CT revealed that tumors in the adrenal glands had shrunk markedly, with the diameter of the left gland having decreased from 50.2 mm (Figure 1B, left panel) to 26.4 mm (Figure 1B, right panel), and the s.c. tumor in the right buttock was no longer detectable.

As far as we are aware, there have been no other reports of a tumor at a nonskeletal site responding to bisphosphonate treatment alone. ZA was recently shown to have efficacy as a preventive agent for cancer recurrence in premenopausal women with early-stage breast cancer [4]. This previous study suggested that ZA was able to prevent cancer recurrence not only in bone but also in nonskeletal organs including the contralateral breast, lung, and liver. The present case supports the notion that ZA targets not only osteoclasts, a major contributor to the tumor microenvironment in bone, but also tumor cells themselves, as has been shown in preclinical studies [3]. Further clinical evaluation of ZA for treatment of cancer is warranted.

K. Okamoto, J. Tsurutani*, M. Terashima, I. Okamoto & K. Nakagawa

Department of Medical Oncology, Kinki University School of Medicine, Osakasayama, Osaka, Japan
(*E-mail: tsurutani_j@dotd.med.kindai.ac.jp)

references

1. Rosen LS, Gordon D, Tchekmedyian NS et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. Cancer 2004; 100: 2613–2621.
2. Aapro M, Abrahamsson PA, Body JJ et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol 2008; 19: 420–432.
3. Tassone P, Tagliaferri P, Viscomi C et al. Zoledronic acid induces antiproliferative and apoptotic effects in human pancreatic cancer cells *in vitro*. Br J Cancer 2003; 88: 1971–1978.
4. Gnant M, Mlineritsch B, Luschin-Ebengreuth G et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. Lancet Oncol 2008; 9: 840–849.

doi:10.1093/annonc/mdp026
Published online 10 March 2009

Phase I Study of YM155, a Novel Survivin Suppressant, in Patients with Advanced Solid Tumors

Taroh Satoh,[1] Isamu Okamoto,[1] Masaki Miyazaki,[1] Ryotaroh Morinaga,[1] Asuka Tsuya,[1] Yoshikazu Hasegawa,[1] Masaaki Terashima,[1] Shinya Ueda,[1] Masahiro Fukuoka,[1] Yutaka Ariyoshi,[3] Toshikazu Saito,[4] Noriyuki Masuda,[5] Hirokazu Watanabe,[6] Tetsuo Taguchi,[2] Toru Kakihara,[7] Yumiko Aoyama,[7] Yohko Hashimoto,[7] and Kazuhiko Nakagawa[1]

Abstract

Purpose: YM155, a novel molecular targeted agent, suppresses survivin, a member of the inhibitor of apoptosis protein family that is overexpressed in many tumor types. The aim of this study was to determine the maximum tolerated dose (MTD) and to assess the safety, pharmacokinetics, and antitumor activity of YM155 in patients with advanced refractory solid tumors.

Experimental Design: Patients with advanced refractory solid tumors were treated with escalating doses of YM155 administered by continuous i.v. infusion for 168 hours in 21-day cycles.

Results: Of the 34 patients enrolled, 33 (median age, 59 years) received at least 1 dose of YM155 (range, 1-19 cycles). The dose levels studied were 1.8, 3.6, 4.8, 6.0, 8.0, and 10.6 mg/m^2/d. The MTD was determined to be 8.0 mg/m^2/d, based on a dose-limiting toxicity of increased blood creatinine observed in 2 patients receiving 10.6 mg/m^2/d. The most common adverse reactions judged to be related to YM155 were urine microalbumin present; fever; injection-site phlebitis; fatigue; and decreased hemoglobin/anemia, blood albumin, and lymphocyte count. The pharmacokinetic profile was almost linear over the dosing range and was similar between cycles 1 and 2. Urinary excretion of YM155 showed no definite difference among doses. Stable disease was achieved in nine patients.

Conclusions: YM155 was safely administered to patients with advanced refractory solid tumors by 168-hour continuous i.v. infusion in 21-day cycles. The MTD was determined to be 8.0 mg/m^2/d. The safety profile, plasma concentrations achieved, and antitumor activity observed merit further studies with this survivin suppressant, alone and in combination regimens.

Survivin, a member of the inhibitor of apoptosis family of proteins, is expressed during embryonic and fetal development, but is undetectable in normal adult human tissues, apart from thymus, placenta, CD34$^+$ cells, and some cells within the basal crypt layer of the gastrointestinal tract (1–5). *In vitro* studies suggest that survivin inhibits cell death induced via the extrinsic and intrinsic apoptotic pathways. In addition, survivin may also confer resistance to apoptosis by directly suppressing caspase activity (3). Overexpression of survivin has been shown in a variety of human cancers and is reportedly associated with a poor prognosis (6–13). It has been shown that the suppression of survivin induces tumor cell apoptosis and also enhances the sensitivity to apoptosis induced by existing anticancer drugs and other apoptotic stimuli (4, 14–16).

YM155 is a novel survivin suppressant that is currently in clinical development by Astellas Pharma, Inc. A preclinical study showed that YM155 suppressed both survivin protein and mRNA expression (17). In addition, sensitivity to YM155 was high in various human tumor cell lines such as hormone-refractory prostate cancer (17) and malignant lymphoma.[8] Furthermore, YM155 exerted greater antitumor activity compared with existing anticancer drugs, and YM155 concentrations were higher in tumor tissue than in plasma. In a toxicologic study, short-term exposure at high blood concentrations caused cardiotoxicity in the form of atrioventricular

Authors' Affiliations: [1]Department of Medical Oncology, Kinki University School of Medicine; and [2]Japan Society for Cancer Chemotherapy, Osaka, Japan; [3]Marumo Hospital, Aichi, Japan; [4]Social Insurance Chuo General Hospital; [5]Kitasato University School of Medicine; [6]National Cancer Center Hospital; and [7]Astellas Pharma, Inc., Tokyo, Japan

Received 7/14/08; revised 2/5/09; accepted 2/23/09; published OnlineFirst 5/26/09.

Grant support: Astellas Pharma, Inc.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Taroh Satoh, Department of Medical Oncology, Kinki University School of Medicine, Osaka, Japan. Phone: 81-72-366-0221; Fax: 81-72-360-5000; E-mail: taroh@med.kindai.ac.jp.

doi:10.1158/1078-0432.CCR-08-1946

[8] Unpublished data.

Translational Relevance

Survivin is a member of the inhibitor of apoptosis protein family that is overexpressed in many tumor types, and as such represents an excellent target for anticancer drug development. YM155 is a small molecule that suppresses survivin and has shown anticancer activity in a range of tumor cell lines *in vitro* and human tumor xenografts models *in vivo*. In this phase I study, YM155 was administered to 33 patients with advanced refractory solid tumors. YM155 seemed to be safe and well-tolerated, with a maximum tolerated dose of 8.0 mg/m^2/d. Stable disease was achieved in nine patients. The position of survivin as an anticancer drug target, together with the safety profile and antitumor activity in heavily pretreated patients with advanced refractory tumors shown in this phase I study, strongly supports the further evaluation of YM155, both as monotherapy and within combination regimens.

block and myocardial degeneration/necrosis, as well as nephrotoxicity, mainly displayed as proximal tubular necrosis and increased serum creatinine. In contrast, long-term exposure at low blood concentrations by 168-hour continuous infusion did not cause cardiotoxicity.[9]

Based on the differential expression of survivin in human malignancies and the negative prognostic role, together with preclinical antitumor activity and encouraging safety data, a phase I study of YM155 in patients with advanced solid tumors was conducted in Japan. The aim of this study was to determine the recommended dose and pharmacokinetic profile of YM155 and to evaluate its safety profile and antitumor effects.

Patients and Methods

Study design. This was an open-label, single-center, nonrandomized, phase I dose-escalation study. The primary objective was to assess the safety of YM155 administered to patients with advanced solid tumors. The secondary objectives included the investigation of the pharmacokinetic profile and tumor activity of YM155. After one cycle, patients could continue further treatment until either an unacceptable toxicity was experienced or disease progression occurred.

Inclusion and exclusion criteria. Eligibility criteria for patients enrolled in this study included refractory advanced solid tumors for which no standard therapy existed; histologic or cytologic diagnosis of cancer; at least 20 y of age; life expectancy of at least 12 wk; Eastern Cooperative Oncology Group performance status of <3; and adequate hematopoietic, hepatic, and renal functions (absolute neutrophil count of $\geq 1.5 \times 10^9$/L, platelets of $\geq 100 \times 10^9$/L, hemoglobin of ≥9 g/dL, bilirubin within 1.5× upper limit of normal, transaminases of ≤2.5× upper limit of normal, and creatinine of <1.5 × upper limit of normal). Patients must have discontinued all cancer therapies for at least 4 wk before study entry. Exclusion criteria included primary brain tumor or known central nervous system metastases, and uncontrolled clinically significant disease unrelated to the primary malignancy.

The study was approved by the ethics board of the participating center, and all patients gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki and the applicable guidelines on good clinical practice.

Dosage and drug administration. YM155 was prepared for administration by dilution of an appropriate volume of concentrated stock solution in 5% dextrose in a light- and temperature-controlled environment. The diluted drug was administered via continuous i.v. infusion over 168 h, followed by 14-d observation (1 cycle). This method of administration was selected because toxicity studies using 168-h continuous infusion in dogs showed no cardiotoxicity and time-dependent antitumor activity.[10] A starting dose of 1.8 mg/m^2/d was chosen on the basis of toxicologic studies in rodents and the data from a U.S. phase I study (18). To avoid renal toxicity with YM155, patients were instructed to take sufficient quantities of water during administration of the drug.

Toxicity (tolerability and safety evaluation). The following safety assessments were done for each patient: subjective/objective symptoms, vital signs, laboratory tests, and 12-lead electrocardiogram. Adverse events were graded according to the Common Terminology Criteria for Adverse Events v3.0. Creatinine clearance was determined by the evaluation of fluctuations in urine creatinine and serum creatinine concentrations. A dose-limiting toxicity (DLT) was defined as an adverse drug reaction including nonhematologic toxicities ≥grade 3, except transient hyperglycemia and anorexia, and serum creatinine increased to ≥2.0 mg/dL; grade 4 hematologic toxicities, except a decreased neutrophil count of grade 4 (<500/μL) persisting for 5 d or less; nausea, vomiting, or diarrhea ≥grade 3 occurring despite prophylaxis after the first episode; and failure to satisfy the criteria for the next cycle within the specified period due to unresolved adverse drug reactions. The maximum tolerated dose (MTD) was defined as the dose that was one level lower than that at which DLT occurred in more than two of six patients.

Pharmacokinetics. The pharmacokinetic parameters of YM155 were evaluated during cycles 1 and 2. Venous blood samples, from a site other than the infusion site, were collected in tubes containing heparin sodium immediately before the start of the infusion (time 0): at 0.25, 0.5, 1, 2, 3, 4, 6, 12, 24, 48, 72, 96, 120, and 144 h after the start of infusion; at the end of infusion (168 h); and at the following times thereafter: 168.25, 168.5, 169, 170, 171, 172, 174, 180, 192, and 216 h. Samples were centrifuged immediately, and the resulting plasma was stored at −20°C before analysis. Urine samples were collected over 216 h after the start of continuous infusion to determine the urinary concentration of YM155 and were stored at −20°C before analysis.

Concentrations of YM155 were measured by Astellas Europe B.V. EDD using validated liquid chromatography tandem mass spectrometry procedures (18) and following Good Laboratory Practice.

The lower limits of quantitation for YM155 were 0.05 ng/mL in plasma and 1.0 ng/mL in urine. The concentrations are expressed as those of the cationic moiety of YM155.

Pharmacokinetic analysis was done in a model-independent manner using actual values of plasma concentration and actual time from the start of continuous infusion. Values below the lower limits of quantitation were treated as zero.

Efficacy (tumor assessment). Evaluations of lesions were done with computed tomography, magnetic resonance imaging, and bone scintigraphy, with tumor markers also evaluated. Assessment of antitumor activity was done in accordance with the Response Evaluation Criteria in Solid Tumors guidelines (19).

Results

Patients. A total of 34 patients were enrolled into 6 dosing cohorts between August 2004 and October 2006; 33 patients received at least 1 cycle of YM155. The demographic and baseline

[9] Unpublished data.

[10] Unpublished data.

Table 1. Patient demographics and disease characteristics

Characteristic	No. of patients
Total patients	33
Male/female	23/10
Age, y	
Median (range)	59 (26-81)
<65	25
≥65	8
ECOG performance status	
0	3
1	29
2	1
Tumor type	
NSCLC	7
Esophageal	6
Colorectal	4
Thymic	3
Thyroid	2
MFH	2
Pleural mesothelioma	2
Others*	7 (1 each)
Prior therapy	
Chemotherapy	32 (97.0%)
No. of prior regimens	
1	7
2	10
3	4
≥4	11
Radiation therapy	17 (51.5%)
Cancer-related surgery	19 (57.6%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non–small cell lung cancer; MFH, malignant fibrous histiocytoma.
*Others: thymoma, synovial sarcoma, duodenal, double cancer of hypopharynx and thoracic esophageal cancer, paranasal sinus, pancreatic, and esophageal leiomyosarcoma.

patient characteristics are listed in Table 1. The most common malignancies in the 33 patients treated were non–small cell lung cancer (7 patients; 21.2%), esophageal cancer (6 patients; 18.2%), colorectal cancer (4 patients; 12.1%), and thymic cancer (3 patients; 9.1%). Thirty-two (97%) of the patients had at least 1 prior chemotherapy. Dose levels studied were 1.8, 3.6, 4.8, 6.0, 8.0, and 10.6 mg/m^2/d, and patients received 1 to 19 cycles of YM155.

DLT. The highest dose of YM155 administered was 10.6 mg/m^2/d, at which level 2 of 5 treated patients experienced a DLT of increased serum creatinine (accompanied by decreased lymphocyte count in 1 patient). Three of 5 patients in the 10.6 mg/m^2/d group had their dose reduced to 8.0 mg/m^2/d from cycle 2 onwards. At the 8.0 mg/m^2/d dose level, serum creatinine levels remained almost unchanged throughout the study. The MTD was therefore determined to be 8.0 mg/m^2/d. Additional DLTs were observed in one patient who received YM155 at the 6.0 mg/m^2/d dose level (grade 3 increased aspartate serum transferase) and in another patient whose dose was reduced to 8.0 mg/m^2/d (grade 4 anemia).

Safety. All 33 patients treated were included in the safety population. Throughout all treatment cycles, adverse events occurred in 97.0% (32 of 33 patients) and adverse drug reactions in 87.9% (29 of 33 patients) of all patients treated with YM155.

The most common drug-related adverse events (occurring in ≥15% of patients) were urine microalbumin present (12 patients; 36.4%), injection-site phlebitis (12 patients; 36.4%), fever (11 patients; 33.3%), decreased hemoglobin/anemia (9 patients; 27.3%), decreased lymphocyte count (8 patients; 24.2%), decreased blood albumin (8 patients; 24.2%), and fatigue (7 patients; 21.2%; Table 2). In most patients with decreased hemoglobin, reductions in hemoglobin were detected immediately after study drug initiation and were rated grade 1 or 2. The events recovered or remitted without treatment. Injection-site phlebitis was frequently reported in patients receiving infusion of lower doses of YM155 via peripheral veins. Consequently, infusion via a central vein was recommended for doses higher than 4.8 mg/m^2/d, which prevented the development of phlebitis.

The vast majority of drug-related adverse events (200 of 217, 92.2%) were judged to be grade 1 or 2 in severity. Grade 3 or 4 drug-related adverse events were reported in 8 patients. Grade 3 decreased lymphocyte count occurred in 6 patients, including 1

Table 2. Adverse events (≥15% incidence overall) related to YM155

Adverse event/YM155 dose (mg/m^2/d)	No. of patients experiencing toxicity during first course (all courses)													
	1.8 (*n* = 3)		3.6 (*n* = 6)		4.8 (*n* = 6)		6.0 (*n* = 7)		8.0 (*n* = 6)		10.6 (*n* = 5)		All (*n* = 33)	
Grade of adverse event	G1/2	G3	G1/2	G3	G1/2	G3	G1/2	G3	G1/2	G3	G1/2	G3/4	G1/2	G3/4
Urine microalbumin present	0	0	0(1)	0	1(1)	0	1(1)	0	4(4)	0	5(5)	0	11 (12)	0
Fever	0	0	1(2)	0	0	0	2(3)	0	2(2)	0	4(4)	0	9 (11)	0
Decreased hemoglobin/anemia	0	0	0(1)	0	1(1)	0	1(2)	0	1(1)	0	3(3)	1(1)*	6 (8)	1 (1)
Injection site phlebitis	2(3)	0	2(4)	0	2(2)	0	2(2)	0	0	0	0(1)†	0	8 (12)†	—
Fatigue	1(1)	0	0(1)	0	0(1)	0	1(1)	0	1(1)	0	2(2)	0	5 (7)	—
Decreased blood albumin	0	0	0	0	1(1)	0	1(1)	0	2(2)	0	4(4)	0	8 (8)	—
Decreased lymphocyte count	0	0	0	1(1)	0	1(1)	1(1)	0	0	1(1)	0	4(4)‡	1 (1)	7 (7)
Abnormal liver function test§	0(1)	0	0(1)	0	0	0	2(2)	1(1)	0	0	1(1)	0	3 (5)	1 (1)
Increased C-reactive protein	0	0	0	0	0	0	1	0	2	0	2(3)†	0	5 (6)†	—
Urine protein present	0	0	0	0	0	0	0	0	1	0	4	0	5 (5)	—

NOTE: * and ‡ are the same patient.
*Grade 4.
†An event after dose reduction to 8.0 mg/m^2/d in one patient.
‡Grade 4 in one patient.
§Abnormal liver function test includes increased aspartate, increased alanine serum transaminase, and increased γ-glutamyl transpeptidase.

each at YM155 doses of 3.6, 4.8, and 8.0 mg/m^2/d and 3 patients at the 10.6 mg/m^2/d YM155 dose level. A grade 4 decreased lymphocyte count was observed in an additional patient at the 10.6 mg/m^2/d dose level. Decreases in lymphocyte count were principally noted on day 3, and typically recovered without treatment during study drug administration, and without causing infection that might lead to study discontinuation. The remaining grade 3/4 drug-related adverse events included decreased hemoglobin/anemia [grade 4 in 1 patient in the 10.6 mg/m^2/d dose level (the same patient in which grade 4 lymphocyte count decreased was observed)] and abnormal liver function test (grade 3 in 1 patient in the 6.0 mg/m^2/d dose level).

The trial established kidney monitoring parameters for patients treated with YM155. Changes in renal parameters that occurred in 2 patients with a DLT in the 10.6 mg/m^2/d dose level in cycle 1 are shown in Fig. 1. Both patients had increased urine microalbumin at days 3 to 7, increased urinary protein at days 6 to 8, and increased serum creatinine and blood urea nitrogen at days 8 to 10 when administration

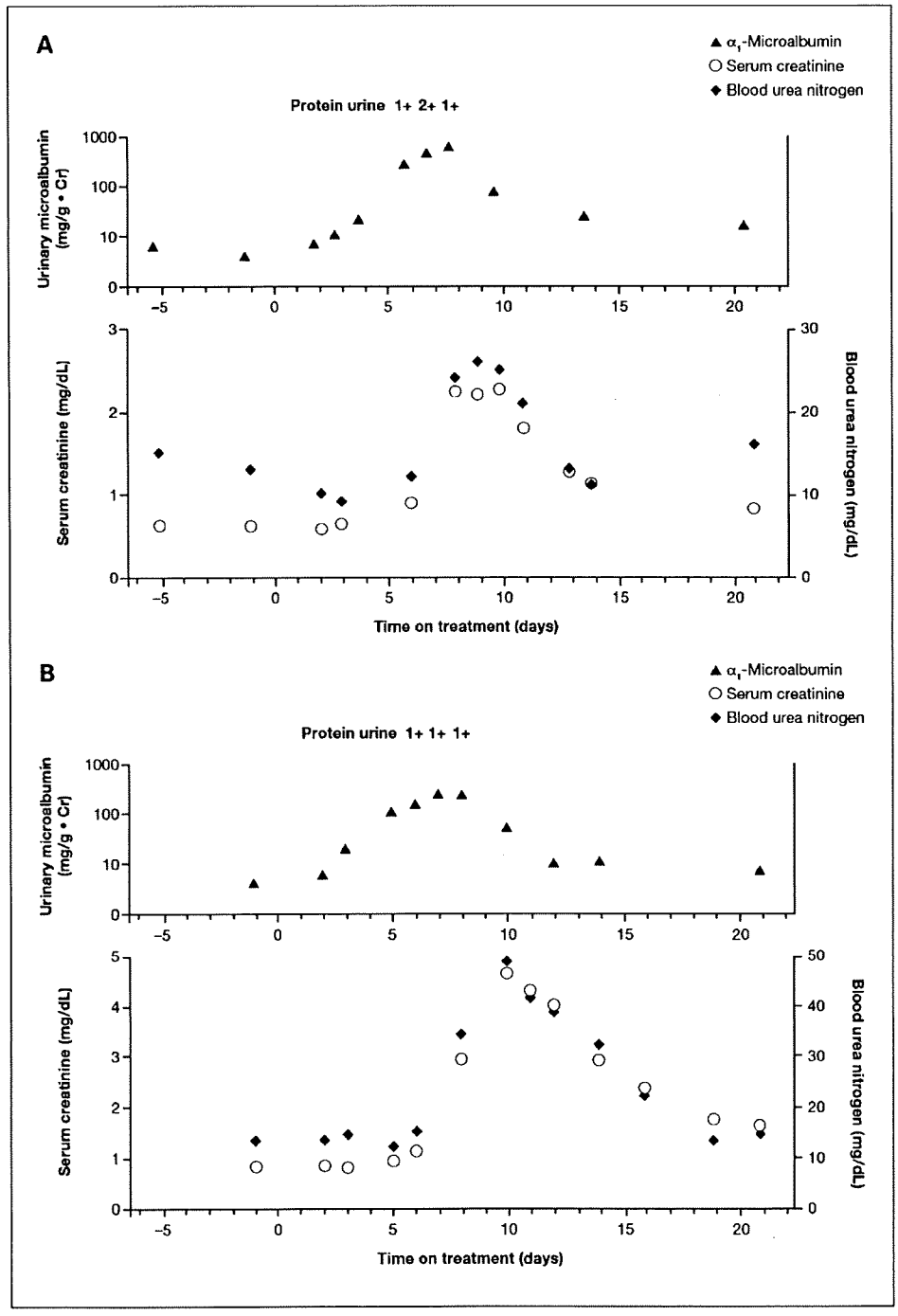

Fig. 1. Changes in renal parameters in patients in the 10.6 mg/m2/d group with thyroid cancer (*A*): esophageal canc -7, (*B*).

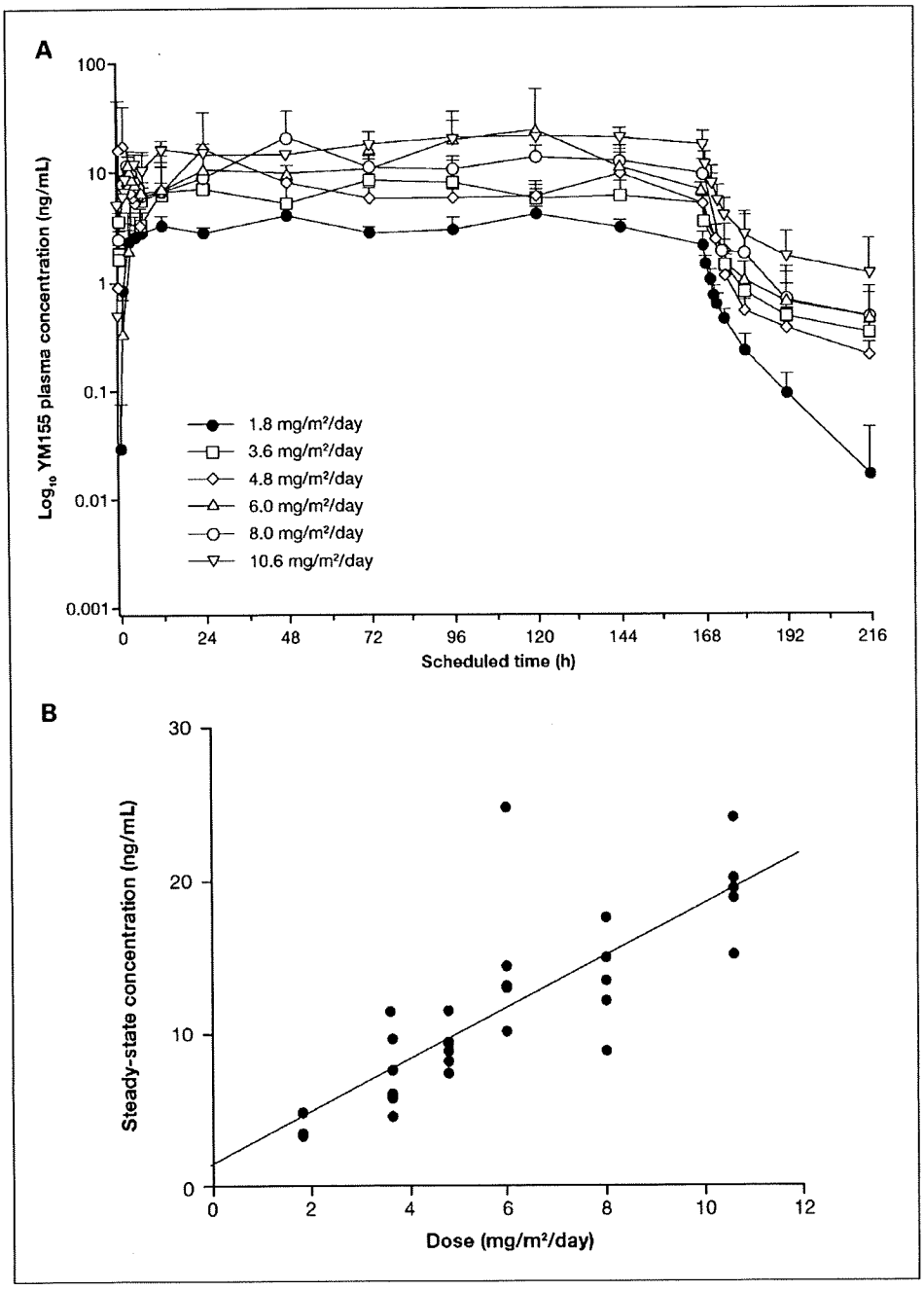

Fig. 2. YM155 plasma concentration. *A*, blood plasma concentrations of YM155 overtime. -h infusion were included; points, mean; bars, SD. *B*, dose versus change in steady-state blood plasma YM155 concentration. A total of 33 patients who completed 168-h infusion during cycle 1 were included.

had been completed. These changes were also temporally associated with decreased creatinine clearance and recovered after completion of administration. In contrast, changes in other parameters, including *N*-acetyl-D-glucosaminidase and α_1-microglobulin, were not consistently associated with renopathy and were not judged to be adverse events of clinical significance.

No other changes in safety variables, including vital signs, were considered to be clinically significant. Although atrial fibrillation on 12-lead electrocardiogram was judged to be an adverse drug reaction to YM155, this was only an asymptomatic finding of grade 1 severity and rapid recovery ensued. There were neither cumulative toxicities due to repeated cycles nor late-onset adverse events occurring in cycle 2 and beyond.

Fevers occurred mainly at days 2 to 4, with C-reactive protein increased. Part of them reached grade 2, but recovered during infusion of YM155 by nonsteroidal anti-inflammatory drugs.

Patient withdrawals. The majority of study discontinuations were due to disease progression (28 of 33 patients). In addition, 3 patients discontinued at their own request; one as a change of a therapy policy; and one as a result of an adverse event of aggravated superior vena caval syndrome, which was observed at a dose level of 4.8 mg/m^2/d, but causal relationship with the study drug was ruled out. Importantly, there were no treatment-related deaths.

Table 3. Tumors showing stable disease after therapy

YM155 dose (mg/m2/d)	Tumor type	No. of completed cycles
1.8	MFH	4
	Thymoma	6
3.6	NSCLC	3
	Synovial sarcoma	4
4.8	NSCLC	3
	Thymic	2
6.0	Thyroid	6
10.6	Esophageal leiomyosarcoma	3
	Thyroid	19

Pharmacokinetic analysis. Of the 33 patients who received at least 1 cycle of YM155, 31 provided full blood samples for pharmacokinetic analysis after a single cycle. The mean plasma concentration-time profiles of YM155 by dose after 168-hour infusion are shown in Fig. 2A. Plasma concentrations almost reached steady state about 24 hours after the start of infusion, with the area under the plasma concentration-time curve (from zero to the last quantifiable concentration) increasing with dose up to 10.6 mg/m^2/d. Mean plasma concentrations declined rapidly in a biphasic manner after the end of infusion. Mean values for an apparent elimination half-life ($t_{1/2}$) and total body clearance of YM155 seemed to be constant across the dose range. Steady-state concentration (C_{ss}) increased with dose up to 10.6 mg/m^2/d (Fig. 2B).

The fraction of dose excreted (F_e) in urine ranged from 25% to 42% and showed no relationship with the dose administered.

Although the dosing was based on body surface area, obvious correlation between body surface area and each pharmacokinetic parameter was unclear.[11]

Efficacy. External evaluation using computed tomography confirmed that 9 of 33 patients achieved stable disease with YM155 treatment (median duration, 81 days; range, 42-438 days; Table 3). The computed tomography images of two of the nine patients are shown in Fig. 3. One patient, a 47-year-old man with malignant fibrous histiocytoma (1.8 mg/m^2/d YM155 dose level), showed a 13% reduction in tumor size after cycle 1 (Fig. 3A and B). Another patient, a 56-year-old woman, had papillary cancer of the thyroid. This patient received 10.6 mg/m^2/d in cycle 1, which was reduced to 8.0 mg/m^2/d in cycle 2. Computed tomography after cycle 2 showed a 14% reduction in tumor size and disappearance of pleural effusion (Fig. 3C and D). External evaluation confirmed stable disease until 62 weeks.

The degree of unconfirmed response of all patients is displayed in the waterfall plot in Fig. 3E. Response was seen in a dose-independent manner.

Discussion

There has been much recent interest in the role of survivin as a potential molecular target in the treatment of cancer (20, 21). This is the result of the differential expression of survivin in human malignancies compared with normal adult tissues, the role of survivin in abrogating apoptosis signaling, and a growing body of promising preclinical data. Clearly, inhibition of survivin may induce tumor regression and, importantly, may increase the effectiveness of current therapies. As a result, YM155 is currently in clinical development as the first survivin suppressant.

In the present study, YM155 was administered by 168-hour continuous infusion to patients with refractory cancer or for whom there were no standard therapies available. The primary end point was an evaluation of the safety of this novel agent. The MTD of YM155 was determined to be 8.0 mg/m^2/d after the occurrence of a DLT of increased serum creatinine in 2 of 5 patients receiving 10.6 mg/m^2/d. In addition, most patients receiving this dose of YM155 showed a consistent tendency in the timing of renal abnormal changes. These results were consistent with the expected nephrotoxicity of YM155 following prior preclinical and clinical studies,[12] and further show the renal effects of YM155. None of the events in the present study led to severe renopathy, and renal parameters recovered in all cases. Increased urine microalbumin was observed at first, followed by increased urinary protein, and resulted in increased serum creatinine and blood urea nitrogen. This is indicative of early renal impairment because it occurs at the three highest doses. It was therefore considered that, by careful monitoring of renal parameters and taking appropriate measures in the event of abnormal changes, severe renopathy can be avoided. In addition, at the MTD of 8.0 mg/m^2/d, minimal changes in creatinine value were found. Increase of urine microalbumin and serum creatinine may suggest that the highest dose of YM155 influenced the glomerulus function. A nonrenal DLT of increased aspartate serum transferase was observed in 1 patient at the 6.0 mg/m^2/d dose level, which was below the MTD; however, this hepatopathy recovered after withdrawal of YM155. Results from a preclinical study have confirmed that the distribution of ^{14}C-YM155 is higher in the kidney and liver compared with other organs (15 and 5.2 times higher than in plasma, respectively), suggesting that this might be responsible for the observed renopathy and hepatopathy with YM155.[13]

In a preclinical study, cardiotoxicities were observed at a mean plasma YM155 C_{ss} of 188 ng/mL or higher. However, the mean C_{ss} in 7-day repeated infusion was 12.8 times the mean C_{ss} in 168-hour continuous infusion at the same total dose, which did not cause any cardiotoxicity.[14] In this study, even the highest dose of 10.6 mg/m^2/d produced only a mean C_{ss} of 19.20 ng/mL, and this did not result in any serious adverse event of cardiotoxicity.

The decreases in hemoglobin/anemia that were frequently observed at the higher doses of YM155 used in this study were typified by a decrease in hemoglobin immediately after the start of study drug administration in almost all patients, given that it is generally not until about 1 to 2 weeks after the start of an anticancer drug that hemoglobin reaches a nadir due to drug-attributable bone marrow suppression. Moreover, hemolysis

[11] Unpublished data.

[12] Unpublished data.

[13] Unpublished data.

[14] Unpublished data.

was unlikely considering that the study drug has a low distribution of ~8% to 11% in blood cells. The cause of the decreases in hemoglobin/anemia therefore remains unidentified. It has been reported that survivin is involved in the regulation of the proliferation of hematopoietic progenitor cells, is essential for steady-state hematopoiesis, and that the high expression of survivin is critical for proper erythroid differentiation (22). Whereas the grade 3 to 4 lymphocytopenia experienced by 7 patients in this study may be indicative of YM155-mediated effects on erythroid and lymphoid differentiation, this must be further evaluated in ongoing and future clinical studies.

Fevers occurred mainly with increase in C-reactive protein, but without significant changes in absolute neutrophil count or leukocytes. The importance of C-reactive protein is under exploration.

In the present study, the majority of study discontinuations were due to disease progression. Indeed, only one patient discontinued because of an adverse event, and this was judged not to be related to YM155. Although the evaluations of the toxicity profile of YM155 remain in the preliminary stages, the data in this study indicate that the adverse reactions observed can be well-controlled by taking due caution and suggest that YM155 has more easily controllable toxicities compared with conventional cytotoxic anticancer drugs.

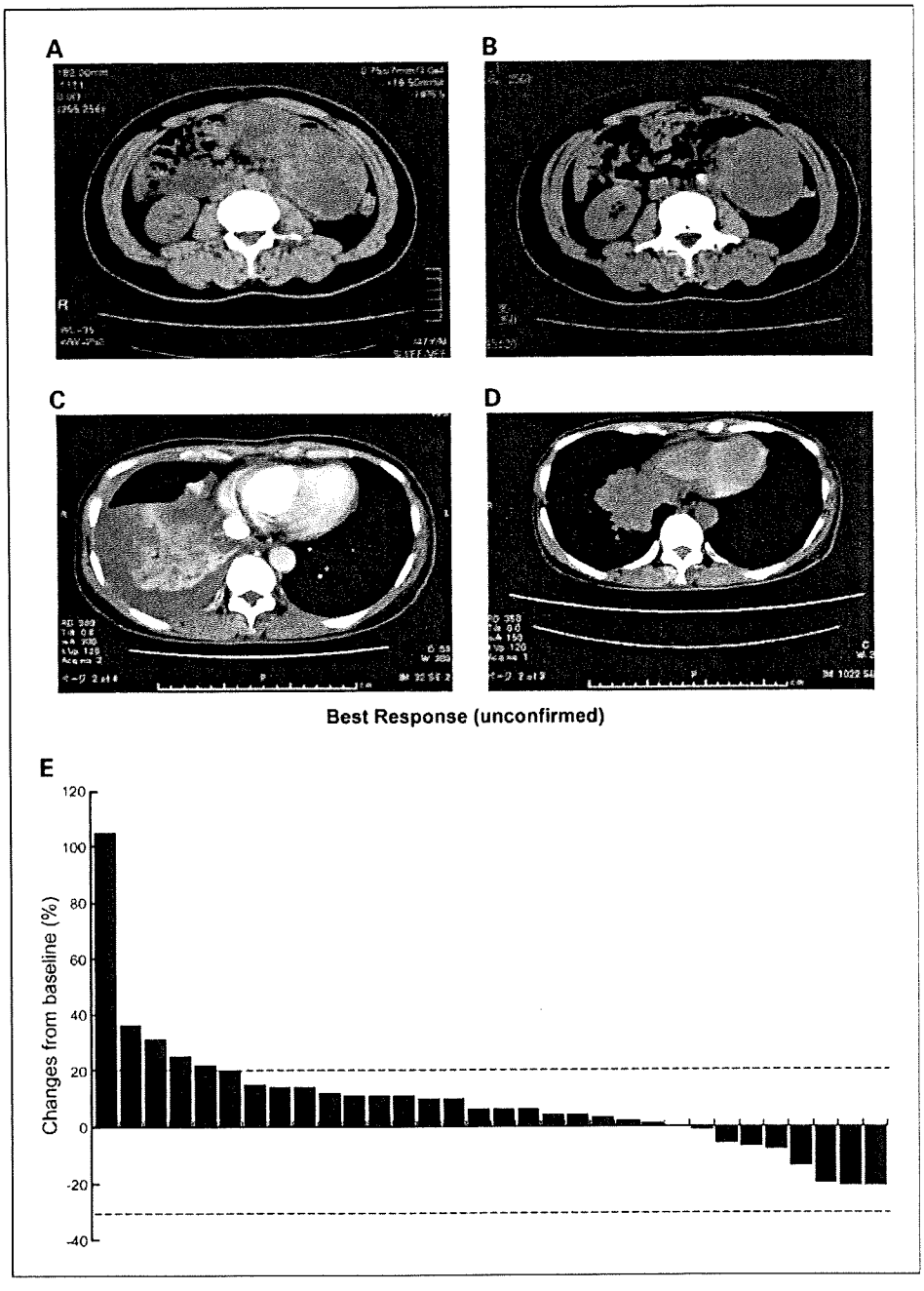

Fig. 3. Computed tomography images of a patient with malignant fibrous histiocytoma before treatment (*A*) and after (*B*).

Both $t_{1/2}$ and clearance seemed to be constant across the dose range. In addition, C_{ss} increased almost dose-proportionally (Fig. 2B), indicating the linear pharmacokinetics of YM155 over the dose range of 1.8 to 10.6 mg/m^2/d. Low concentrations of the study drug remained in systemic circulation for 48 hours after the end of infusion; however, plasma concentrations decreased to below 0.5 ng/mL before the start of cycle 2. Pharmacokinetic parameters in cycle 2 (data not shown) were similar to those in cycle 1, suggesting that there is no accumulation of study drug. We need more samples to explore the details including correlation between body surface area and pharmacokinetic parameters.

The A_e% in urine was estimated as 25% to 42% at a dose range of 1.8 to 10.6 mg/m^2/d, suggesting that urinary excretion is a principal route for the elimination of YM155. This result is well-supported by *in vitro* studies indicating that minimal metabolism of YM155 occurred in human hepatocytes (23).

The MTD of YM155 in the current study was determined to be 8.0 mg/m^2/d, after the occurrence of a DLT of increased serum creatinine in 2 of 5 patients receiving 10.6 mg/m^2/d. In contrast, in an earlier U.S. phase I trial done using the same design as the present Japanese study, the MTD was determined as 4.8 mg/m^2/d, after the occurrence of renal DLTs in 2 patients who received 6.0 mg/m^2/d (18). These DLTs were all reversible. The difference in the MTD between the U.S. and Japanese studies has been investigated by the evaluation of patient demographics, in particular baseline renal function (serum creatinine level) and prior treatment affecting renal function (history of platinum treatment), as well as hydration and pharmacokinetics of the patients with DLT. Serum creatinine levels were 1.1 and 1.4 mg/dL (reference range, 0.6-1.4 mg/dL) in the U.S. patients and 0.59 mg/dL (reference range, 0.5-1.0) and 0.81 mg/dL (reference range, 0.7-1.3 mg/dL) in the Japanese patients. Although these levels were toward the higher end of the reference range in the U.S. patients compared with those in the Japanese patients, any differences observed may be a result of two different testing facilities. Both U.S. patients had a history of platinum treatment, whereas only one of the two Japanese patients did. Furthermore, a comparison of patients receiving 6.0 mg/m^2/d of YM155 revealed that mean baseline serum creatinine levels were lower in Japanese patients than in U.S. patients. Whereas it is difficult to directly compare renal function between the two patient populations, these data do suggest that renal function may have been decreased in the U.S. patients. An additional factor to consider is body surface area. The body surface area of the U.S. patients with a DLT was 2.11 and 2.05 m^2 compared with 1.44 and 1.65 m^2 for the Japanese patients. This is suggestive of a smaller total dose of YM155. There were no essential differences between U.S. and Japanese patients in terms of the time course of plasma drug concentrations and pharmacokinetic parameters, suggesting that the difference in the MTD is unlikely to be attributable to the difference in the pharmacokinetics or exposure level.

In the present study, external evaluation showed that stable disease was achieved in nine patients. It should be noted that this prolongation of stable disease was achieved in heavily pretreated patients and response was seen also at the lowest dose. Indeed, one third of the patients had previously received four or more chemotherapy regimens. Such provocative antitumor activity in refractory solid tumors confirms the previously reported activity in the U.S. phase I trial. In the U.S. study, a partial response was achieved in 3 of 5 patients with non-Hodgkin's lymphoma and a PSA response, and a 50% reduction in 2 patients with hormone-refractory prostate cancer. Furthermore, a minor reduction (23% reduction) in tumor size was noted in one patient with non–small cell lung cancer (18). The results from both studies suggest that YM155 has promising antitumor activity against various tumor types.

In conclusion, YM155 was administered safely in this study to patients with advanced refractory solid tumors by 168-hour continuous infusion in 21-day cycles. The MTD in this patient population was determined to be 8.0 mg/m^2/d. This potential for clinical efficacy is supported by the stable responses in advanced refractory tumors achieved in this study with YM155 treatment, in addition to the antitumor activity shown in the U.S. phase I study. On the basis of the potential shown by these promising results, further randomized clinical studies of YM155 are warranted, both in the monotherapy setting and in combination regimens with established therapies.

Disclosure of Potential Conflicts of Interest

Toru Kakihara, Yumiko Aoyama, and Yohko Hashimoto are employees of Astellas Pharma, Inc.

Acknowledgments

We thank Tom van der Berg, Vincent Hofstede, Hans Mulder, and Nel Volkers (Astellas Europe B.V., Leiderdorp, the Netherlands) for bioanalysis of YM155. The authors take full responsibility for the content of the article but thank Caudex Medical (supported by Astellas Pharma) for their assistance in collating the comments of authors and other named contributors.

References

1. Ambrosini G, Adida C, Altieri DC. A novel anti-apoptosis gene, survivin, expressed in cancer and lymphoma. Nat Med 1997;3:917–21.
2. Rothe M, Pan MG, Henzel WJ, Ayres TM, Goeddel DV. The TNFR2-TRAF signaling complex contains two novel proteins related to baculoviral inhibitor of apoptosis proteins. Cell 1995;83:1243–52.
3. Roy N, Deveraux QL, Takahashi R, Salvesen GS, Reed JC. The c-IAP-1 and c-IAP-2 proteins are direct inhibitors of specific caspases. EMBO J 1997;16:6914–25.
4. Tamm I, Wang Y, Sausville E, et al. IAP-family protein survivin inhibits caspase activity and apoptosis induced by Fas (CD95), Bax, caspases, and anticancer drugs. Cancer Res 1998;58:5315–20.
5. O'Connor DS, Grossman D, Plescia J, et al. Regulation of apoptosis at cell division by p34cdc2 phosphorylation of survivin. Proc Natl Acad Sci U S A 2000;97:13103–7.
6. LaCasse EC, Baird S, Korneluk RG, MacKenzie AE. The inhibitor of apoptosis (IAPs) and their emerging role in cancer. Oncogene 1998;17:3247–59.
7. Jäättelä M. Escaping cell death: survival protein in cancer. Exp Cell Res 1999;248:30–43.
8. Lu CD, Altieri DC, Tanigawa N. Expression of a novel anti-apoptosis gene, survivin, correlated with tumor cell apoptosis and p53 accumulation in gastric carcinomas. Cancer Res 1998;58:1808–12.
9. Adida C, Berrebi D, Peuchmaur M, Reyes-Mugica M, Altieri DC. Anti-apoptosis gene, survivin, and prognosis of neuroblastoma. Lancet 1998;351:882–3.
10. Islam A, Kageyama H, Takada N, et al. High expression of Survivin, mapped to 17q25, is significantly associated with poor prognostic factors and promotes cell survival in human neuroblastoma. Oncogene 2000;19:617–23.
11. Sarela AI, Macadam RC, Farmery SM, Markham AF, Guillou PJ. Expression of the antiapoptosis gene, survivin, predicts death from recurrent colorectal carcinoma. Gut 2000;46:645–50.
12. Monzo M, Rosell R, Felip E, et al. A novel anti-apoptosis gene: reexpression of survivin messenger RNA as a prognosis marker in non-small-cell lung cancers. J Clin Oncol 1999;17:2100–4.
13. Tanaka K, Iwamoto S, Gon G, Nohara T, Iwamoto

M, Tanigawa N. Expression of survivin and its relationship to loss of apoptosis in breast carcinomas. Clin Cancer Res 2000;6:127–34.

14. Yamamoto T, Tanigawa N. The role of survivin as a new target of diagnosis and treatment in human cancer. Med Electron Microsc 2001;34: 207–12.
15. Giodini A, Kallio MJ, Wall NR, et al. Regulation of microtubule stability and mitotic progression by survivin. Cancer Res 2002;62:2462–7.
16. Mesri M, Morales-Ruiz M, Ackermann EJ, et al. Suppression of vascular endothelial growth factor-mediated endothelial cell protection by survivin targeting. Am J Pathol 2001; 158:1757–65.
17. Nakahara T, Masahiro T. YM155, a novel small-molecule survivin suppressant, induces regression of established human hormone-refractory prostate tumor xenografts. Cancer Res 2007;67:8014–21.
18. Tolcher AW, Mita A, Lewis L, et al. Phase I and pharmacokinetic study of YM155, a small molecule inhibitor of survivin. J Clin Oncol 2008;26: 5198–203.
19. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.
20. Pennati M, Folini M, Zaffaroni N. Targeting survivin in cancer therapy. Expert Opin Ther Targets 2008;14:463–76.
21. Altieri DC. Survivin, cancer networks and pathway-directed drug discovery. Nat Rev Cancer 2008;8:61–70.
22. Leung CG, Xu Y, Mularski B, Liu H, Gurbuxani S, Crispino JD. Requirements for survivin in terminal differentiation of erythroid cells and maintenance of hematopoietic stem and progenitor cells. J Exp Med 2007;204:1603–11.
23. Sohda K, Suzuki K, Nakamura E, et al. Metabolism of YM155 monobromide, a novel survivin suppressant: *in vitro* species comparison and identification of metabolites in rats. The Proceeding of 8th International ISSX meeting 2007 (Sendai Japan). Drug Metab Rev 39:235.

original article

Annals of Oncology 20: 1483–1488, 2009
doi:10.1093/annonc/mdp031
Published online 12 March 2009

Quality of life and disease-related symptoms in previously treated Japanese patients with non-small-cell lung cancer: results of a randomized phase III study (V-15-32) of gefitinib versus docetaxel

I. Sekine[1]*, Y. Ichinose[2], Y. Nishiwaki[3], N. Yamamoto[4], M. Tsuboi[5], K. Nakagawa[6], T. Shinkai[7], S. Negoro[8], F. Imamura[9], K. Eguchi[10], K. Takeda[11], Y. Itoh[12], T. Tamura[1], N. Saijo[3] & M. Fukuoka[6]

[1]*Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tokyo;* [2]*Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka;* [3]*Department of Thoracic Oncology, National Cancer Center Hospital East, Chiba;* [4]*Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka;* [5]*Department of Thoracic Surgery and Oncology, Tokyo Medical University Hospital, Tokyo;* [6]*Department of Medical Oncology, Kinki University School of Medicine, Osaka;* [7]*Department of Internal Medicine, Respiratory Division, NHO Shikoku Cancer Center, Ehime;* [8]*Department of Thoracic Oncology, Hyogo Cancer Center, Hyogo;* [9]*Department of Pulmonary Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka;* [10]*Department of Internal Medicine and Medical Oncology, Teikyo University School of Medicine, Kanagawa;* [11]*Department of Clinical Oncology, Osaka City General Hospital, Osaka and* [12]*Clinical Division, Research and Development, AstraZeneca KK, Osaka, Japan*

Received 11 November 2008; revised 14 January 2009; accepted 26 January 2009

Background: This report describes quality of life (QoL) findings of a randomized study comparing gefitinib with docetaxel in patients with advanced/metastatic pretreated non-small-cell lung cancer.

Patients and methods: This open-label, phase III study randomized 490 Japanese patients to gefitinib (250 mg/day) or docetaxel (60 mg/m^2/3 weeks), with survival as the primary outcome. Preplanned QoL analyses included Functional Assessment of Cancer Therapy-Lung (FACT-L), Trial Outcome Index (TOI) and Lung Cancer Subscale (LCS) improvement rates, and mean change from baseline.

Results: Gefitinib showed statistically significant benefits over docetaxel in QoL improvement rates (FACT-L 23% versus 14%, $P = 0.023$; TOI 21% versus 9%, $P = 0.002$) and mean change from baseline score [mean treatment difference: FACT-L 3.72 points, 95% confidence interval (CI) 0.55–6.89, $P = 0.022$; TOI 4.31 points, 95% CI 2.13–6.49, $P < 0.001$], although differences did not meet the clinically relevant six-point change. There were no significant differences between treatments in LCS improvement rates (23% versus 20%, $P = 0.562$) or mean change from baseline score (0.63 points, 95% CI −0.07 to 1.34, $P = 0.077$).

Conclusions: Gefitinib improved aspects of QoL over docetaxel, with superior objective response rate and a more favorable tolerability profile and no statistically significant difference in overall survival (although noninferiority was not statistically proven).

Key words: docetaxel, gefitinib, non-small-cell lung cancer, quality of life

original article

introduction

Docetaxel is an established treatment of patients with previously treated advanced non-small-cell lung cancer (NSCLC) worldwide, including Japan; however, this is associated with typical cytotoxic side-effects including hematological toxicity, especially grade 3/4 neutropenia [1, 2]. Alternative agents with an improved tolerability profile, such as the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) gefitinib, have been investigated in this setting [3–5].

In this randomized phase III study (V-15-32) comparing gefitinib versus docetaxel in previously treated Japanese patients with NSCLC, the primary objective (noninferiority of gefitinib versus docetaxel) was not statistically proven for overall survival (OS) [hazard ratio (HR) 1.12, 95.24% confidence interval (CI) 0.89–1.40], according to the predefined noninferiority criterion (upper CI for HR < 1.25) [6]. However, there were no statistically significant differences in OS ($P = 0.330$) or progression-free survival (PFS; $P = 0.335$) and gefitinib had a superior objective response rate (ORR) and a more favorable tolerability profile than docetaxel. Because of the significant

Correspondence to: Dr I. Sekine, Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. Tel: +81-3-3542-2511; Fax: +81-3-3542-3815; E-mail: isekine@ncc.go.jp

burden of disease-related symptoms in patients with advanced NSCLC, improvements in health-related quality of life (QoL) and symptoms are an important additional parameter to guide treatment choice, particularly with the introduction of agents with better tolerability profiles. Here, we report in detail the QoL and symptom analyses of the V-15-32 study.

patients and methods

study design

This phase III study compared the effects of gefitinib versus docetaxel in Japanese patients with advanced/metastatic (stage IIIb/IV) or recurrent NSCLC who failed one or two chemotherapy regimens. Details of the study design and eligibility criteria have been published [6]. The primary end point was OS; the study aimed to show noninferiority of gefitinib versus docetaxel. Secondary end points were PFS, time-to-treatment failure, ORR, disease control rate, QoL, disease-related symptoms, safety, and tolerability.

The study was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics. The study protocol was approved by each institutional review board and written informed consent was obtained from all patients.

QoL assessments and analyses

The Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire was used to assess QoL at baseline and every 4 weeks during study treatment until week 12. The FACT-L questionnaire is a validated, self-report questionnaire comprising physical, functional, social/family, emotional well-being subscales and Lung Cancer Subscale (LCS) [7]. The Trial Outcome Index (TOI), the sum of the physical, functional subscales, and LCS is reported to be a precise indicator of functional outcomes [7]. Disease-related symptoms were assessed weekly using the LCS. As previously reported [8], clinically relevant improvement was defined as change from baseline of ≥+6 for FACT-L or TOI or ≥+2 for LCS, on two visits at least 28 days apart. The assessable for LCS and assessable for QoL populations were subsets of the intent-to-treat (ITT) population with nonmissing baseline and one or more nonmissing post-baseline LCS and QoL assessments, respectively.

Preplanned analyses of FACT-L, TOI, and LCS scores included the following: mean change from baseline and 95% CI of the difference in mean change from baseline scores between the groups (based on the *t*-distribution; calculated as the difference between the mean overall patients on a treatment of the within-patient average change from baseline score); improvement, control (improvement or no change), and worsening rates and the odds ratio between treatments (with 95% CI and *P* value from a logistic regression model without covariates); and HR (gefitinib/docetaxel) for time to worsening (with 95% CI and *P* value using a proportional hazard model without covariates).

Supporting *post hoc* analyses of FACT-L, TOI, and LCS scores included the following: similar analyses using best change from baseline score instead of mean change; mean and best change from baseline for each subscale with two-sample *t*-test comparing treatments; mean and best change from baseline for individual questions; and correlation between mean change and best change from baseline and tumor response.

results

patients

Of 245 gefitinib and 244 docetaxel patients (one patient in the docetaxel arm was excluded due to GCP violation) in the ITT population, 185 (76%) and 173 (71%) patients, respectively, were assessable for QoL and 225 (92%) and 211 (86%) patients, respectively, were assessable for LCS. The demographic characteristics of the assessable for QoL and assessable for LCS populations (Supplemental Table 1, available at *Annals of Oncology* online) were representative of the overall study population [6].

QoL and disease-related symptoms at baseline

The baseline FACT-L, TOI, and LCS scores were similar between treatment groups (Table 1).

compliance and evaluability

Baseline compliance rates [(evaluable questionnaires during the treatment period)/(expected questionnaires) × 100] for gefitinib and docetaxel were high: 92% and 86%, respectively, for FACT-L and 93% and 87%, respectively, for LCS. During the first 12-weeks treatment, compliance rates for gefitinib and docetaxel were between 77% and 89% and 77% and 93%, respectively, for FACT-L completion and between 76% and 98% and 71% and 98%, respectively, for LCS completion, with smaller numbers of patients as time progressed as expected (Supplemental Table 2, available at *Annals of Oncology* online). Evaluability rates [(evaluable questionnaires during the treatment period)/(received questionnaires) × 100] were also high at between 88% and 100% (Supplemental Table 2, available at *Annals of Oncology* online).

QoL and symptom improvement

Significantly, more gefitinib-treated patients experienced a clinically relevant improvement in QoL (FACT-L and TOI) compared with docetaxel (Figure 1). There was no evidence of a difference between treatments in terms of symptom improvement rates measured by LCS (Figure 1).

Table 1. Baseline FACT-L, TOI, and LCS scores (assessable population)

Variable	Gefitinib			Docetaxel		
	n	Median (range)	Mean ± SD	*n*	Median (range)	Mean ± SD
FACT-L	185	98.5 (64.0–100.0)	98.7 ± 17.2	173	98.0 (49.3–138.0)	97.3 ± 17.5
TOI	185	58.4 (26.0–84.0)	58.0 ± 12.4	173	59.0 (28.0–82.0)	57.8 ± 12.6
LCS	225	19.0 (5.0–28.0)	19.4 ± 4.75	211	19.6 (5.0–28.0)	19.4 ± 4.91

SD, standard deviation; FACT-L, Functional Assessment of Cancer Therapy-Lung; TOI, Trial Outcome Index; LCS, Lung Cancer Subscale.

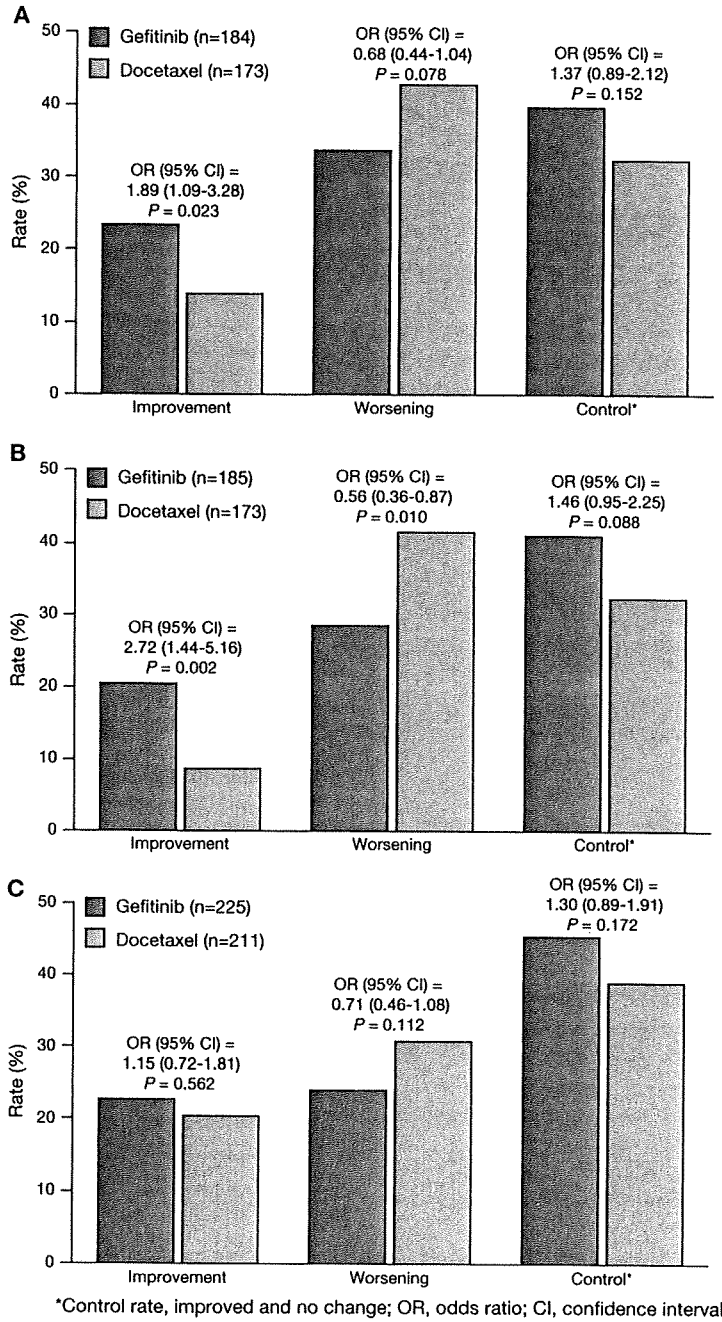

Figure 1. Improvement, worsening and control rates of (A) Functional Assessment of Cancer Therapy-Lung total, (B) Trial Outcome Index, and (C) Lung Cancer Subscale score (assessable population).

Time to worsening was significantly longer on gefitinib than docetaxel for TOI, numerically longer for FACT-L, and slightly longer for LCS (Figure 2).

Mean change from baseline for FACT-L, TOI, and LCS at each visit during the first 12 weeks of treatment is shown in Supplemental Figure 1 (available at *Annals of Oncology* online).

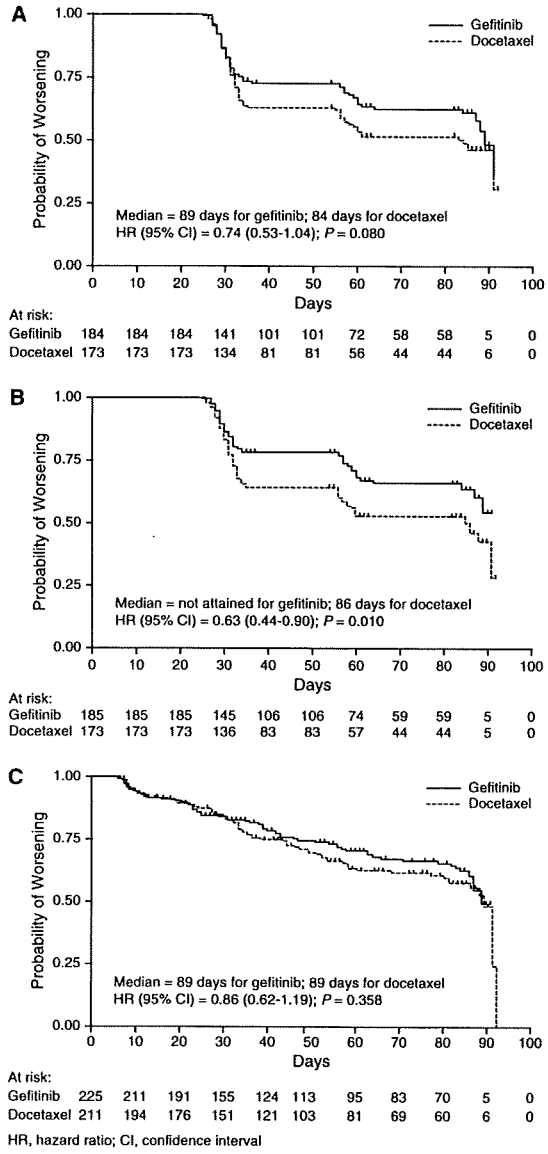

Figure 2. Time to worsening of (A) Functional Assessment of Cancer Therapy-Lung total, (B) Trial Outcome Index, and (C) Lung Cancer Subscale score (assessable population).

Statistically significant differences between treatments in mean change from baseline for QoL score (FACT-L and TOI) in favor of gefitinib were observed, but the differences did not meet the predefined, clinically relevant six-point change (FACT-L: 3.72 points, 95% CI 0.55–6.89, $P = 0.022$; TOI: 4.31 points, 95% CI 2.13–6.49, $P < 0.001$) (Table 2). There was no significant difference between treatments in mean change from baseline for LCS score (0.63 points, 95% CI −0.07 to 1.34, $P = 0.077$) (Table 2).

Table 2. Mean change during the first 12 weeks of treatment (assessable populations)

Variable	Gefitinib			Docetaxel			Difference	*P* value
	n	Mean	SD	*n*	Mean	SD	(95% CI)	by *t*-test
FACT-L	184	0.94	15.48	173	−2.78	14.96	3.72 (0.55 to 6.89)	0.022
TOI	185	0.81	10.22	173	−3.50	10.78	4.31 (2.13 to 6.49)	<0.001
LCS	225	1.38	3.58	211	0.75	3.89	0.63 (−0.07 to 1.34)	0.077

SD, standard deviation; CI, confidence interval; FACT-L, Functional Assessment of Cancer Therapy-Lung; TOI, Trial Outcome Index; LCS, Lung Cancer Subscale.

Post hoc analyses of mean change from baseline in the FACT-L subscales identified significant differences in favor of gefitinib over docetaxel in the physical ($P = 0.002$) and functional well-being subscales ($P = 0.002$) but not in the social/family ($P = 0.494$) or emotional well-being subscales ($P = 0.663$) (Figure 3).

In *post hoc* analyses, individual FACT-L questions with the largest differences between treatments in mean change from baseline (≥0.3 points difference of absolute value, all favoring gefitinib) were 'I am bothered by hair loss' (difference 2.03 points; question not included in calculating FACT-L, TOI, and LCS scores); 'I am content with the quality of my life right now' (0.47 points); 'I am forced to spend time in bed' (0.39 points); 'I am enjoying the things I usually do for fun' (0.33 points); 'I am sleeping well' (0.31 points); and 'I have a good appetite' (0.31 points). No question favored docetaxel by >0.21 points (Supplemental Table 3, available at *Annals of Oncology* online).

The results of *post hoc* analyses of best change from baseline score were consistent with the preplanned mean change from baseline score analyses.

QoL and symptom improvement by objective tumor response

Mean change from baseline in FACT-L, TOI, and LCS improved as best overall objective tumor response improved for both gefitinib and docetaxel (Supplemental Table 4, available at *Annals of Oncology* online). There was a higher correlation between changes and tumor response for gefitinib than docetaxel, which may be caused by more disperse distribution of objective tumor response for gefitinib. Similar results with slightly higher correlations were seen using best change from baseline.

discussion

In this randomized phase III study in previously treated advanced NSCLC, noninferiority of gefitinib versus docetaxel was not statistically proven for OS, although there were no statistically significant differences in OS or PFS between treatments. However, gefitinib demonstrated statistically significant benefits over docetaxel in QoL improvement rates and mean change from baseline QoL score (measured by

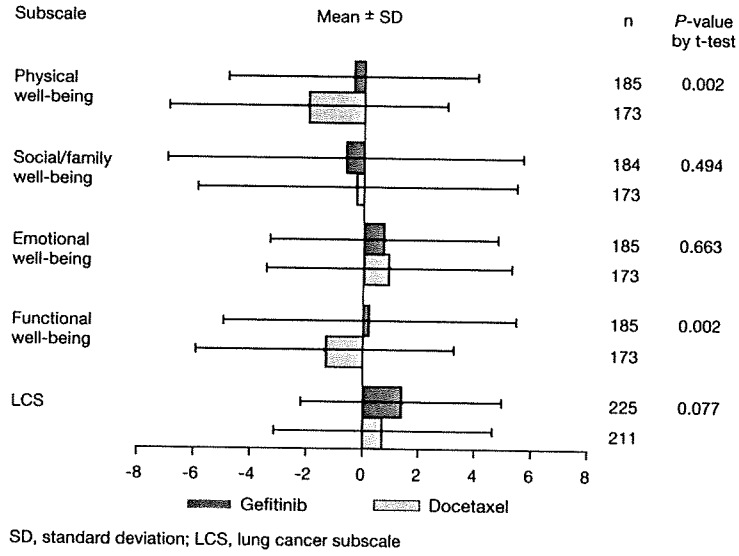

Figure 3. Mean change of mean score from baseline for Functional Assessment of Cancer Therapy-Lung subscales (assessable population).

FACT-L and TOI) in addition to superior ORR and a more favorable tolerability profile for gefitinib. *Post hoc* analyses showed that the biggest differences in favor of gefitinib were in the FACT-L physical and functional well-being subscales, the two subscales thought the most responsive to short-term changes [7]. Conversely, there were no significant differences between treatments in symptom improvement rates or mean change from baseline symptom score as measured by the LCS. In line with these results, time to worsening of QoL tended to be longer for gefitinib than docetaxel, significantly so for TOI. Further, *post hoc* analyses showed that there appeared to be a higher correlation between QoL and symptom changes and objective tumor response with gefitinib compared with docetaxel. Compliance and evaluability rates were high supporting the validity of these/QoL data [9].

The QoL benefits seen in this study are consistent with other studies of gefitinib and docetaxel [3, 4, 10–13]. Docetaxel has demonstrated symptom relief including improvements in patient-rated pain scores ($P = 0.005$) and QoL with less deterioration in Lung Cancer Symptom Scale (LCSS) pain score ($P < 0.05$) in pretreated patients with advanced NSCLC compared with best supportive care [11]. Despite an improved tolerability profile with pemetrexed, no improvements were observed in QoL measurements compared with docetaxel in a phase III second-line setting in predominantly Western patients: symptom improvement rates (21% versus 22%, respectively, measured by LCSS) and rates of improvement or stabilization of anorexia (56% versus 61%), fatigue (55% versus 57%), cough (64% versus 64%), dyspnea (64% versus 60%), hemoptysis (70% versus 73%), and pain (64% versus 62%) were similar for pemetrexed and docetaxel [12]. In a phase II study in previously treated patients with advanced NSCLC (SIGN), QoL improvement rate of gefitinib was higher than docetaxel (34% versus 26%) and the mean change from baseline in FACT-L score was similar between the treatments (1.55 versus 0.39, $P = 0.63$) [10]. A larger international phase III study (INTEREST) with a very similar design to V-15-32 but in predominantly Western patients has established noninferior survival of gefitinib versus docetaxel in 1466 patients with pretreated advanced NSCLC [13]. Statistically significant benefits in QoL improvement rates for gefitinib over docetaxel were also observed in this study (FACT-L 25% versus 15%, $P < 0.0001$; TOI 17% versus 10%, $P = 0.0026$), with no significant difference between treatments in symptom improvement rates (LCS 20% versus 17%, $P = 0.1329$) [13]. Another EGFR TKI, erlotinib, was associated with QoL improvements [using the European Organization for Research and Treatment of Cancer QoL questionnaire (QLQ-C30)] compared with placebo [14] but no comparative data for erlotinib versus docetaxel exist.

In conclusion, gefitinib demonstrated statistically significant QoL benefits compared with docetaxel in the current study. From this study, we believe that treatment with gefitinib remains an effective treatment option with potential QoL advantages for previously treated Japanese patients with locally advanced/metastatic NSCLC.

funding

AstraZeneca.

acknowledgements

We thank all the patients and investigators who participated in the V-15-32 study. We also thank Annette Smith, from Complete Medical Communications, who provided medical writing support funded by AstraZeneca. We thank Haiyi Jiang

(AstraZeneca KK) for critical review and assistance with data analysis and interpretation. KN: honorarium from Astrazeneca company and Sanofy-Aventis company; SN: honorarium from Astrazeneca and Sanofy-Aventis Kenji Eguchi: honoraria from Astrazeneca and Chugai; YI: I have been an Astrazeneca employee since 2000; Haiyi Jiang: I have been an Astrazeneca employee since 2001; TT: honoraria from Astrazeneca; NS: honorarium from Astrazeneca, Eli Lilly, Chugai and Taiho pharmaceutical companies; MF: honorarium from Astrazeneca, Eli Lilly and Chugai pharmaceutical companies

references

1. Mukohara T, Takeda K, Miyazaki M et al. Japanese experience with second-line chemotherapy with low-dose (60 mg/m^2) docetaxel in patients with advanced non-small-cell lung cancer. Cancer Chemother Pharmacol 2001; 48: 356–360.
2. Shepherd FA, Dancey J, Ramlau R et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000; 18: 2095–2103.
3. Fukuoka M, Yano S, Giaccone G et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. J Clin Oncol 2003; 21: 2237–2246.
4. Kris MG, Natale RB, Herbst RS et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA 2003; 290: 2149–2158.
5. Thatcher N, Chang A, Parikh P et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005; 366: 1527–1537.
6. Maruyama R, Nishiwaki Y, Tamura T et al. Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. J Clin Oncol 2008; 26: 4244–4252.
7. Cella DF, Bonomi AE, Lloyd SR et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer 1995; 12: 199–220.
8. Cella D, Eton DT, Fairclough DL et al. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) Study 5592. J Clin Epidemiol 2002; 55: 285–295.
9. Osoba D, Bezjak A, Brundage M et al. Analysis and interpretation of health-related quality of life data from clinical trials: basic approach of The National Cancer Institute of Canada Clinical Trials Group. Eur J Cancer 2005; 41: 280–287.
10. Cufer T, Vrdoljak E, Gaafar R et al. Phase II, open-label, randomized study (SIGN) of single-agent gefitinib (IRESSA) or docetaxel as second-line therapy in patients with advanced (stage IIIb or IV) non-small-cell lung cancer. Anticancer Drugs 2006; 17: 401–409.
11. Dancey J, Shepherd FA, Gralla RJ, Kim YS. Quality of life assessment of second-line docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy: results of a prospective, randomized phase III trial. Lung Cancer 2004; 43: 183–194.
12. Hanna N, Shepherd FA, Fossella FV et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004; 22: 1589–1597.
13. Kim ES, Hirsch V, Mok T et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer: a randomised phase III trial (INTEREST). Lancet 2008; 372: 1809–1818.
14. Bezjak A, Tu D, Seymour L et al. Symptom improvement in lung cancer patients treated with erlotinib: quality of life analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 2006; 24: 3831–3837.