Although response was not a primary outcome of our study, two of three patients treated with RAD001 at a daily dose of 10 mg manifested marked tumor shrinkage. This anti-tumor activity occurred in patients with esophageal and gastric cancer. One esophagogastric cancer patient also exhibited a partial response to RAD001 treatment at a daily dose of 5 mg in a previous Phase I study (16). The likelihood that these findings will extend to other patients is supported by recent studies suggesting that defects in the mTOR signaling pathway are important in the pathogenesis of these cancers. mTOR is an upstream regulator of hypoxia-inducible factor-1α, which is a key mediator of gastric cancer growth (24). Pre-clinical studies have shown that the mTOR inhibitor rapamycin inhibits the growth of human gastric adenocarcinoma cell lines, gastric cancer, gastrointestinal tumors, and the development of peritoneal carcinomatosis from gastric cancer *in vitro* or *in vivo* (24–27).

In conclusion, the results of our Phase I study suggest that RAD001 can be safely administered at a daily dose of 10 mg to Japanese patients with advanced solid malignancies. The pharmacokinetic characteristics of RAD001 in Japanese patients did not appear to differ from those previously observed in Caucasian patients. The safety profile and potential broad-spectrum efficacy of RAD001 thus warrant additional clinical evaluation of this new agent.

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Conflict of interest statement

The authors Katsutoshi Kurei and Ken Kobayashi are employed by Novartis Pharma.

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PHASE I STUDIES

Phase I clinical and pharmacokinetic study of sorafenib in combination with carboplatin and paclitaxel in patients with advanced non–small cell lung cancer

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Summary *Objectives* Unsatisfactory efficacy of current treatments for advanced lung cancer has prompted the search for new therapies, with sorafenib, a multikinase inhibitor, being one candidate drug. This phase I trial was conducted to evaluate drug safety and pharmacokinetics as well as tumor response of sorafenib in combination with paclitaxel and carboplatin in patients with advanced non-small cell lung cancer (NSCLC). *Methods* Eligible patients received paclitaxel (200 mg/m^2) and carboplatin (area under the curve [AUC]of 6 mg min mL^{-1}) on day 1 and sorafenib (400 mg, twice daily) on days 2 through 19 of a 21-day cycle. *Results* Four of the initial six patients (cohort 1) experienced dose-limiting toxicities (DLTs), resulting in amendment of the treatment protocol. An additional seven patients (cohort 2) were enrolled, two of whom developed DLTs. DLTs included erythema multiforme, hand-foot skin reaction, and elevated plasma alanine aminotransferase in cohort 1 as well as gastrointestinal perforation at a site of metastasis and pneumonia in cohort 2. Most adverse events were manageable. One complete and six partial responses were observed among the 12 evaluable patients. Coadministration of the three drugs had no impact on their respective pharmacokinetics. *Conclusion* The present study confirmed that sorafenib at 400 mg once daily in combination with carboplatin AUC 5 mg min mL^{-1} and paclitaxel 200 mg/m^2 is feasible in Japanese patients with advanced NSCLC. The results of this study also showed that this combination therapy had encouraging antitumor activity and was not associated with relevant pharmacokinetic interaction in Japanese NSCLC patients.

Keywords Carboplatin · Lung cancer · Paclitaxel · Pharmacokinetics · Safety · Sorafenib

Introduction

Non–small cell lung cancer (NSCLC) accounts for ~75% of all lung cancers and is the most common cause of cancer-related deaths worldwide [1]. Individuals with metastatic NSCLC are candidates for palliative systemic chemotherapy that confers only a limited survival benefit [2, 3]. The dismal outlook for patients with advanced NSCLC who receive currently available therapies has prompted a search for new, more effective chemotherapeutic agents and combination regimens. Target-based therapies are therefore being pursued as potential treatment alternatives.

Sorafenib (BAY 43-9006; Nexavar; Bayer HealthCare, Montville, NJ; Onyx Pharmaceuticals, Emeryville, CA), is an oral multikinase inhibitor that inhibits Raf serine-threonine kinases and several receptor tyrosine kinases

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that function in tumor growth and angiogenesis [4]. The Ras-Raf-MEK-ERK signaling pathway plays a pivotal role in the regulation of tumor cell growth by relaying signals from the cell surface to the nucleus, with the components of this pathway, including Raf, thus representing potential targets for anticancer treatment [5, 6]. Sorafenib also targets the vascular endothelial growth factor (VEGF) receptors VEGFR-2 and VEGFR-3 as well as platelet-derived growth factor receptor–β (PDGFR-β), the ligands for which (VEGF and PDGF) are pro-angiogenic factors essential for tumor growth and metastasis [4]. Sorafenib has recently been approved for treatment of advanced renal cell carcinoma and hepatocellular carcinoma in the United States, Europe, and several other countries. Furthermore, sorafenib is currently undergoing clinical evaluation for a variety of additional cancers, including NSCLC.

Although several phase I clinical trials of sorafenib alone or in combination with other drugs have been conducted [7–19], no such phase I study for a specific type of lung cancer has been performed. The aim of the present phase I study was to evaluate the safety and pharmacokinetics of sorafenib in combination with carboplatin and paclitaxel in patients with advanced NSCLC.

Patients and methods

Patient selection

Eligible patients were 18 years of age or older with unresectable NSCLC, as confirmed histologically or cytologically, and with a life expectancy of at least 12 weeks. They were required to be naïve to chemotherapy and to have an Eastern Cooperative Oncology Group performance status of 0 or 1. The eligibility criteria also included adequate bone marrow, hepatic, and renal function as well as normal blood coagulation parameters. Individuals were excluded if they had previous or concurrent cancer distinct in primary site or histology from NSCLC or any cancer curatively treated >3 years prior to study entry; clinically active or significant cardiovascular disease; human immunodeficiency virus infection, chronic hepatitis B or C, or other serious infections; a seizure disorder requiring medication; a history of organ allograft, substance abuse, or medical, psychological, or social conditions that might interfere with participation in the study; or allergy to the study treatment. Pregnant or breast-feeding patients were also excluded. All patients received information regarding the nature and purpose of the study, and they provided written informed consent in accordance with institutional guidelines. The study protocol was approved by the Institutional Review Board of Kinki University Hospital.

Study design

The study was designed as a single-center, open-label, non–placebo-controlled phase I trial to define the safety, tolerability, pharmacokinetics, and tumor response profile of sorafenib administered according to a dosing schedule of 18 days on and 3 days off and in combination with paclitaxel and carboplatin chemotherapy in chemonaïve patients with advanced NSCLC. The other phase I trial of sorafenib in combination with paclitaxel and carboplatin had already confirmed the safety of sorafenib 400 mg twice daily in combination with paclitaxel at 225 mg/m^2 and carboplatin at area under the curve [AUC] of 6 mg min mL^{-1} in a dose-escalation manner [16]. Based on this result, the starting doses of the present study were decided as follows; Paclitaxel (200 mg/m^2, infused over 3 h) and carboplatin (AUC 6 mg min mL^{-1} during infusion for 30 min) were administered consecutively on day 1, and sorafenib (400 mg, twice daily) was administered for 18 days starting on day 2. There was a concern that sorafenib may inhibit cytochrome P450 enzymes responsible for the clearance of paclitaxel. Based on this possible pharmacokinetic interaction and antagonistic effects, sorafenib administration was discontinued for two days (days 20 and 21) before the next administration of paclitaxel in both the present study and the other phase I trial [16]. This treatment cycle was repeated every 21 days until unacceptable toxicity, tumor progression, or death occurred. Carboplatin-paclitaxel chemotherapy was not allowed to exceed six cycles, after which sorafenib administration could continue until the occurrence of intolerable toxicity, disease progression. If fewer than two of the first six patients experienced dose limiting toxicity (DLT) in the first cycle, the dose level was to be recommended for subsequent clinical trials and an additional six patients were to be enrolled to the cohort.

Patient evaluation

All observations pertinent to the safety of sorafenib were recorded, including results of physical examinations, vital signs, adverse events, use of concomitant medications, and laboratory test data. Patients were routinely monitored for adverse events, which were recorded with severity and relation to study medication according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Assessment of the chest and abdomen for tumors was performed radiologically (computed tomography or magnetic resonance imaging) according to the Response Evaluation Criteria in Solid Tumors (RECIST) [20]. The same radiological method was performed to maintain consistency of evaluation. Patients for whom antitumor efficacy (complete or partial response)

was observed or who had stable disease were continuously treated according to the study protocol. Measurements were repeated in patients with a complete or partial response at a time more than 4 weeks after the response criteria were first met in order to confirm tumor response according to RECIST.

Pharmacokinetics

To investigate the effect of paclitaxel-carboplatin on the pharmacokinetics of sorafenib, we collected blood samples on days 2 and 19 of treatment cycle 1 for cohort 1 and determined the plasma concentration of sorafenib. On both days, samples were collected at 0 h (pre–morning dose of sorafenib); at 0.5, 1, 3, 6, and 12 h (pre–evening dose); and at 24 h (pre–morning dose on day 3). After dosing on day 19, additional samples were collected at 48 and 72 h (before infusion of paclitaxel in cycle 2). The evening dose of sorafenib was not administered on day 19 of cycle 1 for the purpose of pharmacokinetic sampling. As a result of amendment to the treatment protocol for cohort 2, a modified schedule of blood sampling was adopted. For determination of the plasma concentration of sorafenib, blood samples were collected at the same time points in cycle 2 as in cycle 1, with the exception that the blood sample obtained at 12 h after the morning administration of sorafenib on day 2 was collected before the evening dose on day 2 in cohort 2. The concentration of sorafenib in plasma samples was determined with the use of a validated high-performance liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay.

To investigate the effects of sorafenib on the pharmacokinetics of paclitaxel and carboplatin, we collected blood samples on day 1 of cycle 1 for cohort 1 and determined the plasma concentrations of carboplatin, paclitaxel, and the paclitaxel metabolite 6-hydroxy-paclitaxel. Samples were collected at 0 h, 1.5 h (during paclitaxel infusion), 3 h (within 5 min before completion of paclitaxel infusion), 3.5 h (within 5 min before completion of carboplatin infusion), as well as 4, 5, 7, 11, 24, and 48 h. The amended treatment protocol for cohort 2 was accommodated by collection of blood samples immediately before, 1.5 h after the start of, within 5 min before completion of, as well as 0.5, 1, 2, 4, 8, 21, and 45 h after completion of paclitaxel infusion on day 1 of cycles 1, 2, and 3 for paclitaxel, and immediately before, within 5 min before completion of, as well as 0.5, 1, 3, 7, 20, 31, and 44 h after completion of carboplatin infusion on day 1 of cycles 1, 2, and 3 for carboplatin. The plasma concentrations of free (unbound) platinum derived from carboplatin, of paclitaxel, and of 6-hydroxy-paclitaxel were measured with the use of atomic absorption spectrophotometry and were validated by LC-MS/MS assays.

Pharmacokinetic parameters, including the AUC, maximum concentration (C_{max}), and elimination half-life ($t_{1/2}$), for sorafenib, paclitaxel, and carboplatin were calculated by noncompartment analysis as previously described [17].

Results

Patient demographics

A total of 13 chemonaïve patients with advanced NSCLC was enrolled in the study, six in cohort 1 and seven in cohort 2. The baseline demographics for all patients are shown in Table 1. Histological diagnosis revealed that the most common histology was adenocarcinoma (eight patients, or 61.5%), followed by large cell carcinoma and squamous cell carcinoma (each with two patients, or 15.4%).

DLT

Table 2 summarizes the dosing regimens for evaluated cohorts together with DLTs. The first six patients enrolled in cohort 1 were treated with 400 mg of sorafenib twice daily (days 2 to 19) combined with paclitaxel at 200 mg/m^2 and carboplatin at an AUC of 6 mg min mL^{-1} (30-min infusion). Four of these six patients experienced DLTs during the first cycle of treatment (two with erythema

Table 1 Patient demographics

	No. of patients
Total enrolled	13
Cohort 1	6
Cohort 2	7
Age (years)	
Median	66
Range	41–76
Sex	
Male	9
Female	4
ECOG performance status	
0	4
1	9
Disease stage	
IV	13
Histology	
Adenocarcinoma	8
Large cell carcinoma	2
Squamous cell carcinoma	2
Undifferentiated carcinoma	1

ECOG Eastern Cooperative Oncology Group

Table 2 Observed DLTs according to dose level

Cohort	Paclitaxel (mg/m^2)	Carboplatin ($mgminmL^{-1}$)	Sorafenib (mg)	No. of patients	No. of patients with DLTs	DLTs
1	200	6	400 twice daily	6	4	Erythema multiforme, grade 3 ($n=2$)
						Hand-foot skin reaction, grade 3 ($n=1$)
						ALT elevation, grade 3 ($n=1$)
2 (cycle 1)	200	5	400 once daily	7	0	None
2 (cycle 2)	200	5	400 twice daily	7	2	Perforation, GI, small bowel NOS, grade 3 ($n=1$)
						Infection-lung (pneumonia) of grade 3 with neutrophil of grade 4 ($n=1$)

DLTs dose-limiting toxicities, *ALT* alanine aminotransferase, *GI* gastrointestinal, *NOS* not otherwise specified

multiforme of grade 3, one with a hand and foot skin reaction of grade 3, and one with elevation of plasma alanine aminotransferase [ALT] of grade 3). One of the patients diagnosed with erythema multiforme developed a rash of grade 1 on the arms, thigh, and hip on day 5; by day 15, the rash had spread to the entire body with development of pruritus (grade 3), and histopathologic analysis of skin biopsy specimens revealed superficial dermal vasodilation as well as perivascular lymphocyte and plasma cell infiltration, consistent with erythema multiforme (Fig. 1a, b). The second patient also developed a localized rash of grade 1 that appeared in the right lower part of the abdomen on day 5 and had spread to the entire body with the development of a high fever on day 12; histopathologic analysis of skin biopsy specimens again supported a diagnosis of erythema multiforme. Both patients responded well to steroid therapy and improved.

Given that the incidence of DLT at the adopted dose level exceeded that predefined for the maximum tolerated dose, a modified dose level consisting of 400 mg of sorafenib once daily (days 2 to 19) combined with paclitaxel at 200 mg/m^2 and carboplatin at an AUC of 5 mg min mL^{-1} (60-min infusion) was evaluated for the seven additional patients of cohort 2. None of these seven patients experienced DLT during cycle 1. Intrapatient escalation of sorafenib dose was allowed if the patient did not experience DLT in cycle 1 of cohort 2; the dose of sorafenib was thus increased to 400 mg twice daily from day 2 to day 19 in subsequent courses. Among the seven patients who received sorafenib at 400 mg twice daily combined with paclitaxel (200 mg/m^2) and carboplatin (AUC of 5 mg min mL^{-1}), two individuals developed DLT: one a perforation of the small bowel of grade 4 and one pneumonia of grade 3. The patient with gastrointestinal perforation, who had metastases in the left adrenal gland and small intestine, developed abdominal pain, fever, and peritonitis 26 days after initiation of sorafenib at 400 mg twice daily and required emergency surgery. He recovered after surgery, and pathological examination of the surgical specimen confirmed the presence of tumor cells at the site of perforation. Given the marked tumor response of the patient on radiographic examination, the perforation event was likely associated with the antitumor effect of the study treatment.

Safety

All 13 enrolled patients were evaluable for safety analysis. Treatment-emergent adverse events (Table 3) occurred in all patients, the most common being hematologic or dermatologic in nature, sensory neuropathy, anorexia, and nausea. Neutropenia of grade 4 occurred in nine (69%) patients (four in cohort 1 and five in cohort 2). Hand-foot skin reaction occurred in five patients (three in cohort 1 and two in cohort 2), hypertension in four patients (two in cohort 1 and two in cohort 2), elevated plasma lipase in four patients (three in cohort 1 and one in cohort 2), and erythema multiforme in three patients (two in cohort 1 and one in cohort 2).

Antitumor activity

Tumor response was evaluated in 12 of the 13 patients (Fig. 2), with the remaining patient in cohort 2 not being available for assessment of such response. One patient in cohort 1 had a confirmed complete response, and six patients (three in each cohort) had a confirmed partial response; the overall response rate was thus 58% (95% confidence interval of 28 to 85%). Five patients, two in cohort 1 and three in cohort 2, had stable disease. Cavitation of lung lesions was observed in one patient (Fig. 1c, d). The median time to disease progression was 5.7 months (95% confidence interval of 4.3 to 20.1 months).

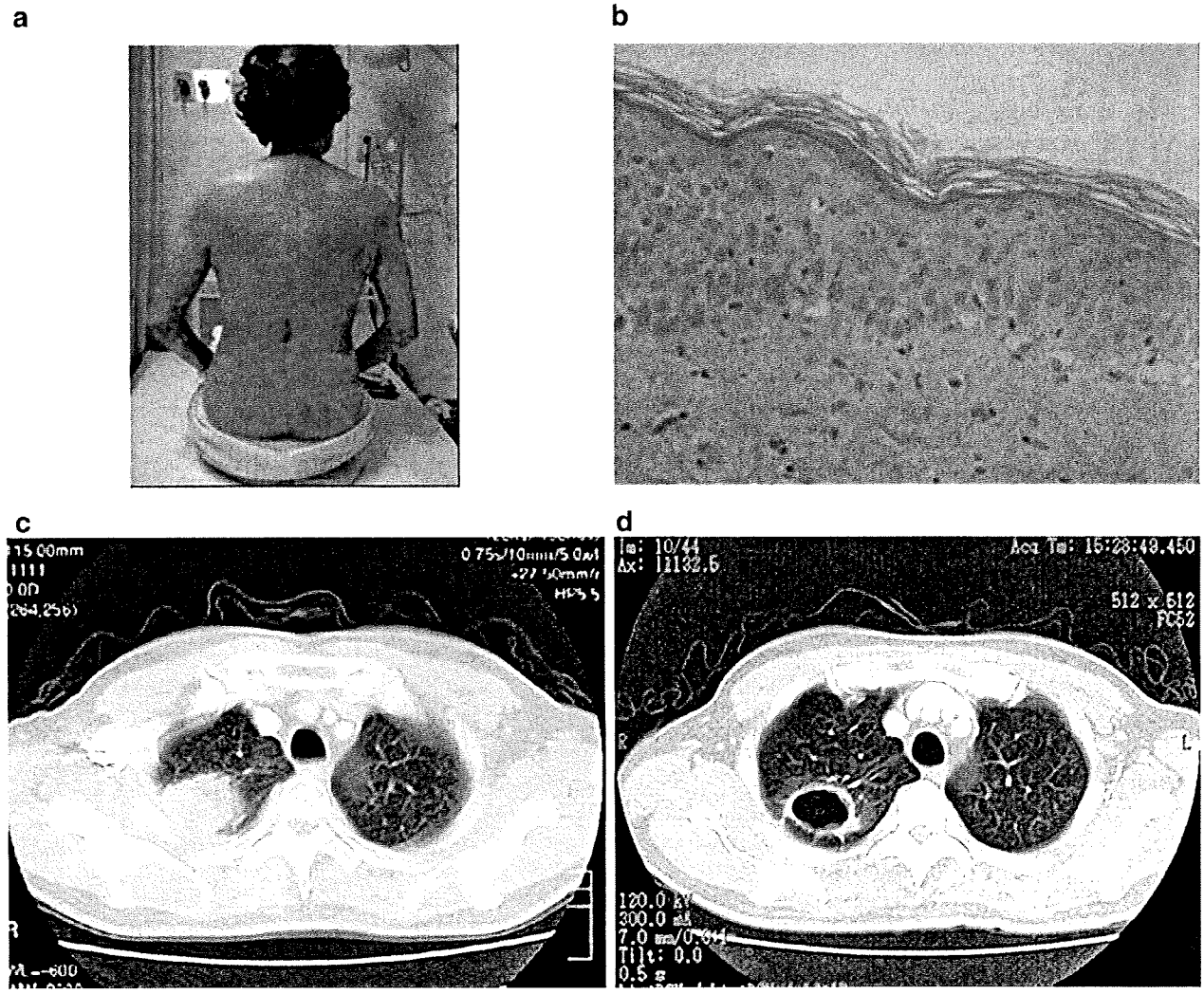

Fig. 1 Development of erythema multiforme and tumor cavitation in patients with advanced NSCLC treated with sorafenib in combination with carboplatin-paclitaxel. **a** A rash, initially localized to the arms, thigh, and hip, spread to the entire body. **b** Hematoxylin-eosin staining of a skin lesion from the patient shown in (**a**) revealed infiltration of inflammatory cells, mostly lymphocytes, around superficial dermal blood vessels and the epidermal-dermal junction. Liquefaction degeneration in basal epidermal layers and cavernous transformation in part of the epidermal squamous cell layer were also observed. **c**, **d** Computed tomography revealed a solid tumor without cavitation in the right lung of a patient at baseline (**c**), whereas the same tumor showed marked central cavitation on day 19 of cycle 1 (**d**)

Pharmacokinetics

Pharmacokinetic analysis for sorafenib in the presence of paclitaxel and carboplatin (Table 4) was based on the patients in cohort 1 (cycle 1) and cohort 2 (cycles 1 and 2) after administration of a single dose (day 2) or multiple doses (day 19). The increases in mean C_{max} from days 2 to 19 were consistent with those in mean AUC_{0-12}, likely reflecting the long mean $t_{1/2}$ (20.4 to 26.8 h on day 19). In cohort 2, the increases in the mean values of AUC_{0-12} and C_{max} in cycle 2 (400 mg, twice daily) compared with those in cycle 1 (400 mg, once daily) were consistent with the increase in sorafenib dosing. At steady state, after multiple administrations of sorafenib at 400 mg twice daily together with paclitaxel and carboplatin, the mean values of AUC_{0-12} and C_{max} in cohort 1 (cycle 1, day 19) were 31.3 mg h L^{-1} and 4.6 mg/L, respectively, and those in cohort 2 (cycle 2, day 19) were 39.1 mg h L^{-1} and 5.9 mg/L, respectively.

Given that treatment was discontinued after cycle 1 in four of the six patients in cohort 1, the effects of multiple doses of sorafenib on the pharmacokinetics of paclitaxel and carboplatin were evaluated in cohort 2. Pharmacokinetic analysis for paclitaxel and carboplatin was performed during cycle 1 before sorafenib administration and during cycles 2 and 3 after sorafenib administration (Table 4). Small increases in the mean AUC and C_{max} values for

Table 3 Numbers of patients with treatment-emergent adverse events including those with a CTCAE worst grade of 3 or 4

Event category	CTCAE term	Cohort 1			Cohort 2		
		(n=6)			(n=7)		
		CTCAE grade			CTCAE grade		
		Any	3	4	Any	3	4
Allergy/immunology	Allergic reaction	2			2		1
Blood/bone marrow	Hemoglobin	2			5	3	
	Leukocytes	5	4		6	3	1
	Lymphopenia	2	2		5	3	1
	Neutrophils	5		4	7		5
	Platelets	3			5	2	1
Cardiac, general	Hypertension	2			2	1	
Constitutional symptoms	Weight loss	1			4	1	
Dermatology/skin	Erythema multiforme	2	2		1		
	Hand-foot skin reaction	3	1		2		
	Rash/desquamation	4			5		
Gastrointestinal	Anorexia	5			6	3	
	Dehydration				2	1	
	Nausea	4			5	1	
	Perforation, GI, small bowel NOS				1		1
Infection	Febrile neutropenia	1	1				
	Infection with G4 neutrophils, lung (pneumonia)				1	1	
Metabolic/laboratory	ALT	3	1	1	1		
	AST	2	1		1		
	Hypokalemia				1	1	
	Hyponatremia				2	2	
	Hypophosphatemia	4	2				
	Lipase	3	2		1		
Neurology	Neuropathy, motor				1	1	
	Neuropathy, sensory	4			6	2	
Pulmonary/upper respiratory	Dyspnea	1			1	1	

CTCAE Common Terminology Criteria for Adverse Events, *GI* gastrointestinal, *NOS* not otherwise specified, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

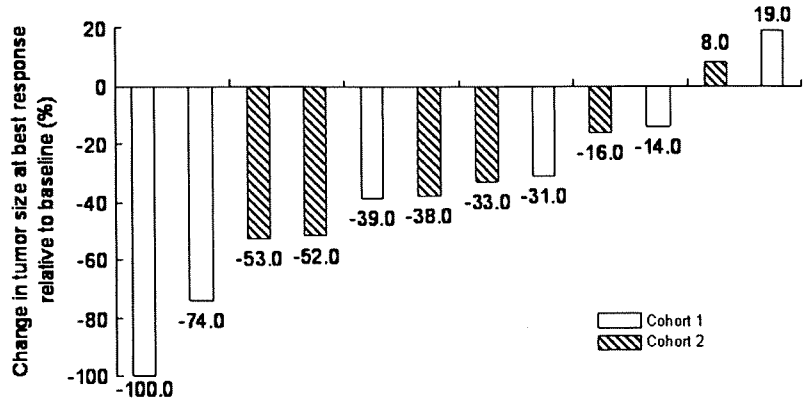

Fig. 2 Tumor response. Ten of the 12 evaluable patients showed tumor shrinkage, with one individual manifesting a complete response (−100%)

Table 4 Pharmacokinetic analysis

Sorafenib	Cohort 1		Cohort 2			
	Cycle 1		Cycle 1		Cycle 2	
	Day 2 400 mg sd (n=6)	Day 19 400 mg bid (n=3)	Day 2 400 mg sd (n=7)	Day 19 400 mg od (n=7)	Day 2 400 mg sd (n=6)	Day 19 400 mg bid (n=4)
AUC_{0-12} (mg h L^{-1})	18.2 (74)	31.3 (32)	9.0 (82)	24.4 (25)	14.6 (25)	39.1 (51)
C_{max} (mg/L)	2.5 (96)	4.6 (36)	1.2 (93)	3.2 (22)	2.0 (21)	5.9 (38)
$t_{1/2}$ (h)		20.4 (18)		26.8 (41)		23.9 (29)

Paclitaxel	Cohort 2		
	Cycle 1 (n=7)	Cycle 2 (n=6)	Cycle 3 (n=4)
AUC (mg h L^{-1})	27889.1 (36)	29538.6 (23)	34712.8 (51)
Ratio [90% CI]		1.05 [0.88–1.25]	1.26 [1.02–1.55]
C_{max} (mg/L)	8016.5 (53)	10076.4 (18)	11218.8 (65)
Ratio [90% CI]		1.19 [0.80–1.77]	1.39 [0.88–2.21]
$t_{1/2}$ (h)	10.7 (10)	11.1 (6)	11.4 (3)

Free platinum	Cohort 2		
	Cycle 1 (n=7)	Cycle 2 (n=6)	Cycle 3 (n=4)
AUC (mg h L^{-1})	44.9 (23)	44.4 (25)	38.5 (10)
Ratio [90% CI]		1.00 [0.91–1.10]	0.90 [0.80–1.00]
C_{max} (mg/L)	17.5 (36)	17.4 (34)	17.5 (9)
Ratio [90% CI]		0.92 [0.82–1.02]	0.97 [0.85–1.11]

Pharmacokinetic parameters are presented as geometric means (% coefficient of variation). Ratios for AUC and C_{max} values of paclitaxel and free platinum are dose-adjusted ratios in cycles 2 or 3 relative to those in cycle 1

sd single dose, *od* once daily, *bid* twice daily, *CI* confidence interval

paclitaxel were observed with progress of the cycles; however, these changes were not significant based on the inclusion of 1.00 in the 90% confidence interval for the ratio of AUC or C_{max} in cycles 2 or 3 to the corresponding value in cycle 1. Similar results were obtained for 6-hydroxy-paclitaxel (data not shown). There were also no significant differences in the mean AUC or C_{max} values of free platinum when standard chemotherapy was administered with or without sorafenib.

Discussion

We have investigated the effects of sorafenib, an oral multikinase inhibitor, in combination with standard chemotherapy (paclitaxel and carboplatin) in chemonaïve individuals with advanced NSCLC. Our results show that sorafenib can be integrated with the combination of paclitaxel and carboplatin. In the present study, the dose of carboplatin had to be capped one dose level lower (AUC of 5 mg min mL^{-1}) than is typical for administration of paclitaxel and carboplatin alone, because four out of six patients developed DLTs in cohort 1.

Two of the patients with DLTs in cohort 1 experienced erythema multiforme of grade 3. Previous studies have reported that most patients receiving sorafenib as monotherapy manifested dermatologic toxicities, mostly of grade 1 or 2, including rash or desquamation (18 to 66%), hand-foot syndrome (25 to 62%), and alopecia (18 to 53%) [15, 21, 22]. Erythema multiforme was reported to occur in only 0.1 to <1% of patients [22, 23]. In the two cases of erythema multiforme in the present study, skin rashes occurred within a week after initiation of sorafenib treatment and spread to the entire body without organ dysfunction. Histopathologic examination of skin specimens supported the diagnosis of erythema multiforme. Steroid treatment and discontinuation of sorafenib resulted in marked improvement of the patients within days. A drug lymphocyte stimulation test was performed for both patients, with the results being positive for sorafenib and

negative for both paclitaxel and carboplatin, suggesting that the exanthematous rashes were caused by drug allergy to sorafenib rather than by dose-dependent toxicity. Indeed, serious erythema multiforme was not observed in any of the seven patients in cohort 2, for whom sorafenib was administered at 400 mg twice daily in cycle 2 and subsequent cycles. The only differences between the treatment regimen in cohort 1 and that of cycle 2 and subsequent cycles in cohort 2 were the dose (AUC) and infusion time of carboplatin, which were 6 mg min mL^{-1} over 30 min and 5 mg min mL^{-1} over 60 min, respectively, and pharmacokinetic analysis revealed that the triplet regimen had no significant effects on the pharmacokinetics of the individual agents. These data thus suggest that the sorafenib-related erythema multiforme observed in cohort 1 was likely the result of classic skin hypersensitivity to the drug.

Two additional DLTs (hand-foot skin reaction and elevation of ALT, both of grade 3) were observed in cohort 1, both of which were manageable and resolved by treatment interruption and remedial therapy. Although the study treatment was discontinued after the first cycle in the four patients with DLTs in cohort 1, one patient showing a partial response received three cycles of carboplatin-paclitaxel-sorafenib and an additional 13 cycles of sorafenib maintenance monotherapy, and another patient showing a complete response received four cycles of the combination therapy and an additional 23 cycles of sorafenib monotherapy. A previous phase I study of sorafenib combined with paclitaxel and carboplatin for advanced solid tumors (mostly malignant melanoma) recommended doses for future trials of sorafenib at 400 mg twice daily, carboplatin at an AUC of 6 mg min mL^{-1}, and paclitaxel at 225 mg/m^2. In a recently completed randomized phase III study of advanced NSCLC, patients were randomly assigned to treatment either with sorafenib at 400 mg twice daily plus carboplatin (AUC of 6 mg min mL^{-1}) and paclitaxel (200 mg/m^2) or with carboplatin and paclitaxel alone [24]. The present study suggests that the dose of sorafenib tolerated by Japanese patients is likely to be lower than that tolerated by Western patients when this agent is combined with standard doses of carboplatin and paclitaxel.

We examined the pharmacokinetics of paclitaxel, carboplatin, and sorafenib in order to detect any relevant drug-drug interactions. The pharmacokinetics of sorafenib in the present combination study were similar to those described in previous monotherapy [7, 17] and combination [16] trials, in which there was no evidence of drug-drug interactions. Neither of the carboplatin doses administered in the present study (AUC of 5 or 6 mg min mL^{-1}) appeared to affect the pharmacokinetics of sorafenib. Furthermore, we have shown for the first time that administration of sorafenib at 400 mg twice daily had no effect on the pharmacokinetics of carboplatin. Whereas small increases in the AUC and C_{max} values of paclitaxel and 6-hydroxy-paclitaxel were observed after sorafenib administration at 400 mg twice daily, these increases were not statistically significant. Paclitaxel is primarily metabolized in the liver by the CYP2C8 pathway to 6-hydroxy-paclitaxel and is also metabolized by CYP3A4 [25]. Although we are not able to exclude possible inhibition by sorafenib of the metabolic clearance of paclitaxel, the observed increase in paclitaxel exposure was not associated with increased clinical toxicity. Together, our pharmacokinetic results suggest that concomitant administration of sorafenib, carboplatin, and paclitaxel had no significant impact on the pharmacokinetics of any of these three drugs in this treatment schedule, although our finding on pharmacokinetics will need to be reproduced in larger cohort of patients treated with this combination.

Although tumor evaluation was not the primary objective of our study, the combination treatment yielded promising results, with one complete response and six partial responses observed among the 12 evaluable patients. Despite this substantial antitumor activity observed in the present study, a phase III trial (ESCAPE: Evaluation of Sorafenib, Carboplatin, and Paclitaxel Efficacy) of 926 patients with advanced NSCLC receiving first-line therapy with paclitaxel and carboplatin in the absence or presence of sorafenib failed to show an improvement in efficacy with the addition of sorafenib to the standard combination chemotherapy [24]. Indeed, a subset analysis of the 219 patients with squamous histology was suggestive of a detrimental effect of sorafenib inclusion. The complete response and all partial responses in our phase I study occurred in patients with non-squamous NSCLC. Although the biological basis for a possible ethnic difference in sorafenib efficacy and toxicity remains unknown, further investigation are warranted to identify the patients who are more likely to benefit from this agent.

In conclusion, in combination with carboplatin AUC 5 mg min mL^{-1} and paclitaxel 200 mg/m^2, administration of sorafenib at 400 mg once daily was confirmed to be feasible in Japanese patients with advanced NSCLC. There was no relevant pharmacokinetic interaction and the observed antitumor activity was encouraging in this study.

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Conflicts of interest Two of the co-authors, Koichi Fukino and Takahiko Tanigawa, are employees of Bayer Yakuhin Ltd.

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Disturbance of the Growth Hormone–Insulin-like Growth Factor-1 Axis Associated with Poor Performance Status in Patients with Solid Tumors

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Objective: Hormonal imbalance characterized by excessive production of growth hormone (GH) and a low circulating concentration of insulin-like growth factor (IGF)-1 has been demonstrated in individuals with various serious conditions. However, little is known about changes in the GH–IGF-1 axis in cancer patients.
Methods: We prospectively examined the circulating levels of several hormones in 58 patients with solid tumors who were classified according to Eastern Cooperative Oncology Group performance status (PS): PS 0–1, $n = 15$; PS 2, $n = 15$; PS 3, $n = 15$; and PS 4, $n = 13$. The relations of hormone concentrations, with a focus on the GH–IGF-1 system, to PS were evaluated by Spearman's rank correlation test and regression analysis.
Results: The circulating levels of IGF-1, IGF-binding protein-3 and thyroid hormones (total T_3 and T_4) were inversely correlated with PS score. The concentration of GH was increased irrespective of PS but not statistically significant. The ratio of IGF-I to GH was inversely correlated with PS. The levels of GH and IGF-1 in all patients were also inversely correlated.
Conclusions: The present study suggests that the GH–IGF-1 axis is disturbed in patients with cancer.

Key words: growth hormone – insulin-like growth factor-1 – performance status

INTRODUCTION

Medical oncology has made substantial advances with the development of new treatment strategies based on a better understanding of cancer biology. Despite such progress, however, a large proportion of individuals with advanced cancer still experience a fatal outcome (1).

Performance status (PS) refers to the level of activity that cancer patients are capable of achieving and is an important prognostic factor independent of the anatomic extent or histological characteristics of cancer (2). After cancer diagnosis, patients will be exposed to the detrimental consequences not only of the cancer itself but also of anticancer treatment. Most patients with advanced cancer thus exhibit a deterioration in PS at some point during the course of their disease. Such a decreased PS is associated with a substantial impairment in quality of life, reduced responsiveness to anticancer therapies and increased mortality. To date, however, an effective treatment for the cancer-related deterioration in PS has not been developed, largely as a result of its multifactorial pathogenesis. New insights into the underlying pathophysiological mechanisms are likely to provide a basis for the development of effective therapeutic strategies to improve the PS of cancer patients.

Hormonal aberrations characterized by excessive production of growth hormone (GH) and a low circulating concentration of insulin-like growth factor (IGF)-1 have been

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detected in patients with diverse conditions including sepsis, burns, renal failure, AIDS and anorexia nervosa as well as in individuals who have undergone surgery (3,4). Such perturbation of the GH–IGF-1 system may contribute adversely to the condition of critically ill patients, and treatments to correct the hormonal imbalance, by administration of GH or IGF-1, have been explored (4,5). Although circulating GH levels have also been found to be increased in individuals with various types of cancers, including those of the colon, lung, breast, liver and endometrium as well as lymphoma (6–12), the influence of cancer on the GH–IGF-1 axis has not been defined. We have now prospectively examined the circulating levels of several hormones in cancer patients with different PS scores and have investigated the relation of changes in hormonal profile, with a focus on the GH–IGF-1 system, to PS.

PATIENTS AND METHODS

Patients with histologically proven cancer were eligible for the study. Other inclusion criteria were an age of at least 20 years and a projected life expectancy of at least 1 month. The main exclusion criteria were blood malignancies or use of corticosteroids. The study subjects were sequentially enrolled in each institution and divided into four groups on the basis of Eastern Cooperative Oncology Group (ECOG) PS score (0–1, 2, 3 or 4), with a targeted accrual of 15 patients in each group. The number of patients enrolled in each group was counted by the patient registration office and feedback to each institution to enroll planned number of patients. Written informed consent was obtained from all patients, and the study protocol was approved by the institutional ethics committee of each of the participating institutions.

Blood samples were once collected for each patient in the early morning before the subjects had had breakfast and after they had fasted overnight or in the morning excluding 1 h after breakfast and 1 h before lunch. This was planned to avoid possible peaks of GH value in the circadian rhythm. Serum and plasma samples were obtained by centrifugation and stored at −20°C until assay. Serum GH and IGF-I levels were determined by solid-phase radioimmunoassay and immune radiometric assay, respectively. Serum triiodothyronine (total T_3), thyroxine (total T_4) and thyroid-stimulating hormone (TSH) levels were determined by electro chemiluminescent immunoassay. Serum concentrations of IGF-binding protein-3 (IGFBP-3) and thyroxine-binding globulin (TBG) were measured by competitive radioimmunoassay. All assays were performed in a blinded manner in the outside laboratory. Other laboratory variables such as total protein, albumin, cholesterol, triglyceride, C-reactive protein, creatinine and hemoglobin as well as markers of liver function were measured in routine hospital tests. Height, weight, body mass index (BMI) and food intake were also recorded for all patients. Primary endpoint of this study was defined as the relation between serum GH levels, IGF-I levels and PS.

Data are presented as means ± SD, and Spearman's rank correlation test was applied to assess the correlation between two variables. A P value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 58 patients (34 men and 24 women) were enrolled in the study at five centers in Japan between January 2005 and March 2006. Median age at enrollment was 64 years (range, 28–81 years). The most frequent principal diagnoses were lung cancer (33%, $n = 19$), gastric cancer (22%, $n = 13$) and colorectal cancer (19%, $n = 11$). The numbers of patients in each PS group at study entry were 15, 15, 15 and 13 for PS 0–1, 2, 3 and 4, respectively. The baseline clinical characteristics of the patients according to the PS group are shown in Table 1. Complete blood test data were available for all patients.

Food Intake, BMI and Laboratory Variables

The Spearman test revealed that PS score was inversely correlated with weight ($r = -0.54$, $P < 0.001$), BMI ($r = -0.53$, $P < 0.001$) and food intake ($r = -0.73$, $P < 0.001$) (Table 2). Inverse correlations were also apparent between PS and circulating levels of total protein ($r = -0.59$, $P < 0.001$), albumin ($r = -0.66$, $P < 0.001$), total cholesterol ($r = -0.33$, $P = 0.014$), choline esterase ($r = -0.61$, $P < 0.001$) and hemoglobin ($r = -0.37$, $P = 0.004$). PS also tended to be positively correlated with levels of alkaline phosphatase ($r = 0.23$) and lactate dehydrogenase ($r = 0.09$), but these relations did not achieve statistical significance. Significant positive correlations were detected between PS and the concentration of C-reactive protein ($r = 0.59$, $P < 0.001$) and the number of white blood cells ($r = 0.42$, $P = 0.001$).

Hormone Levels

The plasma concentration of GH was not significantly correlated with PS ($r = 0.15$, $P = 0.25$), whereas that of IGF-1 was inversely correlated with PS ($r = -0.44$, $P = 0.001$) (Table 3). An inverse correlation was also apparent between PS and the concentration of IGFBP-3 ($r = -0.39$, $P = 0.002$), the major carrier protein for IGF-1 in the circulation. The concentration of GH was inversely correlated with that of IGF-1 ($r = -0.314$, $P = 0.018$). Whereas TSH level was not correlated with PS ($r = 0.04$, $P = 0.76$), the concentrations of total T_3 (-0.57, $P < 0.001$), total T_4 (-0.38, $P = 0.003$) and TBG (-0.44, $P = 0.001$) were inversely correlated with PS. The ratio of IGF-I to GH (IGF-I/GH), a

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combined indicator of GH and IGF-I, also showed correlation with PS ($r = 0.262$, $P = 0.049$) (Table 4).

Table 1. Patient characteristics

	Performance status			
	0–1	2	3	4
Assessable patients	15	15	15	13
Median age (range)	64 (49–73)	66 (50–81)	60 (28–77)	69 (54–81)
Sex (male/female)	11/4	7/8	9/6	7/6
Principal diagnosis				
Lung cancer	9	5	3	2
Gastric cancer	1	3	4	5
Colorectal cancer	2	5	4	0
Esophageal cancer	0	1	1	1
Pancreatic cancer	1	0	0	2
Breast cancer	0	0	1	1
Sarcoma	1	1	0	0
Renal cancer	1	0	0	0
Adenoid cystic cancer	0	0	1	0
Biliary tract cancer	0	0	1	0
Head and neck cancer	0	0	0	1
Cervical cancer	0	0	0	1

DISCUSSION

In this prospective evaluation of hormonal status in cancer patients, we have shown that the circulating levels of thyroid hormones (T_3 and T_4) and of components of the IGF system (IGF-1 and IGFBP-3) were inversely correlated with PS score. Given that the GH concentration also tended to be increased in patients with a high PS score, our results are indicative of an imbalance between GH and the IGF system in such patients.

Increased interpulse levels of GH have been described in critically ill patients including those with several types of cancer (4,13–15). Fasting levels of GH were also found to be significantly greater in patients with colon cancer than in control subjects (2.9 ± 3.1 versus 0.5 ± 0.2 ng/ml) (11). Our data now show a similarly high plasma concentration of GH (3.0 ± 3.7 ng/ml) in cancer patients irrespective of PS, although we did not determine values for matched controls.

Most circulating IGF-1 and IGFBP-3 are synthesized in the liver, where expression of each is increased by GH (Fig. 1). IGF-1 has a long half-life in plasma (up to 12 h), and its circulating level is highly correlated with that of GH. IGFBP-3 binds >95% of plasma IGF-1 and influences cell proliferation by controlling the access of IGF-1 to IGF receptors (16,17). In most instances, the circulating level of IGFBP-3 has been found to correlate with that of IGF-1 and is thought to reflect the status of IGF-1 in plasma. Our prospective data now show that the circulating

Table 2. Laboratory variables stratified by performance status

	Performance status				*P* value
	0–1	2	3	4	
Height (cm)	162 ± 7	158 ± 10	163 ± 9	156 ± 8	NS
Weight (kg)	58 ± 10	53 ± 15	49 ± 10	40 ± 4	<0.001
BMI (kg/m^2)	22 ± 3	21 ± 4	19 ± 4	16 ± 2	<0.001
Food intake (%)	82 ± 25	62 ± 27	27 ± 29	15 ± 19	<0.001
TP (g/dl)	7.1 ± 0.4	6.5 ± 0.4	6.2 ± 0.7	5.8 ± 0.9	<0.001
Albumin (g/dl)	3.9 ± 0.3	3.4 ± 0.5	3.0 ± 0.6	2.4 ± 0.7	<0.001
TC (mg/dl)	180 ± 32	186 ± 53	169 ± 48	125 ± 54	0.014
TG (mg/dl)	126 ± 76	113 ± 51	122 ± 80	88 ± 27	NS
ChE (IU/l)	258 ± 54	178 ± 77	174 ± 82	105 ± 48	<0.001
ALP (IU/l)	450 ± 353	480 ± 344	540 ± 446	741 ± 477	NS
LDH (IU/l)	250 ± 103	256 ± 119	323 ± 265	371 ± 434	NS
Cre (mg/dl)	0.7 ± 0.2	0.6 ± 0.2	0.9 ± 1.2	0.7 ± 0.5	NS
CRP (mg/dl)	0.8 ± 1.0	2.1 ± 2.1	4.6 ± 5.2	10.6 ± 10.5	<0.001
WBC ($10^3/\mu$l)	5.9 ± 1.9	5.3 ± 2.4	8.3 ± 4.8	11.7 ± 6.7	0.001
Hb (g/dl)	12.0 ± 1.6	10.3 ± 1.4	11.5 ± 2.4	9.3 ± 1.7	0.004
Platelets ($10^4/\mu$l)	27.9 ± 7.7	30.6 ± 22.7	25.6 ± 9.5	29.9 ± 12.6	NS

Data are means ± SD. *P* values were determined by Spearman's rank correlation test. NS, not significant; BMI, body mass index; TP, total protein; TC, total cholesterol; TG, triglyceride; ChE, choline esterase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; Cre, creatinine; CRP, C-reactive protein; WBC, white blood cells; Hb, hemoglobin.

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Table 3. Circulating hormone levels according to performance status

	Performance status				*P* value
	0–1	2	3	4	
GH (ng/ml)	2.5 ± 2.4	2.5 ± 3.1	3.1 ± 3.7	4.1 ± 5.5	NS
IGF-1 (ng/ml)	149 ± 49	96 ± 60	135 ± 102	64 ± 42	0.001
IGFBP-3 (μg/ml)	1.9 ± 0.5	1.9 ± 0.8	1.9 ± 0.8	1.0 ± 0.6	0.002
TSH (μIU/ml)	2.6 ± 1.9	2.3 ± 1.8	2.2 ± 1.0	2.5 ± 1.6	NS
Total T_3 (ng/ml)	1.1 ± 0.3	0.9 ± 0.2	0.9 ± 0.2	0.7 ± 0.2	<0.001
Total T_4 (μg/dl)	9.8 ± 1.8	9.8 ± 1.9	9.6 ± 1.6	7.1 ± 2.4	0.003
TBG (μg/ml)	22.3 ± 3.9	24.4 ± 7.0	20.8 ± 4.3	15.7 ± 4.3	0.001

Data are means ± SD. *P* values were determined by Spearman's rank correlation test. GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor-binding protein-3; TSH, thyroid-stimulating hormone; TBG, thyroxine-binding globulin.

Table 4. Ratio of IGF-1 to GH according to performance status

	Performance status				*P* value
	0–1	2	3	4	
IGF-1/GH (ng/ml)	366 ± 645	201 ± 405	185 ± 229	62 ± 98	0.049

Data are means ± SD. *P* values were determined by regression analysis.

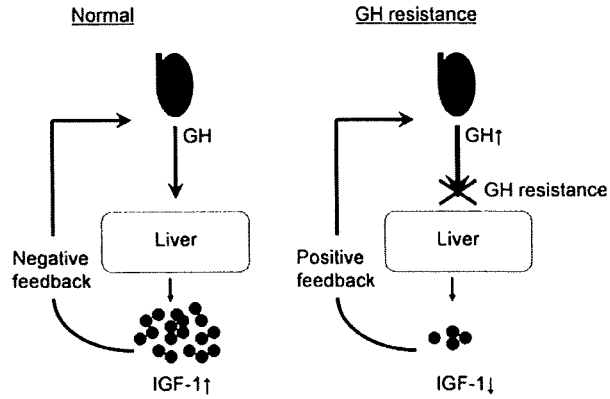

Figure 1. Diagram of the growth hormone (GH) and insulin-like growth factor I (IGF-I) axis in healthy persons (left) and those with acquired GH resistance. Under normal conditions, GH secreted by the pituitary gland stimulates production of IGF-1 by liver. IGF-1 exerts feedback suppression. The primary defect in acquired GH resistance is a reduction in IGF-1 concentration which then leads to increased GH concentration; however, low levels of IGF-1 are not improved, despite increased or normal levels of GH.

concentration of IGF-1 and IGFBP-3 was negatively correlated with PS score but GH did not show clear correlation with PS score. The ratio of IGF-I/GH also showed correlation with PS. These results thus suggest that the relation between GH secretion and circulating IGF-1 levels is disturbed in cancer patients.

Under normal conditions, GH secreted by the pituitary gland induces hepatic IGF-1 production, which in turn exerts feedback suppression of GH secretion (Fig. 1). Acquired GH resistance characterized by the combination of high levels of GH and low levels of IGF-1 has been demonstrated to varying extents in patients with a wide range of conditions including sepsis, trauma, burns, renal failure and AIDS (3,4,18,19). The primary defect in acquired GH resistance is a reduction in IGF-1 concentration which then leads to increased GH concentration; however, low levels of IGF-1 are not improved, despite increased or normal levels of GH (Fig. 1) (3,20). In the present study, a significant inverse correlation was apparent between circulating GH and IGF-1 levels in the entire cohort, consistent with the pattern of acquired GH resistance.

It remains unclear, however, whether the disturbance of the GH–IGF-1 axis is merely a non-specific consequence of cancer or whether it contributes adversely to the complex pathophysiology of cancer. Nutritional state is known to affect the function of the GH–IGF-1 axis. Acute dietary restriction and chronic malnutrition, especially accompanied by severe protein deficiency, have been shown to lead to increased levels of GH and reduced levels of IGF-1 (21,22). In the present study, the circulating concentration of IGF-1 was significantly correlated with BMI ($r = 0.46$, $P < 0.001$), albumin level ($r = 0.41$, $P = 0.002$) and total protein level ($r = 0.36$, $P = 0.007$). The circulating level of GH was negatively correlated with BMI ($r = -0.40$, $P = 0.003$) but was not related to total protein and albumin levels. Patients with lung cancer were previously shown to have a reduced IGF-1 concentration and an increased GH pulse frequency before the development of malnutrition (23). Furthermore, acquired GH resistance in cachectic patients with colorectal cancer has been proposed not to be an adaptation to malnutrition but to be caused by the tumor itself (24). Together, these various observations suggest that although inadequate nutrition is likely to contribute to the altered GH/IGF-I axis in cancer patients, other factors also play a role. It has been shown that in rat hepatocytes in primary culture cytokines, interleukin-1β

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and tumor necrosis factor-α inhibit GH-stimulated IGF-1 synthesis at least partly due to suppression of hepatic GH receptor synthesis (25). Given the significant positive correlation between PS and C-reactive protein observed in the present study, inflammatory cytokine deregulation in cancer patients can participate in the development of acquired GH resistance. Further studies to investigate the mechanism for acquired GH resistance in cancer patients are warranted.

A wide range of conditions sharing the common feature of catabolism exhibit a similar pattern of disturbance of the GH–IGF-1 axis characterized by high GH and low IGF-1 levels (4). Treatment to reverse this defect by restoring IGF-1 levels through administration of GH has been shown to result in improvement in metabolic parameters and to provide clinical benefit in well-defined groups of patients, such as those with AIDS or anorexia nervosa (4,26). On the other hand, a small pilot study with 10 terminally ill cancer patients showed that GH administration for 3 days had limited effects on metabolic parameters (23). Given that the various conditions associated with acquired GH resistance have different pathophysiological mechanisms, GH administration in cancer patients may not necessarily be clinically beneficial.

In conclusion, the results of the present study show that the GH–IGF-1 system is disturbed in cancer patients and that this anomaly may play a role in the deterioration of PS. Therapeutic strategies for correcting this hormonal imbalance merit investigation. Such approaches may alleviate the cachexia and malaise associated with cancer.

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Conflict of interest statement

None declared.

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Original Article

Cisplatin and Etoposide Chemotherapy Combined with Early Concurrent Twice-daily Thoracic Radiotherapy for Limited-disease Small Cell Lung Cancer in Elderly Patients

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Objective: The optimal management of elderly patients with limited-disease small cell lung cancer (LD-SCLC) has not been established.
Methods: The records of elderly (≥70 years of age) patients with LD-SCLC who had been treated with etoposide and cisplatin chemotherapy with early concurrent twice-daily thoracic radiotherapy (TRT) were reviewed retrospectively.
Results: Of the 25 elderly patients with LD-SCLC identified, 12 (48%) individuals received etoposide–cisplatin chemotherapy with early concurrent twice-daily TRT. The main toxicities of this treatment regimen were hematologic, with neutropenia of Grade 4 being observed in all patients and febrile neutropenia of Grade 3 in eight patients during the first cycle of chemoradiotherapy. The toxicity of TRT was acceptable, with all patients completing the planned radiotherapy within a median of 29 days (range, 19–33). No treatment-related deaths were observed. The median progression-free survival and overall survival times were 14.2 months (95% confidence interval, 4.3–18.2) and 24.1 months (95% confidence interval, 11.3–27.2), respectively.
Conclusions: Etoposide–cisplatin chemotherapy with early concurrent twice-daily TRT was highly myelotoxic in elderly patients with LD-SCLC, although no treatment-related deaths were observed in our cohort. Prospective studies are required to establish the optimal schedule and dose of chemotherapy and TRT in such patients.

Key words: elderly – small cell lung cancer – chemoradiotherapy – cisplatin – etoposide – concurrent thoracic radiotherapy

INTRODUCTION

Small cell lung cancer (SCLC) accounts for 10–15% of all lung cancer cases, with individuals aged 70 years or older constituting up to 25–40% of the SCLC patients (1,2). Limited-disease (LD) SCLC is a disease that is confined to one hemithorax and its regional lymph nodes and which can be encompassed by a single radiation therapy port. About 30–40% of all SCLC patients present with LD-SCLC (1,2). The proportion of elderly SCLC patients continues to increase with the growing geriatric population (1,3).

The combination of radiotherapy and chemotherapy, specifically etoposide and cisplatin chemotherapy with early concurrent twice-daily thoracic radiotherapy (TRT), is now regarded as the standard treatment for LD-SCLC (4). However, many clinical trials of potential new treatments for LD-SCLC have excluded elderly patients for various reasons, such as the presence of concomitant chronic illness,

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a decline in organ function that may interfere with drug clearance and possible decreased bone marrow tolerance to myelosuppressive agents (5). The optimal management of elderly patients with LD-SCLC has therefore not been defined to date.

We have now performed a retrospective analysis to evaluate patient characteristics as well as treatment delivery, toxicity and antitumor efficacy for elderly individuals (70 years or older) with LD-SCLC who were treated with etoposide and cisplatin chemotherapy and early concurrent twice-daily TRT.

PATIENTS AND METHODS

We retrospectively evaluated the records of elderly (≥70 years) patients with LD-SCLC who were treated at Kinki University School of Medicine from January 2003 to December 2008. All patients had a pathological diagnosis of SCLC. LD-SCLC was defined as cancer that is confined to one hemithorax including contralateral mediastinal and hilar lymph nodes as well as ipsilateral or bilateral supraclavicular lymph nodes, but excluding malignant pleural effusion. Response evaluation was assessed after completion of treatment on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST). Laboratory testing and toxicities were graded weekly during the whole treatment according to the National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3). Progression-free survival time was measured from the date of initiation of treatment to the date of disease progression. Overall survival time was measured from the date of initiation of treatment to death or to the time that the patient was last known to be alive. After completion of all treatment, patients were followed up at 1- to 2-month intervals until the time of progression or death. Median progression-free survival time and overall survival time were estimated by the Kaplan–Meier method.

RESULTS

Patient Characteristics

Of the 170 SCLC patients treated between 2003 and 2008, 48 individuals were diagnosed with LD-SCLC and 25 of these individuals were 70 years of age or older. Among these 25 patients, 12 (48%) elderly patients with LD-SCLC received etoposide and cisplatin chemotherapy with early concurrent twice-daily TRT. The characteristics of these 12 patients are shown in Table 1. They included eight men and four women as well as seven individuals aged between 70 and 74 years and five aged 75 years or older. All the patients were in good general condition, although they had some complications. The remaining 13 patients' characteristics are shown in Table 2. Two of the 13 elderly patients with LD-SCLC were treated with chemotherapy and sequential TRT, and 1 patient was treated with etoposide–carboplatin and concurrent TRT. Chemotherapy alone was administered in 4 of the 13 patients. Two patients were subjected to surgery followed by chemotherapy. Four patients did not receive intensive therapy.

Treatment Delivery

The treatment plan consisted of an initial cycle of concurrent chemoradiotherapy followed by three cycles of consolidation chemotherapy (Table 3). All patients received the same chemotherapy regimen of cisplatin at 40–80 mg/m^2 on day 1 combined with etoposide at 80–100 mg/m^2 on days 1–3.

Table 1. Characteristics of the study cohort

Patient	Age/sex	TNM stage	PS	Complications	Smoking history
1	70/M	T2N1M0	1	HT	20/day × 50 years
2	70/M	T3N1M0	0	Berger disease, old TB	40/day × 50 years
3	71/M	T3N2M0	0	DM, bladder cancer	20/day × 50 years
4	71/M	T1N2M0	1	Harada disease	20/day × 50 years
5	72/F	T2N2M0	1	HT, old TB, asthma, one kidney	20/day × 35 years
6	72/M	T1N2M0	0	HT, hyperlithuria	10/day × 50 years
7	73/M	T1N2M0	1	HT	25/day × 60 years
8	76/M	T2N1M0	0	None	20/day × 50 years
9	77/F	T3N0M0	1	Deafness	15/day × 57 years
10	78/M	T3N0M0	0	DM, ASO, old TB	20/day × 58 years
11	79/F	T2N2M0	1	None	None
12	79/F	T1N2M0	0	HT	5/day × 50 years

PS, Eastern Cooperative Oncology Group performance status; HT, hypertension; TB, tuberculosis; DM, type 2 diabetes mellitus; ASO, arteriosclerosis obliterans.

Table 2. Characteristics of patients who did not received EP with concurrent TRT

Patient	Age/sex	TNM stage	PS	Complications	Treatment	Reason[a]
1	70/M	T4N2M0	1	HT, renal dysfunction	CE and sequential TRT	Complication
2	70/M	T1N0M0	1	HT, DM	Surgery	Physician's decision
3	71/M	T3N2M0	1	HT	Best supportive care	Patient's refusal
4	72/M	T2N1M0	1	DM, renal dysfunction	CE and concurrent TRT	Complication
5	74/M	T3N2M0	1	HT, renal dysfunction	CE and sequential TRT	Complication
6	74/M	T2N1M0	2	DM, IP, chronic renal failure, dialysis, old TB	Chemotherapy	Complication
7	75/M	T3N2M0	3	HCC, chronic HCV	Best supportive care	Complication
8	77/M	T2N1M0	2	renal dysfunction, dementia	Chemotherapy	Complication
9	78/M	T1N1M0	1	SSS, HT, DM	Chemotherapy	Physician's decision
10	81/M	T2N2M0	1	renal dysfunction	Chemotherapy	Patient's refusal
11	82/M	T1N2M0	1	HT	Surgery	Physician's decision
12	84/M	T2N0M0	2	HT	Best supportive care	Patient's refusal
13	84/M	T2N0M0	2	HT, asthma, heart failure, cerebral infarction	Best supportive care	Complication

EP, etoposide and cisplatin; TRT, thoracic radiotherapy; CE, carboplatin and etoposide; IP, interstitial pneumonia; HCC, hepatic cancer; HCV, hepatitis C virus; SSS, sick sinus syndrome.
[a]The reason for not to select the combination therapy of etoposide and cisplatin with early concurrent TRT.

Twice-daily TRT was performed with X-rays at 6–10 MV and with an interval of at least 6 h and a total dose of 45 Gy (1.5 Gy bid) over 3 weeks. TRT was initiated on day 1 of the first cycle of chemotherapy. All patients completed the TRT protocol, with the days of irradiation ranging from 19 to 33 (median of 29). Reasons for a delay in TRT included febrile neutropenia of Grade 3 in eight patients and leukopenia of Grade 4 in three patients. All patients proceeded to consolidation chemotherapy. However, five patients (42%) did not complete the planned three cycles of consolidation chemotherapy because of the development of pneumonitis of Grade 3 in one patient, a decline in renal function in one patient, suspected invasive aspergillosis in one patient and refusal by two patients. A dose reduction was necessary in seven patients because of the development of febrile neutropenia of Grade 3 in three patients, leukopenia of Grade 4 in two patients and nausea–vomiting of Grade 3 in two patients. The actual dose intensities of cisplatin and etoposide were 13.7 mg/m^2/week (68.7% of the planned dose intensity) and 52.4 mg/m^2/week (69.9% of the planned dose intensity), respectively.

Toxicities

Reported toxicities during the concurrent chemoradiotherapy are listed in Table 4. Leukopenia and neutropenia of Grade 3 or 4 were observed in all patients (100%), and eight patients (67%) had febrile neutropenia of Grade 3. Thrombocytopenia of Grade 3 or 4 was apparent in three patients (25%), with one patient requiring platelet transfusion. Reported toxicities during the consolidation chemotherapy are listed in Table 5. Leukopenia and neutropenia of Grade 3 or 4 were observed in 8 (67%) and 11 (92%) patients, respectively, and 4 patients (33%) developed febrile neutropenia of Grade 3. Anemia and thrombocytopenia of Grade 3 or 4 were each observed in four patients (33%). The major non-hematologic toxicity observed during the entire treatment period was nausea–vomiting. None of the patients developed esophagitis of Grade 3 or 4, but one patient manifested radiation pneumonitis of Grade 3 during consolidation chemotherapy. There were no treatment-related deaths.

Response and Survival

All 12 patients were evaluated for progression-free survival and overall survival. With a median follow-up time of 23.1 months (ranged, 7.2–45.0 months), six patients were still alive. An objective tumor response was observed in all patients: a complete response (CR) in five patients and a partial response in seven patients (Table 3). Prophylactic cranial irradiation was not routinely administered and delivered to three patients who achieved CR after completion of the planned treatment. The median progression-free survival time was 14.2 months, and the median overall survival time was 24.1 months.

Pattern of Relapse

Seven of the 12 patients relapsed, 3 with local regional failure inside the radiation field and 4 with distant failure. Among the latter four patients, three individuals manifested metastases in the brain as the sole site and the remaining individual had both local and distant failure including the liver.