Int J Hematol (2010) 92:111–117
DOI 10.1007/s12185-010-0621-x

ORIGINAL ARTICLE

Imatinib for newly diagnosed chronic-phase chronic myeloid leukemia: results of a prospective study in Japan

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Received: 22 December 2009 / Revised: 7 May 2010 / Accepted: 31 May 2010 / Published online: 25 June 2010

Abstract Although imatinib has become the current standard treatment for chronic myeloid leukemia (CML), there is limited information regarding its efficacy and safety among Japanese patients. We therefore conducted a prospective multi-center open-label study of imatinib for Japanese patients with newly diagnosed chronic-phase CML (CP-CML). A total of 107 patients were enrolled and treated with imatinib at an initial daily dose of 400 mg. Eighty-three patients completed 3 years of study treatment. The cumulative rates of major cytogenetic response and complete cytogenetic response (CCyR) were 90.9 and 90.2% at 3 years, respectively. The safety profile was not very different from that reported in the IRIS study, although grade ≥3 neutropenia occurred relatively frequently (31.8 vs. 14.3%). Only seven patients discontinued the study due to adverse events, as did four patients due to

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insufficient efficacy. The 3-year probabilities of overall survival and progression-free survival were 93.2 and 91.4%, respectively. Higher average daily doses (i.e., ≥350 mg) were significantly associated not only with higher rates of achieving CCyR, but also with longer duration of CCyR. These findings confirm the clinical utility of imatinib in Japanese patients with newly diagnosed CP-CML, and suggest detrimental effect of low average daily dose on treatment results.

Keywords Chronic myeloid leukemia · Chronic phase · Newly diagnosed · Imatinib

1 Introduction

Imatinib is a molecule-targeting drug that inhibits BCR-ABL tyrosine kinase and exerts a selective proliferation-inhibitory effect in chronic myeloid leukemia (CML) [1, 2]. Several international trials have documented excellent clinical efficacy of imatinib in patients with chronic-phase CML (CP-CML) [3–5], as well as in patients in accelerated phase (AP) [6] and blast crisis (BC) [7]. Based on those studies along with Japanese phase I and phase II studies [8], imatinib was approved in Japan in November 2001, and has been available in clinical practice since December 2001. However, there is very limited information regarding efficacy and safety of imatinib among Japanese patients. We therefore conducted a post-marketing study to confirm clinical utility of imatinib in Japanese patients with newly diagnosed CP-CML.

2 Patients and methods

2.1 Study design

This was a prospective, multi-center, non-controlled study to evaluate efficacy and safety of imatinib in Japanese patients 15–74 years of age with Philadelphia chromosome positive (Ph+) CP-CML. Eligible patients were those with Eastern Cooperative Oncology Group performance status 0–3 who had been previously untreated with interferon (IFN) or imatinib. Patients were excluded if serum bilirubin or serum creatinine levels were ≥3 times the upper limit of the normal range, if serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels were ≥5 times the upper limit of the normal range, if they received hydroxycarbamide within a week prior to enrollment or any other antileukemic drug within 2 weeks, or if there was any evidence of AP or BC in association with any of the following conditions: ≥15% blasts in the peripheral blood or bone marrow; ≥30% blasts plus promyelocytes in the peripheral blood or bone marrow; ≥20% basophils in the peripheral blood; or extramedullary leukemic infiltrates with the exception of spleen or liver. Women who were pregnant or possibly pregnant were also excluded.

Patients were treated with imatinib at a daily dose of 400 mg. Dose escalation to 600 mg was implemented if they had failed to achieve complete hematologic response (CHR) at 3 months or major cytogenetic response (MCyR) at 6 months. If the patient had failed to achieve MCyR at 9 months, IFN was started at a daily dose of 300 million unit per body two or three times a week while on imatinib. Dose modification of imatinib was generally based on the following guidelines. For grade ≥3 liver dysfunction (elevated bilirubin, AST, or ALT), administration was interrupted until recovery to grade <2, and then resumed at 300 mg/day. For grade ≥3 neutropenia or thrombocytopenia, administration was interrupted until recovery to grade <2, and then resumed at 400 mg/day. If grade ≥3 toxicity recurred after resuming, dose reduction to 300 mg/day was implemented. The study was discontinued in the event of failure to achieve CHR at 6 months, intolerance to imatinib, disease progression to AP or BC, death, patient request, and lost to follow-up, or at the discretion of the investigator. Patients were followed up to 3 years from the day of starting imatinib.

2.2 Endpoints

The primary endpoints were overall survival (OS) and progression-free survival (PFS). OS was defined as the time from the day of first dose of imatinib to death or last follow-up, and PFS was defined as the time from the day of first dose of imatinib to progression to AP or BC, death or last follow-up. Secondary endpoints were hematologic, cytogenetic and molecular response, and adverse events. Cytogenetic response was assessed by using bone marrow cells every 3 months until 12 months and every 6 months thereafter until 36 months. Complete cytogenetic response (CCyR) was defined as complete disappearance of the Philadelphia chromosome. MCyR was defined as decrease in Philadelphia chromosome to 35% or lower. Adverse events were assessed according to the National Cancer Institute Common Toxicity Criteria version 2.0.

Cumulative rates of hematologic and cytogenetic response, PFS, event-free survival (EFS), and OS were evaluated in accordance with the IRIS study reports [3, 9]. EFS was defined as the time from the day of first dose of imatinib to death, progression to AP or BC, loss of CHR, loss of MCyR, increase in white blood cell count to 20000/μL, or last follow-up.

This study was conducted in compliance with the Declaration of Helsinki and was approved by local Institutional Review Boards. All patients provided written informed consent prior to initiation of study medication.

2.3 Statistical methods

OS, PFS, and EFS were estimated by using the Kaplan–Meier method. Efficacy endpoints were compared by patient age (≥60 years and <60 years), and by average daily dose of imatinib (i.e., ≥350 mg/day, 250 to <350 mg/day and <250 mg/day). The Wilcoxon two-sample test was used to compare the average daily dose between the age groups. In patients who had achieved CCyR, CCyR duration was compared by average daily dose of imatinib after achieving CCyR. Average daily dose was calculated as cumulative dosage divided by the total days on study.

3 Results

3.1 Patients

A total of 107 patients were enrolled in the study between November 2002 and June 2004, and administered imatinib. All patients were evaluable for efficacy and safety, and the median duration of imatinib exposure was 1091 days (range, 82–1156 days). Among these patients, 83 completed 3 years of study treatment, whereas 24 discontinued the study due to adverse events ($n = 7$), withdrawal of consent ($n = 5$), insufficient efficacy ($n = 4$), allogeneic bone marrow transplantation ($n = 4$), and other reasons ($n = 4$). Demographic characteristics of patients in the full analysis set are summarized in Table 1. The median age was 47 years (range, 16–74 years), with 71 males and 36 females. Prior therapies for CML included hydroxycarbamide ($n = 7$), and leukapheresis ($n = 1$). The median time from diagnosis of CML to initiation of imatinib was 8.0 days (range, 1–1526 days).

The initial dose of imatinib was 400 mg/day for all patients. The mean (±standard deviation) dose administered during the study was 343 (±90) mg/day. Dose modification was required in 70.1% of patients mainly due to adverse events. Details of dose modification are summarized in Table 2. There were no patients in whom IFN was added to imatinib. Average daily doses were ≥350 mg, 250 to <350 mg, and <250 mg in 68 (63.6%), 21 (19.6%) and 18 patients (16.8%), respectively. As shown in Table 3, the percentage of patients who continued imatinib at 400 mg/day without any dose modification was 48.6% during week 1–13, 57.5% during week 14–26, and was around 60% thereafter.

3.2 Treatment results

The cumulative rate of CHR was 99.1% at 1 year, and the cumulative rates of MCyR and CCyR were 90.9 and 90.2% at 3 years, respectively (Fig. 1). The median time to CHR

Table 1 Patient characteristics

Characteristics	Category	Number of patients
Total number of subjects		107
Sex	Male	71 (66.4)
	Female	36 (33.6)
Age	10s	4 (3.7)
	20s	10 (9.3)
	30s	24 (22.4)
	40s	18 (16.8)
	50s	26 (24.3)
	60s	19 (17.8)
	70s	6 (5.6)
	Mean ± SD	47.1 ± 14.7
	Minimum–maximum	16–74
	Median	47.0
Body weight	40 to <50 kg	13 (12.1)
	50 to <60 kg	34 (31.8)
	60 to <70 kg	40 (37.4)
	70 to <80 kg	13 (12.1)
	80 to <90 kg	5 (4.7)
	≥90 kg	2 (1.9)
	Mean ± SD	61.66 ± 10.88
	Minimum–maximum	43.0–103.0
	Median	61.50
Body surface area	1.2 to <1.4 m^2	5 (4.7)
	1.4 to <1.6 m^2	31 (29.0)
	1.6 to <1.8 m^2	53 (49.5)
	1.8 to <2.0 m^2	15 (14.0)
	≥2.0 m^2	3 (2.8)
	Mean ± SD	1.6705 ± 0.1670
	Minimum–maximum	1.307–2.151
	Median	1.6800
Previous CML therapy	No	99 (92.5)
	Yes	8 (7.5)
	Hydroxycarbamide	7 (6.5)
	Leukapheresis	1 (0.9)
ECOG performance status	0	95 (88.8)
	1	10 (9.3)
	2	2 (1.9)
Time elapsed from the first day of CML diagnosis to the start of study treatment	<4 weeks	92 (86.0)
	4 to <13 weeks	14 (13.1)
	≥52 weeks	1 (0.9)
	Mean ± SD	27.0 ± 146.9
	Minimum–maximum	1–1526
	Median	8.0

Values within parenthesis are given in percentage

SD standard deviation, *CML* chronic myeloid leukemia, *ECOG* Eastern Cooperative Oncology Group

and CCyR were 92.5 days (range, 75–207 days) and 179.5 days (range, 70–589 days), respectively. In 92 patients who had achieved CCyR, 77 patients remained in CCyR until the end of 3 years of imatinib treatment. All of the 15 patients who hadn't achieved CCyR discontinued the study. Among them, 4 patients progressed to AP or BC, and 5 patients proceeded to hematopoietic stem cell transplantation.

Of 107 patients, progression to AP or BC and death occurred in nine and seven patients, respectively. One death, which was because of pneumonia, was reported during the study and the remaining six deaths were reported after patients discontinued the study. The probabilities of OS, PFS and EFS at 3 years were 93.2% [95% confidence interval (CI) 88.3–98.1%), 91.4% (95% CI 86.1–96.8%), and 81.9% (95% CI 74.6–89.3%), respectively (Fig. 2).

3.3 Response and survival by average daily dose

Next, we evaluated cumulative CCyR rate, OS, PFS, and EFS according to the average daily dose of imatinib (≥350 mg/day, 250 to <350 mg/day, and <250 mg/day). As shown in Figs. 3, 4, CCyR and EFS were significantly associated with the average daily dose ($p < 0.001$, respectively). In particular, patients with the average daily dose <250 mg had low rates of CCyR and EFS. CCyR duration was also significantly different according to the average daily dose ($p < 0.001$, Fig. 5). OS and PFS seemed lower in those with lower average daily dose, although the differences did not reach statistical significance.

The average daily doses were significantly different by age group, with 360 (±81) mg in patients aged <60, and 287 (±97) mg in patients aged ≥60 years ($p < 0.001$). Patients aged <60 had statistically non-significant better EFS than those aged ≥60 years (85.3 vs. 70.6% at 3 years, $p = 0.101$). In terms of OS or PFS, there were no significant differences between the age groups.

Table 2 Summary of dose modification

	n	%
No dose change	32	29.9
Dose change	75	70.1
Reduction only	7	6.5
Reduction and interruption	43	40.2
Reduction and increase	1	0.9
Increase only	1	0.9
Increase and interruption	4	3.7
Interruption only	19	17.8
Total	107	100.0

3.4 Adverse events

Adverse events were reported in all of the 107 patients. Serious adverse events which developed in ≥2 patients included neutropenia ($n = 4$), blast crisis ($n = 3$), anemia, intestinal obstruction, gastric antral vascular ectasia, appendicitis, herpes zoster, thrombocytopenia, and leukocytopenia ($n = 2$, each). Grade ≥3 adverse events were reported in 31 patients (29.0%, 47 episodes). As listed in Table 4, grade ≥3 adverse events reported in >5% of patients were neutropenia (31.8%), leukocytopenia (19.6%), lymphocytopenia (17.8%), thrombocytopenia (14.0%), and rash (8.4%). When frequencies of adverse events were compared between this study and the IRIS study [3], nasopharyngitis, rash, upper respiratory tract infection, pyrexia, and grade ≥3 neutropenia seemed more frequent, while nausea, muscle cramp, joint pain seemed less frequent in our study.

4 Discussion

Although it is widely accepted that imatinib is the standard treatment for CP-CML, published experiences of imatinib

Table 3 Average daily dose of imatinib over time

Week:	1–13		14–26		27–39		40–52		53–78		79–104		105–130		131–156	
No. of patients (*n*):	107		106		102		95		92		90		88		88	
Average daily dose (mg)	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
<200	3	2.8	12	11.3	9	8.8	7	7.4	6	6.5	4	4.4	3	3.4	1	1.1
200 to <300	24	22.4	16	15.1	11	10.8	7	7.4	9	9.8	9	10.0	9	10.2	14	15.9
300 to <350	13	12.1	12	11.3	14	13.7	18	18.9	12	13.0	12	13.3	16	18.2	12	13.6
350 to <400	15	14.0	4	3.8	4	3.9	0	0.0	5	5.4	5	5.6	4	4.5	6	6.8
400	52	48.6	61	57.5	61	59.8	61	64.2	58	63.0	58	64.4	54	61.4	52	59.1
>400	0	0.0	1	0.9	3	2.9	2	2.1	2	2.2	2	2.2	2	2.3	3	3.4

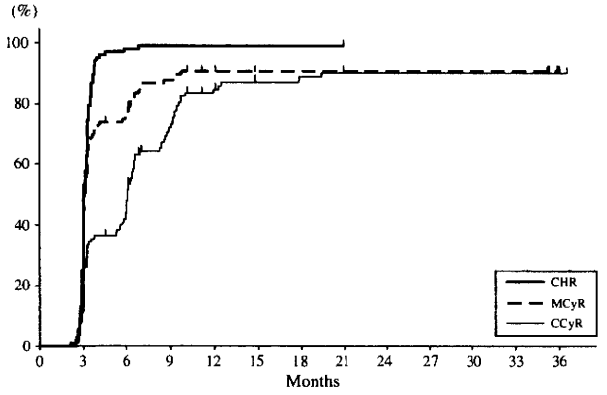
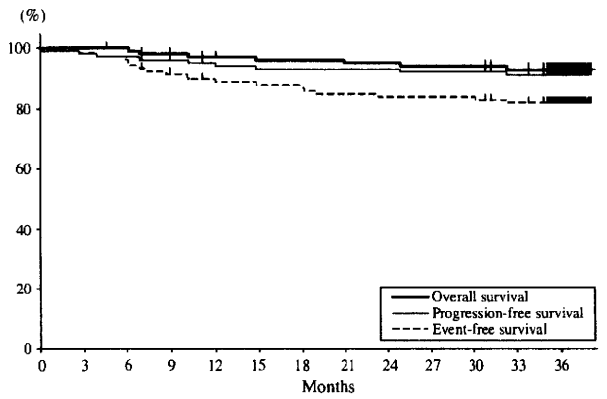


Fig. 1 Kaplan–Meier curves of cumulative rates of complete hematologic response (*CHR*), major cytogenetic response (*MCyR*) and complete cytogenetic response (*CCyR*)



	No. of Events	Estimated 3-year rate (%)
OS	7	93.2
PFS	9	91.4
EFS	19	81.9

Fig. 2 Kaplan–Meier curves of overall survival, progression-free survival and event-free survival of all patients

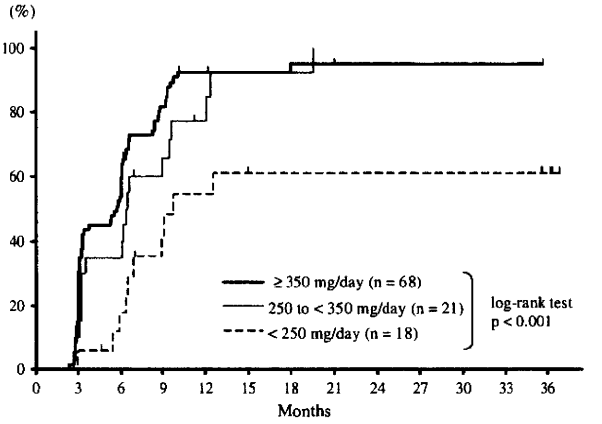


Fig. 3 Kaplan–Meier curves of cumulative rates of complete cytogenetic response (CCyR) by average daily dose of imatinib

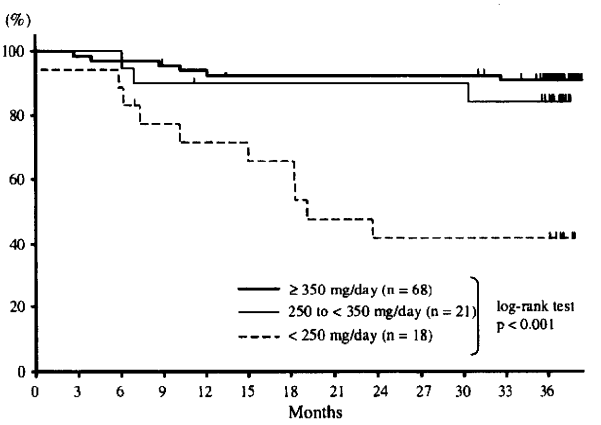


Fig. 4 Kaplan–Meier curves of event-free survival by average daily dose of imatinib

in Japanese patients are limited [8, 10–16]. Under such circumstances, a nationwide registration system for CML has been established by the Japanese Society of Hematology since 2003, and early results were published [15]. To further clarify the clinical utility of imatinib among Japanese patients, we conducted a prospective study of imatinib in 109 patients with newly diagnosed CP-CML. MCyR and CCyR rates at 12 months were 90.9 and 84.8%, which were comparable or even superior to those in the IRIS study (85 and 69%, respectively) [9]. Likewise, long-term outcomes were not different between both studies, because the OS rate in our study was 93.2% at 3 years, whereas, in the IRIS study, it was reported to be 97.2% at 18 months and 89% at 5 years [3, 9]. The safety profile observed in our study was almost comparable with that of the IRIS study, although grade ≥3 neutropenia occurred relatively frequently in our study than in the IRIS study (31.8 vs. 14.3%), while the incidences of neutropenia of all grades were not different (53.3% in our study versus 60.8% in the IRIS study). In both studies, imatinib was initiated at a daily dose of 400 mg and interrupted in the event of grade ≥3 neutropenia or thrombocytopenia until the toxicity resolved to grade <2. The reason for this observation was not clear; however, the finding that only seven of our patients discontinued the study due to adverse events showed feasibility of the treatment. Some non-hematological adverse events like nausea, muscle cramp, and joint pain were less frequent in Japanese than in Caucasians. These efficacy and safety results, taken together, confirmed the clinical utility of imatinib in Japanese patients with newly diagnosed CP-CML.

Based upon observations in a relatively small number of Japanese patients, some authors have suggested the possibility that the daily dose of imatinib could be reduced to less than 400 mg without significant disadvantage, partly

due to smaller body size as compared with Caucasians [12, 13]. Analyses of cumulative rate of CCyR and EFS by average daily dose in our study showed that patients given higher average daily doses of imatinib (≥350 mg) not only achieved higher CCyR rate but also had longer CCyR duration than those given lower average daily doses. EFS was also superior among patients who were treated with higher average daily doses of imatinib. Matsuo et al. [10] reported similar findings of a clear dose–response relationship between imatinib daily dose and treatment results. In that study, CCyR rate at 30 months was higher in patients receiving daily dose of imatinib >300 mg than in those receiving 250–300 mg, or <250 mg. Sugita et al. [16] also reported that mean daily doses of ≥300 mg led to higher CCyR rate, longer CCyR duration, and improved OS as compared to 200–300 mg. These results, taken together, suggest detrimental effect of low average daily dose on treatment results. Our observation that EFS was relatively lower in patients aged ≥60 years than in those aged <60 years might be explained partly by the difference in the average daily dose. To achieve and maintain better response, it would be beneficial to avoid excessive dose

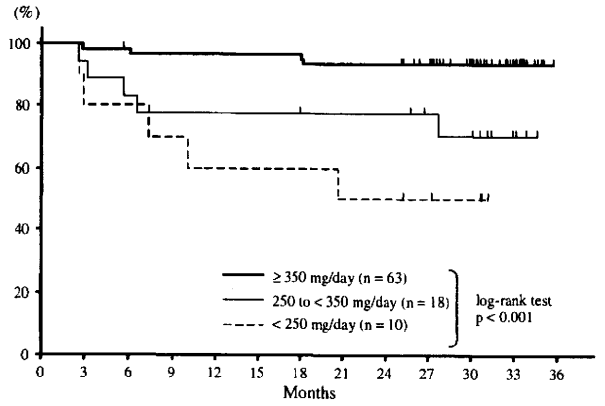


Fig. 5 Kaplan–Meier curves of duration of complete cytogenetic response (CCyR)

Table 4 Comparison of adverse events between this study and the IRIS study

	This study (n = 107)				IRIS study (n = 533) [3]			
	All grades		Grade 3/4		All grades		Grade 3/4	
	n	%	n	%	n	%	n	%
Hematological								
Neutropenia	57	53.3	34	31.8	324	60.8	76	14.3
Leukocytopenia	51	47.7	21	19.6	NR	NR	NR	NR
Lymphocytopenia	48	44.9	19	17.8	NR	NR	NR	NR
Thrombocytopenia	44	41.1	15	14.0	302	56.6	42	7.8
Anemia	33	30.8	3	2.8	238	44.6	17	3.1
Nonhematological								
Surficial edema	71	66.4	0	0.0	296	55.5	5	0.9
Nasopharyngitis	70	65.4	0	0.0	117	22.0	0	0.0
Rash	64	59.8	9	8.4	181	33.9	11	2.0
Diarrhea	44	41.1	3	2.8	175	32.8	10	1.8
Gastroenteritis	37	34.6	3	2.8	NR	NR	NR	NR
Nausea	35	32.7	0	0.0	233	43.7	4	0.7
Malaise	29	27.1	0	0.0	184	34.5	6	1.1
Myalgia	27	25.2	2	1.9	114	21.4	8	1.5
Upper respiratory tract infection	27	25.2	0	0.0	77	14.5	1	0.2
Muscle cramps	26	24.3	0	0.0	204	38.3	7	1.3
Pyrexia	26	24.3	0	0.0	70	13.1	4	0.7
Headache	23	21.5	0	0.0	166	31.2	2	0.4
Dizziness	17	15.9	0	0.0	77	14.5	5	0.9
Vomiting	16	15.0	0	0.0	90	16.9	8	1.5
Joint pain	14	13.1	0	0.0	151	28.3	13	2.4
Cough	13	12.1	0	0.0	77	14.5	1	0.2
Anorexia	11	10.3	0	0.0	28	5.3	0	0.0
Pruritus	11	10.3	0	0.0	39	7.3	1	0.2

NR not reported

reduction and interruption with careful monitoring of safety in individual patients. A similar concept was advocated by a study reported by Kanda et al. [14].

In summary, this prospective study confirmed remarkable efficacy and safety of imatinib in Japanese patients with newly diagnosed CP-CML. It also suggested a clear relationship between higher daily doses of imatinib (i.e., $\geq$350 mg) and better treatment results.

Acknowledgments This study was sponsored by Novartis Pharma K.K. Contributing Investigators: Junji Tanaka, Hokkaido University Hospital; Koumei Kubo, Aomori Prefecture Central Hospital; Shuichi Taniguchi, Toranomon Hospital; Nobuaki Dobashi, Jikei University Hospital; Yasushi Isobe, Juntendo University School of Medicine; Jin Takeuchi, Nihon University Itabashi Hospital; Toshiko Motoji, Tokyo Women's Medical University; Masaaki Higashihara, Kitasato University Hospital; Tadashi Nagai, Jichi Medical University Hospital; Norifumi Tsukamoto, Gunma University Hospital; Chiaki Nakaseko, Chiba University Hospital; Kazuhiro Nishii, Mie University Hospital; Kazunori Ohnishi, Hamamatsu University School of Medicine, University Hospital; Yasuo Morishima, Aichi Cancer Center Hospital; Hitoshi Kiyoi, Nagoya University Hospital; Koji Ezaki, Fujita Health University; Yuzuru Kanakura, Osaka University Hospital; Akira Hiraoka, Osaka Medical Center for Cancer and Cardiovascular Diseases; Chihiro Shimazaki, University Hospital, Kyoto Prefectural University of Medicine; Masaya Okada, the Hospital of Hyogo College of Medicine; Shinji Nakao, Kanazawa University Hospital; Katsuji Shinagawa, Okayama University Hospital; Yasushi Miyazaki, Nagasaki University Hospital; Koji Nagafuji, Kyushu University Hospital.

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Cancer Science

Phase II study of erlotinib plus gemcitabine in Japanese patients with unresectable pancreatic cancer

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(Received April 1, 2010/Revised October 16, 2010/Accepted November 11, 2010/Accepted manuscript online November 26, 2010)

Erlotinib combined with gemcitabine has not been evaluated in Japanese patients with unresectable pancreatic cancer. This two-step phase II study assessed the safety and pharmacokinetics of erlotinib 100 mg/day (oral) plus gemcitabine 1000 mg/m^2 (i.v. days 1, 8, 15) in a 28-day cycle in the first step, and efficacy and safety in the second step. The primary end-point was safety. One hundred and seven patients were enrolled (first step, n = 6; second step, n = 101). The most common adverse event was RASH (compiled using the preferred terms rash, acne, exfoliative rash, dermatitis acneiform, erythema, eczema, dermatitis and pustular rash) in 93.4% of patients. One treatment-related death occurred. While interstitial lung disease-like events were reported in nine patients (8.5%; grade 1/2/3, 3.8/2.8/1.9%), all patients recovered or improved. The median overall survival, the 1-year survival rate and median progression-free survival were 9.23 months, 33.0% and 3.48 months, respectively. The overall response and disease control rates were 20.3% and 50.0%, respectively. In Japanese patients with unresectable pancreatic cancer, erlotinib plus gemcitabine had acceptable toxicity and efficacy that was not inferior to that seen in Western patients. (*Cancer Sci*, doi: 10.1111/j.1349-7006.2010.01810.x, 2010)

Approximately 232 000 individuals are diagnosed with pancreatic cancer worldwide each year, with an annual death rate estimated at 227 000.[1] In Japan, approximately 22 000 new cases were reported in 2005.[2] Furthermore, data from 2007 show that around 24 000 individuals in Japan died from pancreatic cancer, making this tumor type the fifth leading cause of cancer-related death.[3] The majority of pancreatic cancer cases are diagnosed at an unresectable stage when prognosis is extremely poor.

Current treatment for advanced pancreatic cancer is based on systemic chemotherapy with gemcitabine. Single-agent gemcitabine has been shown to extend median overall survival (OS) to 5.65 months in chemonaïve patients compared with 4.41 months in patients who received fluorouracil.[4] Addition of other cytotoxic agents to gemcitabine has not demonstrated survival benefits over gemcitabine alone.[5–13] The potential of combining gemcitabine with biological agents in patients with advanced pancreatic cancer has also been evaluated in several phase III studies, but these trials failed to show a survival benefit.[14–19]

Epidermal growth factor receptor (EGFR)-mediated signaling is associated with various cellular processes, and the dysregulation of these processes is common in tumorigenesis.[20,21] Furthermore, EGFR is overexpressed in many tumors and its overexpression is often associated with poor prognosis.[22–26] EGFR tyrosine-kinase inhibitors (TKI, such as erlotinib) are used in the treatment of various types of solid tumors.

Erlotinib has demonstrated antitumor activity in pancreatic cell lines[27] and was subsequently assessed as a potential therapeutic agent in pancreatic cancer. In the PA.3 study (n = 569), the risk of death with erlotinib plus gemcitabine was reduced by 18% versus gemcitabine alone (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69–0.99; P = 0.038 after adjustment for stratification factors), with a median OS of 6.24 months *vs* 5.91 months, respectively. Erlotinib plus gemcitabine combination therapy provided significant improvements in the 1-year survival rate (23% *vs* 17%; P = 0.023) and progression-free survival (PFS; HR 0.77; 95% CI, 0.64–0.92; P = 0.004).[28] As a result, this combination was approved for use in pancreatic cancer in many countries.

In Japanese patients with non-small-cell lung cancer (NSCLC), a phase II study has specifically shown that erlotinib monotherapy is well tolerated and has promising antitumor activity.[29] However, there are no data on the use of erlotinib combined with gemcitabine in Japanese patients with pancreatic cancer. This phase II study evaluated the safety and efficacy of erlotinib in combination with gemcitabine in Japanese patients with unresectable locally advanced or metastatic pancreatic cancer.

Methods

Patients. Patients aged 20–80 years with histological/cytological evidence of unresectable locally advanced or metastatic adenocarcinoma/adenosquamous carcinoma of the pancreas were eligible for inclusion in the present study. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, adequate hematological, renal and hepatic function and a life expectancy of at least 2 months. No more than one prior regimen for pancreatic cancer was permitted. Patients who had received prior gemcitabine and/or a TKI were excluded from participation, as were those who had previously been exposed to a human epidermal growth factor receptor 2 (HER2) or EGFR inhibitor. Other key

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Clinical trial registry: JAPIC Clinical Trials Information (see links below). http://rctportal.niph.go.jp/examDetail.php?center=3&center_seq=698 http://www.clinicaltrials.jp/user/cteDetail.jsp?clinicalTrialId=839&language=ja. Trial registration number: JapicCTI-060337.

doi: 10.1111/j.1349-7006.2010.01810.x

exclusion criteria were: symptomatic cerebral metastases; a concurrent lung disorder (such as idiopathic pulmonary fibrosis, interstitial lung disease [ILD] or pneumoconiosis); concurrent or previous drug-induced pneumonia; or a history of radiation to the chest.

The study complied with the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was obtained from all patients, and the protocol was approved by ethics committees at all participating institutions.

Study design and treatment. This was a phase II, multicentre, open-label, two-step study. In the first step, six patients were enrolled into the study and treated with oral erlotinib 100 mg/day on days 3–28, plus i.v. gemcitabine 1000 mg/m^2 on days 1, 8 and 15 in a 28-day cycle. The starting doses of erlotinib and gemcitabine were chosen in reference to the PA.3 study. Dose-limiting toxicities (DLT) were assessed in these study participants using the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (NCI-CTCAE, National Cancer Institute, Bethesda, MD, USA). Dose-limiting toxicities were defined in conformity to the P1b study as follows:[30] (i) grade 4 decrease (i.e. to <500/mm^3) in neutrophil count >5 days; (ii) grade ≥3 decrease (i.e. to <1000/mm^3) in neutrophil count with associated fever (≥38.5°C); (iii) grade 4 decrease in platelet count (i.e. to <25 000/mm^3); (iv) any grade ILD; (v) grade 4 elevation of alanine transaminase (ALT)/aspartate transaminase (AST) levels, or grade 3 elevation of ALT/AST levels >7 days; (vi) grade ≥3 non-hematological toxicity (excluding rash, hyperglycemia, γ-GTP and events that were judged to be transient/had no effect on study continuation); and (vii) dose-reduction/interruption required due to persistent adverse events (AE), which meant that the second cycle could not be started.

If treatment-related DLT occurred in no more than two of the six patients, transition to the second step of the study was permissible with approval of the Data Safety and Monitoring Committee (DSMC). If DLT occurred in three or more patients, transition to the second step was limited to those cases that were judged to be safe for this study after the DSMC had evaluated the safety data of the patients with a DLT. In the second step, it was planned that 94 patients would be treated with the same dose as the first step. Treatment was continued until disease progression, death, unacceptable toxicity or patient/investigator request.

The primary end-point of the study was safety, with secondary end-points including OS, 1-year survival rate, PFS, overall response rate (ORR), disease control rate (DCR = complete response [CR] + partial response [PR] + stable disease), pharmacokinetics (PK) and correlation of *EGFR* mutation status with outcomes.

Toxicity evaluation. Adverse events were monitored and graded using NCI-CTCAE v3.0. Clinical and laboratory assessments were conducted throughout the study. Adverse events prespecified in the study to be monitored carefully were rash, diarrhea, vomiting, liver dysfunction and ILD-like events. Chest X-ray examination to assess pulmonary toxicity was conducted weekly until week 4 and every 2 weeks thereafter. In addition, chest computed tomography (CT) scan was performed every 4 weeks. The DSMC reviewed the images and clinical data associated with all potential ILD-like events. All ILD-like events were reported to be serious AE (SAE), regardless of the grade.

Efficacy evaluation. The tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) in patients who had at least one measurable target lesion. Tumors were measured using computed tomography (CT) at baseline and on day 22 of every two cycles thereafter. Median PFS, ORR and DCR were estimated by the extramural review. The relationship between efficacy and the severity of RASH (compiled using the preferred terms rash, acne, exfoliative rash, dermatitis acneiform, erythema, eczema, dermatitis and pustular rash) was also examined.

Pharmacokinetic evaluation. Pharmacokinetic evaluation of erlotinib and its O-desmethylated metabolite (OSI-420) was performed in the six patients enrolled in the first step of the study. Venous blood samples were taken prior to erlotinib dosing on day 3 and day 8 of cycle 1 at 0.5, 1, 2, 4, 6, 8 and 24 h after erlotinib administration. Samples were also taken prior to gemcitabine infusion on days 1 and 8 at 0.5, 0.75, 1, 1.5, 2.5 and 4.5 h after dosing.

The plasma concentrations of erlotinib, OSI-420 and gemcitabine were measured by liquid chromatography, tandem mass spectrometry (LC-MS-MS). The LC-MS-MS analytical methods have been described previously.[31,32] Derived PK parameters included the maximum plasma drug concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma drug concentration-time curve to the last plasma sample (AUC_{last}), terminal half-life ($t_{½}$) and oral clearance (Cl/F).

Biomarker analysis. *EGFR* mutations were assessed in patients with available tumor tissue specimens, which were formalin fixed and paraffin embedded. Samples were analyzed at a central laboratory where DNA was extracted and exons 18–21 sequenced using a nested PCR.

Statistical analysis. Progression-free survival and OS were estimated using the Kaplan–Meier method in all patients who received at least one dose of the study treatment, with 95% CI for the median duration calculated using Greenwood's formula. The Clopper–Pearson method was used to calculate the 95% CI around the ORR, DCR and AE rate. Multivariate analyses were performed for the occurrence of ILD-like events using the logistic regression model. Baseline characteristics investigated for this analysis included gender, age, lung metastasis, emphysema and various baseline laboratory values. The target enrollment was 100 patients, as this was required to evaluate the safety of erlotinib.

Results

Patient characteristics. Between December 2006 and October 2007, a total of 107 patients were enrolled (first step, n = 6; second step, n = 101) from 12 institutions (Fig. 1). One patient who enrolled into the second step did not receive treatment due to deterioration in PS prior to the start of treatment. A total of 106 patients were evaluable for safety (safety population, full analysis set).

The patient demographics and baseline characteristics are shown in Table 1. The median age was 62 years (range, 36–78) and 52.8% of patients were male. Almost all patients were chemonaïve (95.3%). The majority (75.5%) of patients had an ECOG PS of 0 and most (83.0%) had metastatic disease. Over half (63.2%) of the patients had a history of current or past smoking.

Toxicity and dose modifications. The median duration of erlotinib exposure was 102.5 days and its median dose intensity was 100.0 mg/day, with the majority of patients (78.3%) receiving more than 90% of the relative dose intensity. The median duration of gemcitabine treatment was 4.0 cycles and its median dose intensity was 688.0 mg/m^2 per week, with approximately half of the patients (51.4%) receiving more than 90% of the relative dose intensity.

As only one patient had a DLT (grade 3 diarrhea) in the first step, the second step of the study was initiated. One hundred and six patients received at least one dose of erlotinib; these patients were assessable for toxicity. Treatment-related AE and treatment-related changes in laboratory values are summarized in Table 2; most of these were mild to moderate in severity. The most frequently reported AE was RASH, which occurred in

doi: 10.1111/j.1349-7006.2010.01810.x

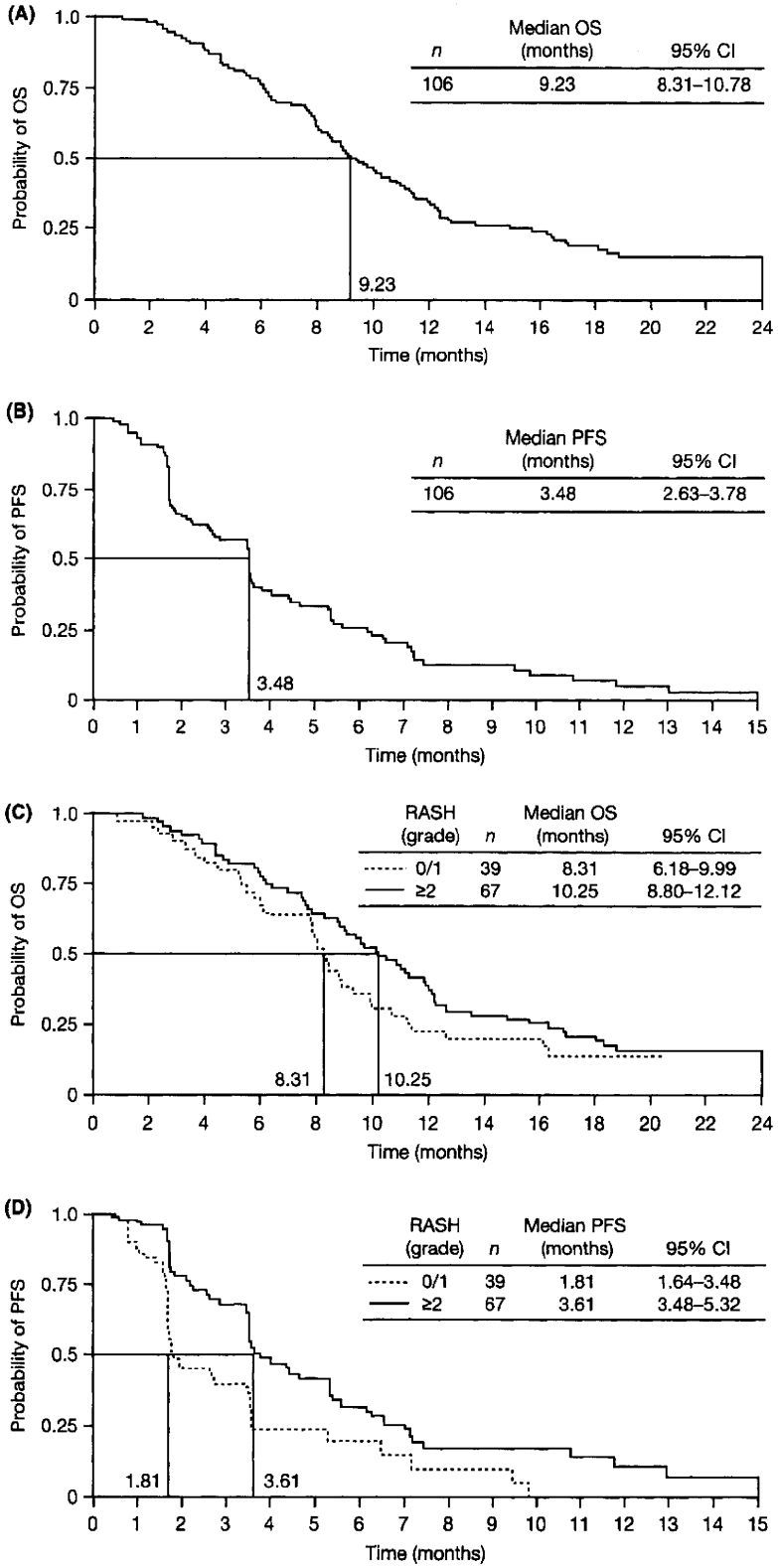

Fig. 1. Kaplan–Meier estimates of (A) overall survival (OS) and (B) progression-free survival (PFS) in the study population (n = 106); (C) OS and (D) PFS according to the severity of RASH (grade ≤1 [n = 39] *vs* grade ≥2 [n = 67]). RASH is a composite of the terms: rash, acne, exfoliative rash, dermatitis acneiform, erythema, eczema, dermatitis and pustular rash. CI, confidence interval.

Table 1. Baseline characteristics and demographics (n = 106)

Characteristic	
Median age (range) (years)	62 (36–78)
Gender, *n* (%)	
Male	56 (52.8)
Female	50 (47.2)
Median bodyweight (range) (kg)	52.3 (33.1–95.0)
Smoking history,† *n* (%)	
Never smoker	39 (36.8)
Past smoker	37 (34.9)
Current smoker	30 (28.3)
ECOG PS, *n* (%)	
0	80 (75.5)
1	26 (24.5)
2	0 (0)
Disease status, *n* (%)	
Metastatic	88 (83.0)
Locally advanced	18 (17.0)
Primary tumor identified, *n* (%)	92 (86.8)
Primary sites, *n* (%)	
Head	46 (43.4)
Body and tail	23 (21.7)
Body	22 (20.8)
Tail	10 (9.4)
Other	5 (4.7)‡
Biliary drainage, *n* (%)	19 (17.9)
Sites of distant metastases, *n* (%)	
Liver	56 (52.8)
Distant lymph nodes	39 (36.8)
Lung	17 (16.0)
Other	26 (24.5)
Prior lines of therapy, *n* (%)	
None	101 (95.3)
One regimen	5 (4.7)§
Median CA19-9 (range) (U/mL)	
Median	776 (0–435 000)
Median CEA (range) (ng/mL)	
Median	4.8 (0.6–1100.1)

†Never smoker, never/hardly smoked; past smoker, passage of at least 1 month since stopping smoking (at the time of registration); current smoker, smoked within 1 month (at the time of registration). ‡Whole of pancreas (n = 1); head and body (n = 3); other (n = 1). §Tegafur, gimeracil, oteracil potassium (S-1) (n = 3); 5-fluorouracil plus leucovorin (n = 2). CA 19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; ECOG, Eastern Co-Operative Group.

93.4% of the patients; most cases were mild to moderate in severity (87.7%, grade ≤2; 5.7%, grade ≥3). Other common non-hematological AE included anorexia, pruritus, fatigue, nausea and diarrhea. Most patients experienced some degree of hematological toxicity, with grade 3 or 4 neutropenia (neutrophil decreased), leucopenia (white blood cell count decreased) and anemia (hemoglobin decreased) occurring in 34.9%, 29.2% and 14.2% of patients, respectively. Only one treatment-related death occurred (due to gastrointestinal hemorrhage), which was probably due to arterial bleeding caused by the invasion of the primary tumor into the gastrointestinal tract. Although the likelihood of this event being treatment-related was deemed remote, a causal relationship could not be completely excluded because the event occurred during the study treatment administration period.

Treatment-related SAE were reported in 26 (24.5%) patients. These included nine ILD-like events (8.5%), the majority of which (n = 7) were grade 1–2 in severity. Importantly, all of these nine patients recovered or improved, and four of these patients did so without any treatment for ILD-like events. Other

Table 2. Treatment-related adverse events occurring in >30% of patients treated with erlotinib and gemcitabine (n = 106)

	Any grade, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Non-hematological			
Rash	78 (73.6)	3 (2.8)	0 (0)
Anorexia	75 (70.8)	15 (14.2)	0 (0)
Pruritus	57 (53.8)	1 (0.9)	0 (0)
Fatigue	56 (52.8)	3 (2.8)	0 (0)
Nausea	56 (52.8)	6 (5.7)	0 (0)
Diarrhea	52 (49.1)	2 (1.9)	0 (0)
Dry skin	49 (46.2)	0 (0)	0 (0)
Stomatitis	38 (35.8)	0 (0)	0 (0)
Pyrexia	32 (30.2)	0 (0)	0 (0)
Hematological			
White blood cell count decreased	85 (80.2)	31 (29.2)	0 (0)
Platelet count decreased	77 (72.6)	9 (8.5)	0 (0)
Hemoglobin decreased	76 (71.7)	13 (12.3)	2 (1.9)
Hematocrit decreased	73 (68.9)	8 (7.5)	0 (0)
Neutrophil decreased	73 (68.9)	32 (30.2)	5 (4.7)
Red blood cell count decreased	72 (67.9)	8 (7.5)	0 (0)
ALT increased	59 (55.7)	10 (9.4)	0 (0)
AST increased	57 (53.8)	4 (3.8)	1 (0.9)
Weight decreased	53 (50.0)	3 (2.8)	0 (0)
Lymphocyte count decreased	46 (43.4)	14 (13.2)	0 (0)
Blood albumin decreased	35 (33.0)	0 (0)	0 (0)
Gamma-glutamyltransferase increased	35 (33.0)	12 (11.3)	1 (0.9)

ALT, alanine amino transferase; AST, aspartate amino transferase.

treatment-related SAE were anorexia (3.8%), vomiting, pyrexia and abnormal hepatic function (1.9% each). The baseline characteristics, treatment and outcomes of patients who developed treatment-related ILD-like events during the study are detailed in Table 3. The onset times of ILD-like events ranged from 7 to 187 days after the start of treatment. In these patients, a relatively long survival was observed (from 119 to 568+ days), and five patients received post-study therapy. All of these nine patients were past or current smokers, and six had emphysema at baseline (not detected prior to treatment, but diagnosed at the extramural review by a radiologist in the DSMC). Multivariate analyses were performed for the occurrence of ILD-like events using the logistic regression model and emphysema at baseline was indicated as a risk factor for onset of ILD-like events (odds ratio [95% CI], 12.13 [1.01–145.7]; P = 0.0491).

Adverse events led to erlotinib discontinuation in 30 patients (28.3%) and gemcitabine discontinuation in 27 patients (25.5%). The main reasons for treatment discontinuation were ILD (n = 6) and anorexia (n = 3); no patient discontinued treatment due to RASH or diarrhea. Due to the onset of AE, a total of 65 patients (61.3%) required one or more interruptions of erlotinib (36 patients [34.0%] for longer than seven consecutive days and 17 patients [16.0%] for longer than 14 consecutive days) and 56 patients (52.8%) had one or more skip of gemcitabine. Modifications in the erlotinib or gemcitabine dosage were required in 17 (16.0%) and 11 (10.4%) patients, respectively, due to AE.

Efficacy. The median OS was 9.23 months (95% CI, 8.31–10.78; Fig. 1A) and the 1-year survival rate was 33% (95% CI, 24–42). Median PFS was 3.48 months (95% CI, 2.63–3.78; Fig. 1B). Among the patients evaluable for tumor response (n = 64), the ORR was 20.3% (13/64; 95% CI, 11.3–32.2) and the DCR was 50.0% (95% CI, 37.2–62.8; CR, n = 0; PR, n = 13; stable disease, n = 19).

doi: 10.1111/j.1349-7006.2010.01810.x

Table 3. Characteristics, treatment and outcomes of patients with treatment-related ILD-like events (n = 9)

Event	Gender	Age (years)	Smoking status†	Days on treatment	ILD maximum grade	Suspicious findings of ILD	Steroids	Oxygen	ILD outcome	Presence of emphysema (assessed by radiologist)	Survival outcome (days)	Post-therapy (chemotherapy)
Lymphoid ILD	M	62	Past	82	1	Pyrexia	None	No	Improved	Yes	362	Yes
ILD	M	42	Current	50	3	Pyrexia	Pulse	Yes	Recovered	Yes	517	Yes
Organising pneumonia	M	60	Past	183	2	Respiratory symptoms	None	No	Improved	Yes	568+	Yes
ILD	F	62	Past	113	2	Cough	Oral	No	Recovered	Yes	376	No
ILD	F	74	Past	111	3	Cough, dyspnea	Pulse	Yes	Improved	None	183	No
ILD	M	60	Current	25	1	Pyrexia	Pulse	No	Recovered	None	119	Yes
ILD	M	77	Past	7	1	X-ray	None	No	Recovered	Yes	255	No
ILD	M	55	Past	187	1	CT	None	No	Recovered	Yes	415	No
ILD	F	60	Current	76	2	Cough	Oral	No	Recovered	None	346	Yes

†Past smoker, passage of at least 1 month since stopping smoking (at the time of registration); current smoker, smoked within 1 month (at the time of registration). CT, computed tomography; F, female; ILD, interstitial lung disease; M, male.

The median OS was longer in patients who experienced RASH of grade ≥2 (n = 67) than in those with RASH of grade ≤1 (n = 39) (10.25 months [95% CI, 8.80–12.12] *vs* 8.31 months [95% CI, 6.18–9.99], respectively; Fig. 1C) and the 1-year survival rate was higher (39% [95% CI, 27–50] *vs* 23% [95% CI, 10–36], respectively). Similarly, the median PFS was longer in patients with RASH of grade ≥2 versus those with RASH grade ≤1 (3.61 months [95% CI, 3.48–5.32] *vs* 1.81 months [95% CI, 1.64–3.48]; Fig. 1D). While there was no notable difference in ORR between patients with RASH grade ≥2 and those with grade ≤1 (21.1% [95% CI, 9.6–37.3] *vs* 19.2% [95% CI, 6.6–39.4]), the DCR was higher in those with more severe RASH (60.5% [95% CI, 43.4–76.0] *vs* 34.6% [95% CI, 17.2–55.7]).

Pharmacokinetics. Plasma sampling for PK analyses was performed in all six patients enrolled in the first step. On day 8, the values of C_{max} were 1760 ± 456.9 ng/mL (mean ± SD) for erlotinib, 169.7 ± 64.5 ng/mL for OSI-420 and 22 700 ± 3272.9 ng/mL for gemcitabine. The AUC_{last} was 29 001 ± 6560 h ng/mL, 2748 ± 788 h ng/mL and 10 717 ± 1458 h ng/mL (mean ± SD), respectively. The mean t_{max} was 8.0 h (range, 2.0–23.9 h), 9.0 h (2.0–23.9 h) and 0.51 h (0.45–0.57 h), respectively. Also on day 8, the mean plasma $t_{1/2}$ was 54.92 h (range, 9.25–144.61 h), 32.79 h (10.36–60.46 h), and 0.63 h (0.31–1.14 h), respectively. The Cl/F of erlotinib and gemcitabine showed interindividual variability; the Cl/F on day 8 was 3972.6 ± 772.1 mL/h (mean ± SD; coefficient of variation 19.4%) and 146 580.4 ± 31 101.3 mL/h (21.2%), respectively.

Biomarker analysis. Of the 106 patients enrolled, *EGFR* mutation status was evaluated in 47 patients (44.3%), all of whom had wild-type *EGFR*. The mutation status of the remaining patients was classified as unknown because samples were not available (30.2%), not examined (9.4%) or the results following sequencing were inconclusive (16.0%).

Discussion

This study was designed to initially assess the safety of erlotinib with gemcitabine for Japanese patients with pancreatic cancer, in whom there had been no prior exposure to either drug. As no significant safety concerns were raised in the first step of the study, enrollment of a further 101 patients was performed. Although the incidence of AE in this study was higher than in the PA.3 study, the incidence of grade 3–4 AE was similar.[28] Despite these results, no new AE specific to Japanese patients were observed. As expected, RASH and gastrointestinal events were among the most common AE in this study, and most of these cases were mild to moderate in severity.

Interstitial lung disease-like events were reported in nine patients (8.5%; grade 1/2/3, 3.8/2.8/1.9%) in the current study, while its incidence was reported to be 2.4% in patients treated in the erlotinib plus gemcitabine arm of the PA.3 study.[28] In addition, in Japanese patients with advanced pancreatic cancer, ILD-like events were reported in two (6.1%) of 33 patients treated with gemcitabine plus S-1, and were reported in three (1.1%) of 264 patients with gemcitabine monotherapy, respectively.[33,34] Likewise, the higher incidence of ILD-like events were documented using S-1 or erlotinib in combination with gemcitabine compared with gemcitabine as monotherapy in patients with pancreatic and biliary tract cancer.[35] On another front, outside of Japan, a high incidence of ILD-like events was reported in gemcitabine and paclitaxel combination therapy in patients with NSCLC.[36] From the above information, considering the higher incidence of ILD when gemcitabine is used in combination, an additive effect from such combinations cannot be ruled out.

In NSCLC, Japanese patients have an increased risk of developing ILD-like events when treated with EGFR TKI.[29,37–39] Fatal cases of ILD-like events have been reported following EGFR TKI administration for the treatment of NSCLC.[37–41] Importantly, however, no patients died due to an ILD-like event in this study. Seven patients experienced ILD-like events of grade 1–2 in severity. This may be due to active management of ILD-like cases during the study period. This management included regular and immediate chest X-rays, in addition to diagnosis with CT scans after any early signs and symptoms were observed (e.g. pyrexia, cough or dyspnea), timely discontinuation of the antitumor drugs (as a precautionary measure in case these drugs were associated with the symptoms) and appropriate treatment for the events (including oral/pulse steroids). By appropriately treating the early symptoms of ILD-like events, patients could restart antitumor therapy (chemotherapy: treatment change). In this study, the onset time for ILD-like events varied markedly between patients (7–187 days). It is therefore necessary to monitor the patients throughout the treatment period.

All of the patients who developed ILD in this study were current or past smokers, and smoking status has been shown to be a risk factor for ILD in the NSCLC population.[38] Results from the multivariate analyses in this study suggest that emphysema is also a risk factor for developing ILD; six of the nine

patients with ILD-like events were diagnosed with emphysema at baseline. Although the number of reports of an ILD-like event may have been artificially elevated due to underlying patient baseline characteristics and the active management of ILD-like events, these results demonstrate the need to consider the risk of ILD-like events in Japanese patients treated with TKI. In particular, it is important that chest CT scans are closely checked for the presence of emphysema or comorbid ILD and that pulmonary status is assessed prior to treatment administration.

This study corroborates the results of the combination of gemcitabine and erlotinib shown in the PA.3 study. The median OS in this study of 9.23 months was longer than those reported in trials with gemcitabine alone. In this study, patients who experienced skin toxicity of grade ≥2 had better outcomes than those with less severe toxicity or the overall study population. Retrospective analyses of data from the PA.3 and AViTA studies have found a significant association between the development of skin toxicity and efficacy in patients with pancreatic cancer treated with erlotinib-based therapy, although the precise mechanisms for the association between skin toxicity and effectiveness are unknown.[28,41,42]

Although the presence of mutations in the tyrosine-kinase region of the *EGFR* gene appears to predict a better response to erlotinib in NSCLC,[43,44] this has not yet been evaluated in pancreatic cancer. *EGFR* mutations are very rare in patients with pancreatic cancer;[45–47] indeed in the present study, no *EGFR* mutations were detected. Further work is required to determine whether *EGFR* mutations can be used as predictive markers for improved survival in Japanese patients receiving erlotinib and gemcitabine as treatment for advanced pancreatic cancer.

In conclusion, the present study shows that erlotinib in combination with gemcitabine is generally well tolerated in Japanese patients with advanced pancreatic cancer. This combination is associated with efficacy and survival outcomes, and the results of this study are consistent with the findings of the global PA.3 study.

Acknowledgments

The authors would like to thank all the patients, investigators and site staff involved in the study. We are grateful to Masahiro Fukuoka for acting as a medical advisor for this study. The authors also thank Abdul Al Khateeb of Gardiner–Caldwell Communications for editorial assistance. This study was sponsored by Chugai Pharmaceutical Co., Ltd. Editorial assistance from Abdul Al Khateeb of Gardiner–Caldwell Communications was funded by Chugai Pharmaceutical Co., Ltd.

Disclosure Statement

Junji Furuse received honoraria for lecture fees from Bayer, Eli Lilly Japan, Taiho Pharmaceutical and Eisai; Kazuhiko Nakagawa received honoraria for lecture fees from Eli Lilly Japan, Chugai Pharmaceutical and AstraZeneca; Takuji Okusaka, Akihiro Funakoshi, Tatsuya Ioka, Kenji Yamao, Shinichi Ohkawa, Narikazu Boku, Yoshito Komatsu, Shoji Nakamori, Haruo Iguchi, Tetsuhide Ito and Kohei Nakachi have no conflict of interest.

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Int J Hematol
DOI 10.1007/s12185-010-0624-7

ORIGINAL ARTICLE

Lenalidomide plus dexamethasone treatment in Japanese patients with relapsed/refractory multiple myeloma

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Received: 26 March 2010 / Revised: 17 May 2010 / Accepted: 31 May 2010

Abstract We conducted a multicenter, open-label study to investigate the safety, efficacy, and pharmacokinetics of lenalidomide in Japanese patients with relapsed or refractory multiple myeloma The study was composed of the "monotherapy phase", a dose-escalation phase, to determine the tolerability to single agent lenalidomide and the "combination phase" to determine the safety and obtain preliminary data on the efficacy of lenalidomide plus dexamethasone. The primary end points were the tolerability to 25 mg lenalidomide and safety. Nine and six patients were enrolled in the monotherapy phase and the combination phase, respectively. Since 25 mg of monotherapy treatment did not satisfy the DLT criteria, this dose was employed in the combination phase. The major adverse event was myelosuppression. At the planned interim analysis (median study duration, 26.3 weeks), grade 3 or grade 4 neutropenia was observed with high frequency (66.7%). However, all adverse events observed were clinically manageable. In the combination cohort, the overall response rate (≥PR) was 100%. The pharmacokinetics of lenalidomide showed rapid absorption and elimination after both single and multiple doses. In conclusion, 25 mg of lenalidomide was given safely as a single agent or in combination with dexamethasone in Japanese patients. The good efficacy of the combination therapy was also demonstrated in this study.

Keywords Multiple myeloma · Lenalidomide · Dexamethasone · Pharmacokinetics

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Published online: 18 June 2010

1 Introduction

Lenalidomide is one of the immunomodulatory drugs (IMiD® brand drugs) developed by Celgene Corporation. Two phase III studies, MM-009 and MM-010, designed to compare lenalidomide plus high-dose dexamethasone combination therapy (LD therapy) with dexamethasone monotherapy (D therapy) in previously treated patients with multiple myeloma (MM) were conducted in US/Canada and Europe/Israel/Australia, respectively [1, 2]. In these studies, 25 mg of lenalidomide was administrated at days 1–21 of a 28-day cycle; 40 mg of dexamethasone was co-administrated with lenalidomide on days 1–4, 9–12, and 17–20 for the first 4 cycles, and on days 1–4 after the 4th cycle. Superiority of the LD regimen was demonstrated based on the following significant differences from D therapy [3]: overall response rate (≥PR) of 60.6% (vs. 21.9% for D therapy), time to progression (TTP) of 13.4 months (vs. 4.6 months), progression-free survival (PFS) of 11.1 months (vs. 4.6 months) and overall survival period of 38 months (vs. 31.6 months). With regard to the safety, the adverse events (AEs) of LD therapy were mainly related to bone marrow suppression, e.g., neutropenia, and all AEs were manageable by supportive care, dose reduction, or interruption of lenalidomide. These data led to approval of lenalidomide as a treatment in combination with dexamethasone for patients with MM who had been treated previously with at least one therapeutic regimen by the US Food and Drug Administration (FDA) in 2006, the European Medicines Evaluation Agency (EMEA) in 2007, and by regulatory agencies on many other countries. The combination therapy is recommended by the clinical practice guidelines of the National Comprehensive Cancer Network (NCCN) as a salvage therapy (category 1) for relapsed or refractory MM [4]. The combination therapy is also category 1 primary therapy for newly diagnosed MM.

Lenalidomide has not yet been approved in Japan. No data are available regarding the safety, efficacy, or pharmacokinetics of LD therapy in Japanese patients. This study was a multicenter, non-randomized, and open-label study to examine the safety, efficacy, and pharmacokinetics of lenalidomide as a single agent or in combination with dexamethasone in Japanese patients with relapsed/refractory MM. The study also examined the pharmacokinetics of higher dose dexamethasone (40 mg), which has not been previously reported.

2 Patients and methods

2.1 Patients

Patients who fulfilled the following inclusion criteria were enrolled in the study: Japanese MM patients aged 20 years or older who were previously treated with at least one prior therapy for myeloma and evaluated to have progressive disease (PD)/disease progression during or after the prior treatment; serum M protein ≥0.5 g/dL or urinary M protein (as measured in a 24-h urine sample) ≥0.2 g; Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. Patients were excluded from the study if they met any of the following exclusion criteria: patients with acute myocardial infarction within the past 6 months, or patients with a history of deep venous thrombosis (DVT) or pulmonary embolism within the past 3 years; pregnant or lactating females; absolute neutrophil count of less than 1,000/μL (1.0×10^9/L); platelet count of less than 75,000/μL (75×10^9/L); serum creatinine level of over 2.5 mg/dL.

2.2 Study design

The study design is based on the previously conducted MM-009/010 studies. Figure 1 illustrates the outline of the study design. The primary end points were the tolerability of 25 mg of single agent lenalidomide and the safety of lenalidomide given alone or in combination with dexamethasone in Japanese patients. The secondary end points

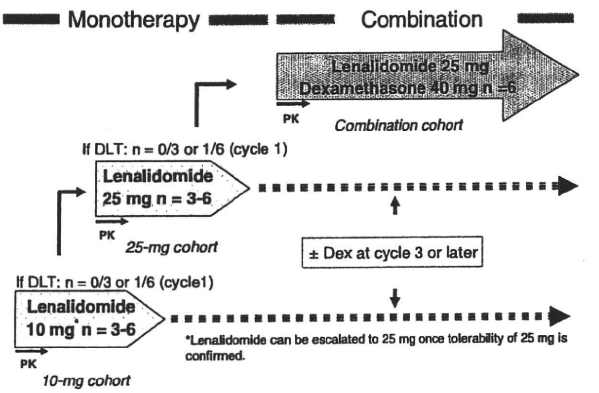

Fig. 1 Study design. This study was composed of the monotherapy phase and the combination phase. In the monotherapy phase, the standard "3 + 3" design of phase I study was employed to determine the safety of single agent lenalidomide. After confirming the tolerability of 25 mg dose, a combination cohort was initiated. In the combination cohort, 6 patients were enrolled. In the 10- or 25-mg monotherapy cohort, patients received 10 or 25 mg lenalidomide once daily, respectively, for 1–21 days a 28-day cycle. In the combination cohort, in addition to the lenalidomide administration, 40 mg of dexamethasone was co-administered with lenalidomide on days 1–4, 9–12, and 17–20 for the first 4 cycles and only on days 1–4 after the 4th cycle. Interim analysis was performed after all patients completed 24 weeks at least after the initiation of the study. Patients who participated in the 10- or 25-mg cohort were allowed to receive 40 mg of dexamethasone and 25 mg of lenalidomide from cycle 3 or later. Pharmacokinetic analysis was performed in cycle 1 in each cohort. Dexamethasone or lenalidomide was not administered on day 1 or 2, respectively, in cycle 1 in the combination cohort to evaluate plasma concentration of each drug when administered alone

were pharmacokinetics and efficacy (response rate, duration of response, and PFS). AEs were reported according to MedDRA Ver. 10. The grade of the AEs was evaluated according to the Common Terminology Criteria for Adverse Events, Ver. 3.0 (NCI-CTCAE). The relationship of AEs to drug was based on the investigators' assessment. Efficacy was evaluated according to the modified EBMT/IBMTR/ABMTR criteria [1, 2, 5].

The study consisted of two phases: the "monotherapy phase" during which patients received lenalidomide alone, followed by the "combination phase" during which lenalidomide was administered in combination with dexamethasone (Fig. 1). A treatment cycle with both phases consisted of 28 days. During each cycle, lenalidomide was administered orally once daily from days 1 to 21, followed by 7 days off therapy. In the monotherapy phase, patients were treated in the "3 + 3" design of phase I study at two different dose levels. DLT (dose limiting toxicity) evaluation was conducted at the end of cycle 1. In this study, DLT was defined as ≥grade 4 neutropenia or thrombocytopenia, or ≥grade 3 febrile neutropenia or non-hematological AEs. The initial dose level tested was 10 mg (10-mg cohort). If no DLTs occurred in 3 patients, a next cohort at 25 mg of lenalidomide was tested. If a DLT occurred in 1 of 3 patients, an additional 3 patients were enrolled; if incidence of DLT resulted in 1 of 6 patients, a 25-mg cohort was enrolled. As with the 10-mg cohort, if DLT did not occur in 3 patients or occurred in 1 of 6 patients in the 25-mg cohort, the 25 mg dose was used for future studies. After the safety of 25 mg of single agent lenalidomide was confirmed, a combination phase with 6 new patients was investigated for the safety and efficacy of LD treatment. In the combination phase, lenalidomide was administered at 25 mg from days 1 to 21 of each cycle. Dexamethasone at a strength of 40 mg (ten 4-mg tablets) was administered orally in combination with lenalidomide once daily from days 1 to 4, 9 to 12, and 17 to 20 for the first 4 cycles, and from days 1 to 4 after cycle 4. Treatment could be continued for up to 156 weeks (3 years) at the investigators' discretion. Patients who participated in the monotherapy phase were allowed to receive 40 mg of dexamethasone and a higher dose (25 mg) of lenalidomide from cycle 3 or later to evaluate the safety of long-term treatment, once the safety of 25 mg dose of lenalidomide was determined.

Interim analysis was performed after all patients completed at least 24 weeks of treatment. Administration of DVT prophylaxis was recommended for the patients who received combination treatment of lenalidomide and dexamethasone. Administration of G-CSF was permitted for treatment of neutropenia.

Dose reduction or dose interruption (temporary suspension of the treatment) of the study drugs due to the study drug-related adverse events was permitted. In accordance with the principles of Good Clinical Practice (GCP), the study protocol was approved by IRB of each institution, and written informed consent was obtained from each patient enrolled in the study.

2.3 Pharmacokinetics

Pharmacokinetic analysis was performed in cycle 1 in each cohort. In the 10- and 25-mg cohorts in the monotherapy phase, plasma concentration of lenalidomide following a single administration or multiple administrations was determined on day 1 or 12, respectively. In the combination phase, to determine the PK of lenalidomide and dexamethasone given alone and in combination, dexamethasone was held on day 1 to determine the plasma concentration of lenalidomide administered alone (day 1). On day 2, dexamethasone was administered but lenalidomide held, so as to determine the plasma concentration of dexamethasone administered alone. On day 12, plasma concentrations of both lenalidomide and dexamethasone were determined with the two drugs given concurrently. Drugs were administrated under fasting conditions.

Blood samples for lenalidomide were collected before and 0.5, 1, 1.5, 2, 4, 6, 9, 12, and 24 h after the drug administration. Blood samples for dexamethasone were collected before and 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 h after the drug administration. The concentrations of *R* and *S*-lenalidomide in plasma were determined by chiral liquid chromatography–tandem mass spectrometry (LC–MS/MS). The concentration of dexamethasone in plasma was determined by LC–MS/MS.

3 Results

3.1 Patient characteristics

A total of 15 patients were enrolled from July 2007 to August 2008. During the monotherapy phase, 3 patients were enrolled in the 10-mg cohort and 6 patients in the 25-mg cohort. After completion of the monotherapy phase, an additional 6 patients were enrolled in the combination cohort. The characteristics of the 15 patients are shown in Table 1. The median age of the patients was 64.0 years (range 43.0–81.0 years), and the median time from initial diagnosis to the screening was 2.0 years (range 0.8–7.6 years). Thirteen of the 15 patients had received more than or equal to 2 prior regimens for MM and 11 patients had previous autologous stem cell transplant (ASCT). Types of myeloma included 6 patients of IgG, 5 of IgA, 2 of IgD, 1 of Bence-Jones protein (BJP)-kappa, and 1 of BJP-lambda type. In patients whose cytogenetic data by fluorescence in

Table 1 Patient characteristics

Characteristic	10 mg ($n = 3$)	25 mg ($n = 6$)	Combo ($n = 6$)	Total ($n = 15$)
Age (years)				
Median	64.0	64.5	64.0	64.0
Range	54.0–68.0	43.0–76.0	47.0–81.0	43.0–81.0
Female:male (*n*)	1:2	2:4	2:4	5:10
Time since MM diagnosis (years)				
Median	4.4	2.1	1.9	2.0
Range	1.4–7.6	0.8–4.8	1.4–4.1	0.8–7.6
No. of previous therapies, *n* (%)				
1	0	2 (33.3)	0	2 (13.3)
≥2	3 (100)	4 (66.7)	6 (100)	13 (86.7)
Type of therapy, *n* (%)				
Thalidomide	1 (33.3)	1 (16.7)	1 (16.7)	3 (20.0)
Bortezomib	0	0	1 (16.7)	1 (6.7)
ASCT	2 (66.7)	4 (66.7)	5 (83.3)	11 (73.3)
Cytogenetic abnormality by FISH				
t(4;14)	1	2	1	4
t(11;14)	0	1	2	3
del(13q)	1	4	3	8

ASCT autologous stem cell transplant

situ hybridization (FISH) were available, t(4:14) (p16;q32) was detected in 4 of 9 patients and del(13q) (13S319) in 8 of 11 patients. Del(17p) was detected in none of the 7 patients.

The median study duration at the data cutoff was 48.3 (range 41.1–51.1), 24.0 (12.0–36.1), and 25.3 (22.7–28.0) weeks in the 10-mg, 25-mg, and the combination cohorts, respectively. It was 26.3 (12.0–51.1) weeks for all cohorts. Two patients had discontinued the study due to AE ($n = 1$) or PD ($n = 1$) in the 25-mg cohort, while none of the patients in the 10-mg or the combination cohort had discontinued the study at the time of data cutoff.

3.2 Safety in the monotherapy phase

Grade 3 or higher lenalidomide-related AEs reported during cycle 1 in the 10-mg cohort were anemia (grade 4, $n = 1$), leukopenia (grade 3, $n = 1$), lymphopenia (grade 3, $n = 1$), and neutropenia (grade 3, $n = 1$). Since none of the AEs corresponded to DLT, 6 patients were additionally enrolled to receive a higher dose of 25 mg.

≥Grade 3 AEs related to lenalidomide during cycle 1 in the 25-mg cohort were leukopenia (grade 3, $n = 1$), neutropenia (grade 3, $n = 1$), lymphopenia (grade 3, $n = 1$), and hypoxia (grade 3, $n = 1$). The grade 3 hypoxia corresponded to DLT. Since only one of the 6 patients in the 25-mg cohort developed DLT, the dose of lenalidomide to be used in Japanese patients with MM was set at 25 mg, as specified in the study protocol. The safety data of the 25 mg dose was reviewed and recommended for the combination cohort by the Independent Data Monitoring Committee. Patients who experienced DLT discontinued the study at cycle 1.

3.3 Safety

All patients who received at least one dose of lenalidomide ($n = 15$) were included in the safety evaluation. Grade 3 or 4 lenalidomide-related AEs were reported in 11 of 15 patients at the data cutoff (Table 2). The major AE was myelosuppression. Neutropenia ($n = 10$) was reported with the highest frequency. None of the patients in the combination cohort had any grade 4 AEs. Regarding neutropenia, median duration of grade 3 or 4 neutropenia was 15 days (range 3–29 days). Median frequency of grade 3 or 4 neutropenia per patient was 1.5 (range 1–5). To manage neutropenia, lenalidomide were interrupted in 2 patients. None of the patients experienced drug reduction due to neutropenia. As dexamethasone-related AEs, hyperglycemia (grade 3, $n = 2$), and osteomyelitis (grade 3, $n = 1$), which was considered equivalent to a recurrence of osteonecrosis of the jaw (ONJ), were reported. The patient who experienced ONJ had a history of bisphosphonate treatment. Peripheral neuropathy, DVT, pulmonary embolism, or thrombosis was not reported in any cohort. Seven of the 12 patients in whom lenalidomide and dexamethasone were administered received low-dose aspirin to prevent DVT.

None of the patients in the 25-mg or combination cohort experienced dose reduction of lenalidomide. Eight of the 15 patients, including the 3 in the 10-mg cohort, 3 in the

Table 2 Lenalidomide-related adverse events with NCI-CTCAE grade 3 or 4 ($n = 15$)

Events	Grade 3	Grade 4	Grade 3 + 4, *n* (%)
Patients with at least one ≤grade 3 adverse event	–	2 (13.3)	11 (73.3)
Anemia	3 (20.0)		2 (13.3)
Leukopenia	3 (20.0)[a]	–	3 (20.0)
Lymphopenia	9 (60.0)	1 (6.7)	3 (20.0)
Neutropenia	1 (6.7)	–	10 (66.7)
Hypoxia	1 (6.7)	–	1 (6.7)
Malaise[b]	1 (6.7)	–	1 (6.7)
Hepatic function abnormality[b]	1 (6.7)	–	1 (6.7)
Decreased blood phosphorus	1 (6.7)	–	1 (6.7)
Increased alanine aminotransferase[b]			1 (6.7)

A subject with multiple occurrence of an adverse event is counted once

[a] In 3 cases of lymphopenia, one was reported as a lenalidomide and/or dexamethasone-related AE

[b] Lenalidomide and/or dexamethasone-related AEs

25-mg cohort and 2 in the combination cohort experienced dose interruption of lenalidomide due to lenalidomide-related AEs including, anemia, neutropenia, malaise, pyrexia, and rash that developed in 2 patients each.

One patient in each cohort experienced lenalidomide-related serious AEs (SAEs) including malaise (grade 2) and pyrexia (grade 1) in the 10-mg cohort, hypoxia (grade 3) and interstitial pneumonia (grade 2) in the 25-mg cohort, and hepatic function abnormality (grade 3) in the combination cohort. None of the SAEs induced study discontinuation except interstitial pneumonia, which might have triggered the hypoxia, a DLT. All lenalidomide-related AEs observed in this study had been previously reported. Moreover, all the AEs were manageable by supportive care or dose interruption/reduction of study drugs.

3.4 Efficacy

All 6 patients in the combination cohort achieved PR at the data cutoff. The overall response rate (ORR), defined as partial or complete response, was 100%. Within 2 months of the interim analysis, CR was achieved in 2 of the 6 patients (33%) in the combination cohort. Median time to response, the time from study start to PR entry, was 4.1 weeks (range 4.0–4.3 weeks) in the combination cohort. Median response duration and progression-free survival (PFS) as determined by the Kaplan–Meier method were not estimable at the time of the interim analysis. The response was continued in 5 of the 6 patients in the combination cohort at the time of data cutoff. Patients in the combination cohort who had a history of prior bortezomib or thalidomide therapy achieved PR at the time of the interim analysis.

3.5 Pharmacokinetics

Mean plasma lenalidomide concentrations following single and multiple doses of 10 or 25 mg lenalidomide are shown in Fig. 2a. Mean plasma lenalidomide concentrations when administered alone (day 1) or in combination with dexamethasone (day 12) are shown in Fig. 2b. The plasma pharmacokinetic parameters of lenalidomide are listed in Table 3.

The profile of the plasma lenalidomide concentration over time was similar between days 1 and 12 following administration of the drug alone at 10 or 25 mg: The plasma concentration of lenalidomide reached a peak at approximately 1 h postdose and levels of lenalidomide declined rapidly in a monophasic manner at both dose levels and on both days. The C_{max} and AUC increased in a dose-dependent manner. Mean accumulation ratios between days 1 and 12 for C_{max} (AR [C_{max}]) or AUC_τ (AR [AUC_τ]) were nearly 1.00, suggesting no drug accumulation following multiple doses of lenalidomide. There were also no meaningful differences in the V_z/F, CL/F, or $t_{1/2}$ between the two dose levels as well as between days 1 and 12.

After oral administration of 25 mg lenalidomide in combination with dexamethasone (day 12), plasma lenalidomide C_{max} was observed at 1 h later than that observed after administration of lenalidomide alone (day 1). A higher variation in the t_{max} value was observed after co-administration of lenalidomide with dexamethasone (t_{max} = 0.53–4.02 h) compared to administration of lenalidomide alone (t_{max} = 1–1.97 h). A higher intersubject variability in C_{max} was also observed on day 12 (CV% = 46.1% on day 12 and 27.1% on day 1). There were no marked differences in $t_{1/2}$ when lenalidomide was administered with or without dexamethasone. The AUC_τ was slightly reduced from days 1 to 12. The accumulation ratio of day 12 to day 1 for the C_{max} and AUC_τ (AR [C_{max}] and AR [AUC_τ]) was 0.914 and 0.868, respectively. These observations indicate a modest change in lenalidomide oral absorption when co-administered with large quantities of dexamethasone tablets (4 mg × 10), which is not considered clinically relevant since other PK parameters were almost the same between days 1 and 12.

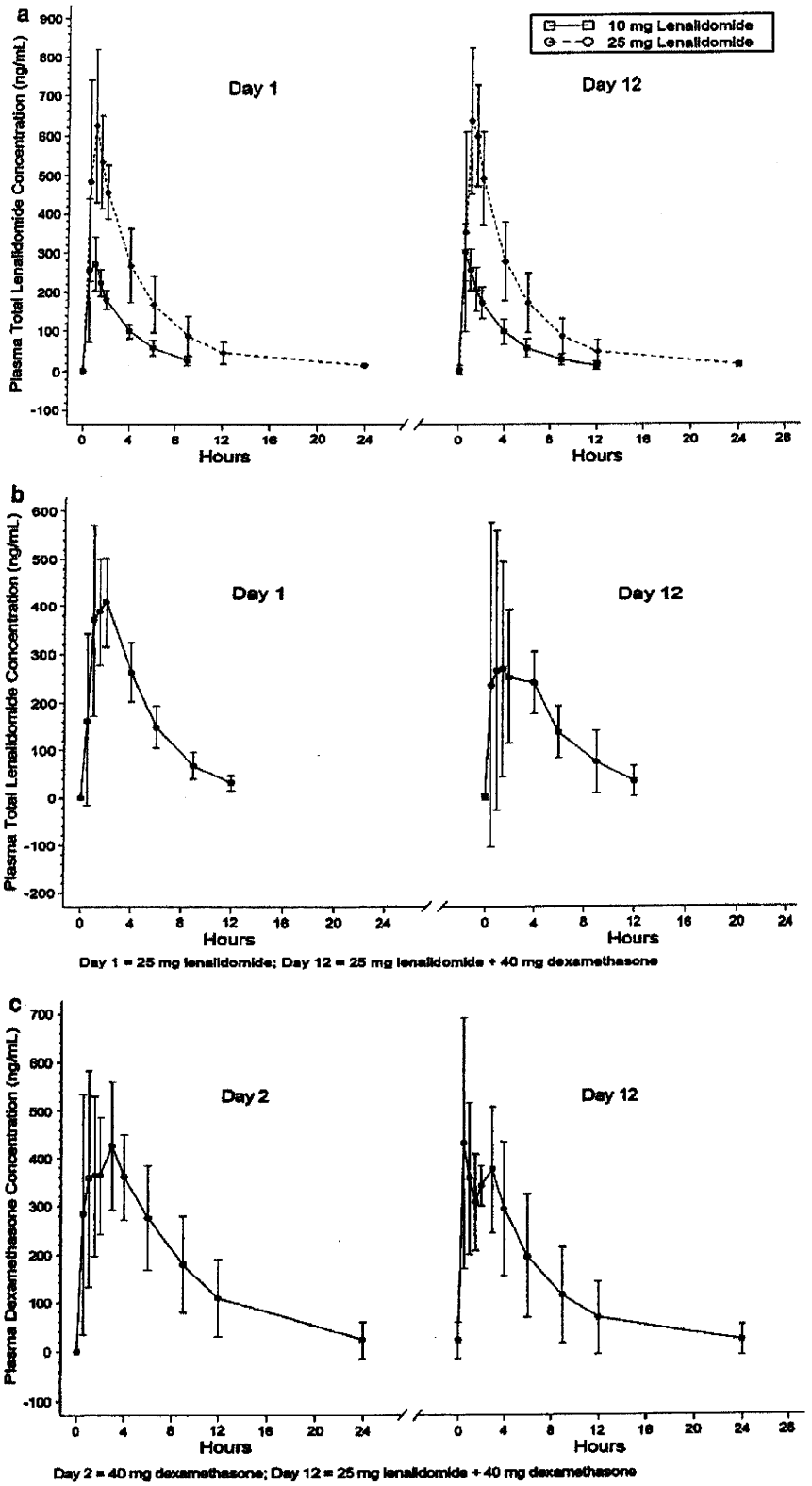

Fig. 2 **a** Mean (±SD) plasma lenalidomide concentrations versus time on days 1 and 12 (monotherapy cohorts). Plasma lenalidomide concentrations following single (day 1) and multiple doses (day 12) of 10 mg ($n = 3$) or 25 mg ($n = 6$) lenalidomide. Data points at 24 h in 10 mg lenalidomide are missing because of BLQ (below the limit of quantitation; 5 ng/mL). **b** Mean (±SD) plasma lenalidomide concentrations versus time on days 1 and 12 (combination cohort). Plasma lenalidomide concentrations when administered alone (day 1, $n = 6$) and in combination with dexamethasone (day 12, $n = 6$). Data points at 24 h are missing because of BLQ. **c** Mean (±SD) plasma dexamethasone concentrations versus time on days 2 and 12 (combination cohort). Plasma dexamethasone concentration when administered alone (day 2, $n = 6$) and in combination with lenalidomide (day 12, $n = 6$)