Table 4. Individual efficacy results

	All $n = 16$	100 mg $n = 9$	150 mg $n = 3$	200 mg $n = 4$
CR/PR	0	0	0	0
SD	5	3	1	1
PD	5	3	1	1
NE	6	3	1	2

CR, complete response; NE, not evaluable, evaluated by RECIST ver. 1.0; PD, progressive disease; PR, partial response; SD, stable disease.

which resulted in the investigator deciding to discontinue the study, and grade 3 dyspnea at 200 mg once daily. At 200 mg once daily, DLT occurred in one of three evaluable patients. However, as grade 2 pleural effusion was observed in four of four patients, the dose of 200 mg once daily was determined to be unacceptable. The MTD was consequently defined as 150 mg once daily. In other phase I studies, the MTD was 120 mg twice daily for a schedule that involved 5 days of treatment followed by 2 days of rest, 70 mg twice daily in a continuous dosing schedule[13] and 180 mg once daily in another continuous dosing schedule.[14] We do not know why the MTD was smaller than other studies, because PK in the present study showed almost the same AUC as the previous studies.

Adverse events of grade 3 or more were anemia, fatigue, lymphopenia, and blood magnesium increased. Although grade 2 or less, dyspnea occurred in four of four patients treated with 200 mg once daily, so in addition to pleural effusion, respiratory toxicity appears to be the most clinically significant adverse effect. Pleural effusion has been reported frequently with dasatinib treatment.[15,16] In a phase I study of solid cancer, dyspnea or pleural effusion occurred in five of 11 patients treated with 180 mg per day, but only one of 11 patients treated with 140 mg per day.[14] The etiology of dasatinib-induced pleural effusion is not known; however, the effusions respond to steroids, are often exudative and contain lymphocytes or neutrophils, so they might be immune mediated. The etiology of dyspnea without massive pleural effusion in the present study is not clear. The other toxicity that had the most pronounced effect on patients' ability to continue therapy was fatigue, although determining the contribution of dasatinib to fatigue is difficult. From 13 to 20% of patients with leukemia also commonly experience fatigue during dasatinib treatment, but fatigue of grade 3 or more is rare (<3%). Another serious toxicity in the present study was perianal abscess in one patient, which might have been the result of the mucosal toxicity of dasatinib. Some studies suggest that dasatinib has an immunosuppressive effect,[17] but in CML studies there is no evidence that dasatinib leads to increased infection. Hematological toxicity was not significant except for anemia in one patient, and is consistent with other studies of solid cancer, compared with more severe hematological toxicities in CML patients.

We also studied the effects of dasatinib on QT intervals. In leukemic patients, long-term treatment with dasatinib (70 mg twice daily) was associated with a 3- to 6-msec increase in the QTc interval compared with baseline. We did not see any significant QTc prolongation even following treatment exceeding 1 year, although the sample size in the present study was small.

Among 10 patients evaluable for tumor response, there was no objective response, but five patients showed SD and three showed long SD. One RCC patient maintained SD for more than a year. Renal cell carcinoma, especially of the clear cell type, overexpresses VEGF and PDGF, and VEGF/PDGF signal inhibitors such as bevacizumab, sunitinib and sorafenib have been shown to be effective for RCC. Dasatinib inhibits PDGFR, but other PDGFR inhibitors such as imatinib have not been effective for RCC. The roles of SFK in RCC have not been fully defined. The transformation of human kidney proximal tubule cells by a SRC-containing retrovirus, and stimulation of VEGF production, angiogenesis and tumor development in a RCC xenograft model have been reported.[18,19] Therefore, dasatinib might inhibit RCC progression by inhibiting SRC-associated signal pathways.

Two of the six patients with large bowel cancer showed SD, and one developed prolonged SD. SRC expression levels are higher in colon adenocarcinoma than normal mucosa, and correlate not only with tumor stage and metastatic potential, but also with poor prognosis.[20,21] The activity of YES has also been reported in premalignant tissues and in carcinoma of the colon.[22,23] Dasatinib did not inhibit the growth of colon cancer cell lines, but inhibited the metastatic potential of these cells.[24] Dasatinib sensitizes K-ras mutant colon cancer cell lines to cetuximab[25] and had synergistic activity with oxaliplatin against colon cancer cells *in vitro* and *in vivo*.[26] Several ongoing clinical studies are examining the activity of SRC inhibitors in colon cancer, as monotherapy or in combination.

One thymoma patient showed prolonged SD. There is one case report of a clinical response of thymoma to dasatinib.[27] Transgenic mice expressing high levels of LCK developed thymic tumors.[28] Dasatinib inhibits LCK at low picomolar concentrations, and inhibits T cell receptor-mediated signal transduction, cellular proliferation, cytokine production and *in vivo* T-cell responses.[29] Thymomas also frequently overexpress

Table 5. Pharmacokinetic data

Dose (mg)	Study day	*n*	C_{max} (ng/mL) geometric mean (CV%)	AUC† (ng•h/mL) geometric mean (CV%)	T_{max} (h) Median (min, max)	t1/2 (h) Mean (SD)	AI geometric mean (CV%)	CLo (L/h) mean(SD)	Vz/F (L) mean(SD)
100	1	9	139.83 (54)	537.98 (33)	1.0 (0.5, 4.0)	4.77 (0.61)	NA	NC	NC
	14	5	137.03 (55)	499.69 (36)	1.0 (0.5, 3.0)	5.75 (1.67)	0.81 (34)	223.0 (134.3)	1709 (2010)
	28	3	253.77 (41)	738.76 (34)	0.5 (0.5, 1.0)	4.36 (1.19)	1.12 (36)	141.6 (53.3)	606 (286)
150	1	3	127.10 (83)	544.36 (54)	1.0 (1.0, 1.0)	4.68 (0.84)	NA	NC	NC
	14	4	166.43 (109)	694.90 (77)	1.0 (1.0, 1.0)	5.04 (1.19)	1.78 (19)‡	273.3 (204.7)	1883 (1967)
	28	2	103.32 (112)	273.10 (75)	0.5 (0.5, 0.5)	8.33 (2.78)	0.48 (11)	649.2 (489.6)	5420 (5920)
200	1	4	124.48 (69)	595.62 (56)	1.3 (0.5, 3.0)	7.62 (4.11)	NA	NC	NC
	14	2	102.61 (127)	716.27 (114)	2.3 (1.5, 3.0)	7.95 (5.62)	2.30 (77)	471.6 (537.4)	9113 (12216)
	28	2	80.92 (113)	534.33 (53)	3.3 (0.5, 6.0)	7.66 (4.24)	1.72 (15)	403.6 (213.3)	5458 (6081)

†AUC (area under the plasma concentration vs time curve from time zero to infinity [INF]) for day 1 and AUC (area under the plasma concentration-time curve for a dosing interval [TAU]) for days 14 and 28. ‡$n = 3$. NA, not applicable; NC, not calculated.

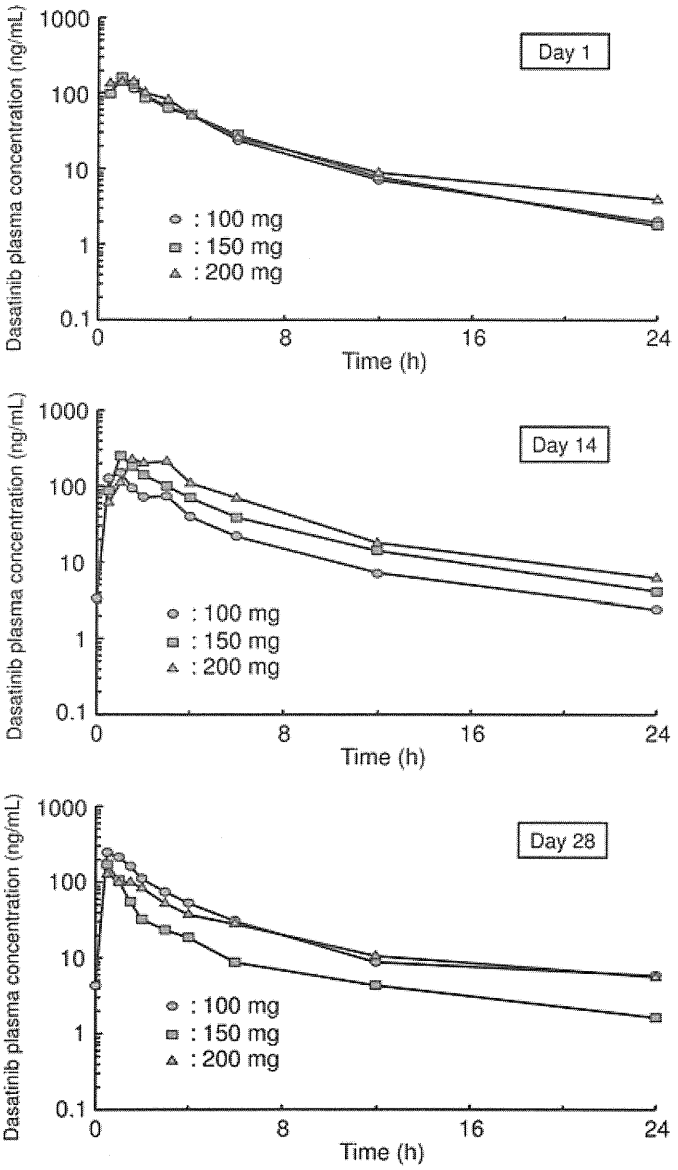

Fig. 1. Mean plasma concentration of dasatinib at days 1, 14 and 28 of the first cycle.

KIT and are sometimes associated with the *c-kit* mutation.[30] There have been reports of thymoma responding to imatinib.[31]

Recently, a better response in dasatinib-treated CML patients with large granular lymphocyte (LGL) lymphocytosis has been reported.[32] No increase of LGL was detected in the present study, although no special attention was paid to the lymphocyte subset at the time of the study. Lymphocytosis was detected in two patients, who showed lymphocyte counts of more than 5000 and 7000 at peak level. These two patients showed long SD, so it is possible that lymphocytosis with LGL expansion might also be correlated with a good response in patients with solid cancers.

Pharmacokinetic data showed that dasatinib was rapidly absorbed and metabolized. C_{max} and AUC were not significantly correlated with dosing, and varied from individual to individual. Due to the small sample size in the present study, no conclusion could be reached regarding linearity. Dasatinib did not accumulate significantly with once daily treatment, although the AUC on days 14 and 28 were slightly increased. The amounts of exposure are within the range for pharmacokinetic data for once daily treatment reported in other studies of solid cancer and CML patients.[33]

Table 6. Pharmacodynamic data

	NTx (nmol BCE/mmol Cr)			TRACP-5b (U/L)		
	n	Mean	SD	*n*	Mean	SD
ALL						
Baseline	16	66.79	45.18	16	5.13	1.89
Day 14	13	48.00	43.24	12	4.13	1.25
Day 28	7	32.64	18.07	7	3.40	0.61
100 mg						
Baseline	9	51.71	39.75	9	4.67	1.84
Day 14	6	51.55	59.74	6	4.03	1.34
Day 28	3	25.33	4.26	3	3.40	0.61
150 mg						
Baseline	3	62.57	15.78	3	5.10	1.57
Day 14	3	36.47	26.00	3	3.90	0.78
Day 28	2	40.10	16.40	2	3.60	0.14
200 mg						
Baseline	4	103.90	57.37	4	6.18	2.25
Day 14	4	51.33	30.08	3	4.57	1.75
Day 28	2	36.15	36.84	2	3.20	1.13

nmol BCE/mmol Cr, nanomolar bone collagen equivalents/millimolar creatinine; NTx, N-telopeptide; TRACP-5b, tartrate-resistant acid phosphatase.

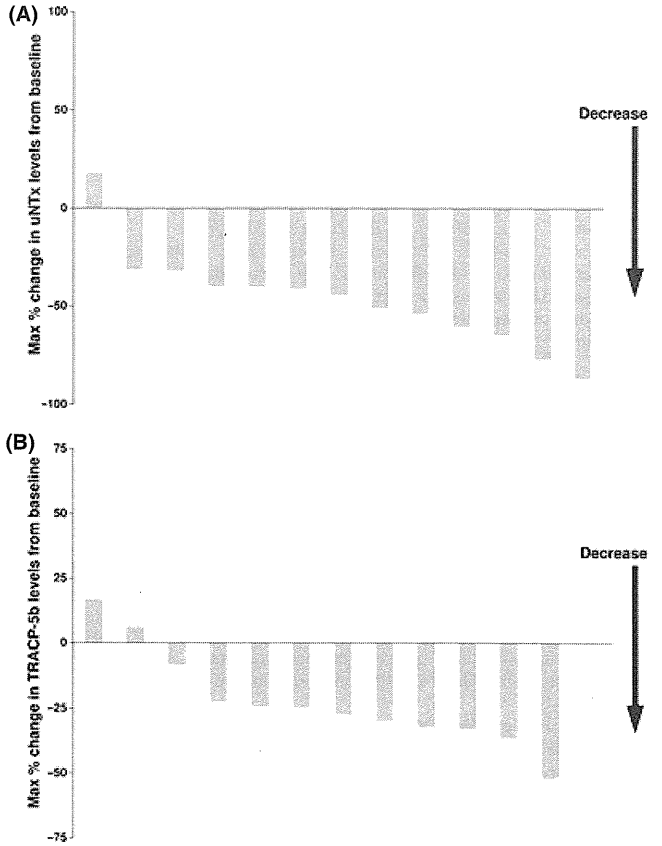

Fig. 2. Maximum changes in bone metabolic markers from baseline. Levels of urine NTX (uNTX) (a) and serum tartrate-resistant acid phosphatase (TRACP-5b) (b) were measured at baseline and during the study.

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We conducted pharmacodynamic studies of bone metabolic markers. Compared with baseline values, mean values of bone resorption markers decreased by 51% (urine NTx) and 34% (TRACP) on day 28 of dasatinib treatment. Recent advances in the treatment for metastatic solid cancers have highlighted the importance of treating bone metastasis to reduce the incidence of skeletal complications and improve patients' quality of life. Currently, bisphosphonates (BP) are commonly used as the standard for treatment of bone metastasis, and receptor activator of nuclear factor kappa B ligand antibody (denosumab) has recently been approved by the FDA as a bone-targeted agent.[34] However, the outcomes of BP or denosumab therapy leave room for improvement with regards to their efficacy, safety and convenience. In a phase II study of dasatinib for castration-resistant prostate cancer, 51% of patients receiving BP and 50% of those not receiving BP achieved a urine NTx decrease of 40% or more when given dasatinib 70 mg twice daily or 100 mg twice daily.[35] Yu *et al.* also showed that 45% of patients not receiving BP achieved a reduction in uNTx to within normal levels. The present study further confirmed the inhibitory activity of dasatinib on bone resorption in solid cancer patients without using BP, and suggests the dasatinib might be effective for bone metastases from solid cancer, as both an antitumor and bone-targeted agent.

In conclusion, dasatinib 150 mg once daily was determined to be the MTD in the present study. The safety profile of dasatinib was generally acceptable in this study population and not significantly different from that in other studies. There was no objective response, but three of 10 evaluable patients achieved prolonged SD that lasted more than 6 months.

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Disclosure Statement

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Abbreviations

AUC	area under the concentration-time curve
AUC(0–t)	AUC from time zero to the time of the last quantifiable concentration
AUC(TAU)	AUC over a dose interval
C_{max}	observed maximum concentration
CV	coefficient of variation
CLo	apparent oral clearance
t1/2	serum elimination half-life
T_{max}	time of maximum concentration
Vz/F	apparent volume of distribution for the terminal disposition phase

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PHASE I STUDIES

A phase I study of oral panobinostat (LBH589) in Japanese patients with advanced solid tumors

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Summary *Objective* The objective was to determine the maximum tolerated dose and the dose-limiting toxicity of panobinostat (LBH589) when administered as a single agent to adult patients with advanced solid tumors or cutaneous T-cell lymphoma whose disease had progressed despite standard therapy or for whom no standard therapy existed. *Methods* Panobinostat was administered orally once daily on Monday, Wednesday, and Friday of each week. A total of 13 patients were treated with one of three initial doses: 10 mg (n=3), 15 mg (n=4), or 20 mg (n=6). *Results* No dose-limiting toxicity was observed in 12 evaluable patients. The most frequently reported adverse events, regardless of whether they were related to the study drug, were diarrhea and nausea in 10 patients (76.9%). Thrombocytopenia was reported in 12 of 13 patients (92.3%). Five of 11 patients (45.4%) had stable disease. *Conclusion* Panobinostat administered orally once daily on Monday, Wednesday, and Friday of each week was well tolerated at doses up to 20 mg in Japanese patients. Dose escalation did not proceed after exploration of the 20 mg dose due to emerging global clinical data at that time.

Keywords Panobinostat · Histone deacetylase inhibitors · Phase 1 clinical trials · Cutaneous T-cell lymphoma

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Introduction

Over the past several years, deacetylase inhibitors (DACIs) have provided novel approaches to cancer treatment. For several decades, cancer has been thought of as a disease characterized by genetic defects involving gene mutations, deletions, amplifications, and chromosomal abnormalities. Recently, however, it has been well recognized that epigenetic and genetic changes play an important role in the initiation and progression of malignant neoplasms. One of the most extensively studied post-translational modifications of chromatin is the acetylation of lysine residues in histone proteins, which are regulated by histone acetyltransferases and histone deacetylase (HDAC) activity. Positively charged deacetylated histones bind tightly to the phosphate backbone of DNA and inhibit transcription. However, acetylated histones generate a more open DNA conformation, which promotes the expression of the corresponding genes [1, 2] HDACs are involved in reversible acetylation, not only of histones but also of other proteins, such as p53, NF- κB, and E2F-1, which play a key role in tumorigenesis and in the antitumor response, and of proteins that regulate DNA repair (Ku70), the cellular cytoskeleton (α-tubulin), and protein stabilization (Hsp90) [1]. At least 18 human HDACs have been identified, and they are grouped into four classes: I, II, III, and IV [3].

Dozens of structurally diverse DACIs have been identified and classified as Class I–specific inhibitors or as pan-

deacetylase (pan-DAC) inhibitors, which confer activity against both Class I and II DACs [4]. Pan-DAC inhibitors include panobinostat, vorinostat (suberoylanilide hydroxamic acid), and belinostat (PXD101). Of the pan-DAC inhibitors, vorinostat is the most extensively studied and was approved by the US Food and Drug Administration for the treatment of cutaneous T-cell lymphoma (CTCL) [3]. Recent evidence suggests that vorinostat has activity against a variety of solid and hematologic tumors [5].

Panobinostat has potent DAC inhibitory activity at low nanomolar concentrations against Class I, II, and IV purified recombinant HDAC enzymes, which suggests true pan-DAC activity [6]. In studies using enzymatic assays, IC_{50} values for panobinostat were consistently lower than those for vorinostat and belinostat; as a pan-DAC inhibitor, panobinostat was at least 10-fold more potent than vorinostat and appeared to be the most potent of the pan-DAC inhibitors in development.

Panobinostat has shown potential in both preclinical and clinical studies. Several phase I studies have been conducted to evaluate the safety, maximum tolerated dose (MTD), tolerability, and preliminary efficacy of panobinostat. In the CLBH589B2101 trial, various dosing schedules of oral panobinostat were evaluated in Western patients with advanced solid tumors or non-Hodgkin lymphoma, including CTCL. Panobinostat was well tolerated, and objective clinical responses were seen in 6 of 10 CTCL patients when administered orally on Monday, Wednesday, and Friday (MWF) of each week on a 28-day cycle. A dose of 30 mg on MWF was considered excessively toxic, and the MTD was determined to be 20 mg (given on MWF) in this Western patient population [7, 8].

On the basis of the above promising data, we conducted a phase I clinical trial to determine the MTD and dose-limiting toxicity (DLT) of panobinostat when administered orally as a single agent to Japanese patients with either advanced solid tumors or CTCL.

Patients and methods

Patient eligibility

Adult Japanese patients with histologically confirmed, advanced solid tumors or cytopathologically confirmed CTCL whose disease had progressed despite standard therapy or for whom no standard therapy existed were selected. All patients were required to have a World Health Organization performance status of ≤2 and acceptable bone marrow and organ function defined as follows: absolute neutrophil count, ≥1500/mm^3; hemoglobin, ≥9 g/dL; platelets, ≥100,000/mm^3; serum aspartate aminotransferase and alanine transaminase, ≤2.5×upper limit of normal (ULN) or ≤5.0×ULN if liver metastases present; serum total bilirubin, ≤1.5×ULN; and serum creatinine, ≤1.5×ULN. Additional ineligibility criteria included a history of primary central nervous system tumors or brain metastases, any peripheral neuropathy of grade ≥ 2 per the Common Terminology Criteria for Adverse Events (CTCAE), unresolved diarrhea of grade ≥ 2 per the CTCAE, impaired cardiac function (left ventricular ejection fraction <45%, complete left bundle branch block, obligate use of a cardiac pacemaker, congenital long QT syndrome, history or presence of significant ventricular or atrial tachyarrhythmias, clinically significant resting bradycardia [<50 beats per minute], QTcF >480 ms on screening electrocardiogram, or other clinically significant heart disease), impairment of gastrointestinal function or gastrointestinal disease, and acute or chronic liver or renal disease.

This study was approved by the institutional review board of each participating institution. All patients gave written informed consent before any screening procedures were conducted.

Trial design and treatment plan

This was a phase I, open-label, dose-escalation study of panobinostat administered orally once daily on MWF weekly on a 28-day cycle. Oral panobinostat was provided by Novartis Pharma K.K. (Tokyo, Japan).

The primary objectives were to determine the MTD and DLT of oral panobinostat when administered as a single agent to adult Japanese patients with advanced solid tumors or CTCL whose disease had progressed despite standard therapy or for whom no standard therapy existed. Secondary objectives included evaluating the safety and tolerability of oral panobinostat in Japanese patients, including acute and chronic toxicities; determining the pharmacokinetic profile of oral panobinostat in plasma; and assessing preliminary evidence of antitumor activity.

This study employed a standard "3+3" design. The starting dose was 10 mg on MWF based on the standard Japanese practice of starting at 50% of the recommended Western dose [8]. Panobinostat was administered according to provisional three-dose cohort levels: 10, 15, and 20 mg on MWF weekly. One treatment cycle consisted of 4 weeks of therapy. DLT was defined as an adverse event (AE) or abnormal laboratory value that was determined to be unrelated to disease progression, intercurrent illness, or concomitant medication use in cycle 1 and that met any one of the criteria shown in Table 1. At least three patients were assigned to each cohort, and individual cohorts were expanded to six patients after the development of one DLT Dose escalation to >20 mg on MWF was not planned in this study; therefore, even if DLT was not observed in the

Table 1 Criteria for defining dose-limiting toxicity (DLT)

Toxicity	Any of the following criteria
Hematologic[a]	CTCAE grade 3 neutropenia for >7 days
	CTCAE grade 3 thrombocytopenia for >7 days
	CTCAE grade 4 neutropenia for >7 days
	Any CTCAE grade 4 thrombocytopenia
	Neutropenic fever: ANC <1000/mm^3 and body temperature ≥38.5°C
Renal	Serum creatinine ≥2.0 × ULN to ≤3.0 × ULN for >7 days
	Any serum creatinine concentration >3 × ULN
Hepatic	Total bilirubin ≥2 × ULN to ≤3.0 × ULN for >7 days
	Any total bilirubin >3 × ULN
	CTCAE grade 3 AST or ALT for >7 days
	Any CTCAE grade 4 AST or ALT
Neurologic	More than one CTCAE grade level increase lasting >7 days
Cardiac	CTCAE grade ≥3
Other adverse events[a]	CTCAE grade 3 adverse events (excluding CTCAE grade 3 elevations in alkaline phosphatase) lasting >7 days
	CTCAE grade 4 adverse events (excluding CTCAE grade 4 elevations in alkaline phosphatase)
	CTCAE grade ≥3 vomiting or CTCAE grade 3 nausea despite the use of optimal antiemetics
	CTCAE grade ≥3 diarrhea despite the use of optimal antidiarrheal treatment
	Any other adverse event unrelated to disease progression, intercurrent illness, or concomitant medication use that did not allow administration of oral panobinostat for >25% of the total 28-day cycle

ALT alanine transaminase, *ANC* absolute neutrophil count, *AST* aspartate aminotransferase, *CTCAE* Common Terminology Criteria for Adverse Events, *ULN* upper limit of normal

[a] CTCAE grade ≥3 anemia was not considered a DLT unless judged to be a hemolytic process secondary to the study drug. CTCAE grade ≥3 lymphopenia was considered a DLT unless clinically significant

first three patients assigned to the 20-mg cohort, three patients would be enrolled at this level and a total of six patients would be evaluated. The MTD was defined as the highest dose with an observed incidence of DLT in no more than one of six patients treated at a particular dose level.

If toxicity necessitating interruption of oral panobinostat dosing was observed, re-administration began when any previously occurring nonlaboratory toxicity had resolved to a CTCAE grade ≤1. In addition, resolution of abnormalities in the following variables was required: absolute neutrophil count to ≥1000/mm^3, platelets to ≥75,000/mm^3, serum creatinine to ≤1.5 × ULN, total bilirubin to ≤1.5 × ULN, and aspartate aminotransferase and alanine transaminase to a CTCAE grade ≤1. If a patient required a dose delay of >21 days from the intended day of the next scheduled dose, the patient was withdrawn from the study.

Treatment was suspended for patients who experienced grade 3 thrombocytopenia before day 13 of a cycle or grade 4 at any time until the platelet count was ≥75,000/mm^3, at which time dosing was resumed at the next lower dose. If a patient experienced grade 3 thrombocytopenia on or after day 13, dosing was suspended until the platelet count was ≥75,000/mm^3. For patients who required a dosing suspension for >7 days, dosing resumed at the next lower dose. If the platelet count recovered to ≥75,000/mm^3 within 7 days, dosing resumed at the same dose but on a modified schedule, i.e., panobinostat was administered on MWF for 2 consecutive weeks followed by 1 week off.

The evaluable population in whom the MTD was determined (MTD-determining population) consisted of patients who had been treated with at least nine doses of panobinostat, had been observed for 28 days following the first dose, and had either completed all required safety evaluations or experienced DLT during cycle 1. Patients who did not meet these requirements were considered ineligible for this evaluation and were replaced.

Safety assessments

Safety assessments included an evaluation of AEs according to the NCI CTCAE (version 3.0), regular monitoring of laboratory variables, and a physical examination that included urinalysis, repeated evaluations of cardiac function (including electrocardiography and measurement of cardiac enzymes), and assessments of vital signs, weight, performance status, and thyroid function.

Pharmacokinetics

To determine pharmacokinetic profiles after single and repeated doses, blood samples were collected at time 0 (predose) and 0.5, 1, 2, 3, 4, 8, 24, and 48 h after the oral administration of panobinostat on days 1 and 15 of cycle.

To assess possible time-dependent changes in the pharmacokinetic profile, predose blood samples were also obtained on days 8, 9, and 22 of cycle 1; on day 15 of cycle 2; and on day 1 of cycle 3.

Pharmacokinetic parameters characterizing the disposition of oral panobinostat, such as the median time to reach the maximum plasma concentration (t_{max}), the maximum concentration (C_{max}), $t_{1/2}$, and the area under the curve (AUC), were calculated individually by using a noncompartmental method and were summarized descriptively by scheduled time point (day 1 and day 15) and initial dose cohort.

Pharmacodynamics

Complete blood counts were determined in blood drawn at baseline and on days 1 and 15 of each cycle, and the amount of fetal hemoglobin (HBF) was measured.

Antitumor activity

Tumors were evaluated on day 26 of cycle 1 and on day 1 of every even-numbered cycle (except cycle 2). Tumor response was assessed on the basis of RECIST Criteria or, in the case of patients with CTCL, on the basis of the Physician's Global Assessment of Clinical Condition (PGA), Composite Assessment of Index Lesion Disease Severity (CA), and extramedullary response [9]. Progression-free survival was defined as the time from the start date of treatment to the date of first documented progression or death due to any cause. Progression-free survival was a secondary efficacy variable for patients with a solid tumor.

Statistical analysis

The safety assessment was based on the type and frequency of AEs and on the number of abnormal laboratory values by using the CTC grade. The occurrence of DLT was also summarized by initial dose cohort. The assessment of efficacy was performed by disease type (i.e., solid tumors and CTCL).

Results

Patient demographics

Although 14 patients were enrolled in the study, only 13 patients actually received the study drug. One patient was considered eligible and enrolled; however, during the screening, his left ventricular ejection fraction was found to be 52%. Given the patient's age and the cardiotoxic potential of panobinostat, the patient was considered to be at excessive risk and was not treated. Three patients were treated at a dose of 10 mg on MWF, 4 patients at a dose of 15 mg on MWF, and 6 patients at a dose of 20 mg on MWF. Patient characteristics are summarized in Table 2. Eleven patients had solid tumors, the most frequent primary site of which was the lung (23.1%), and two patients had CTCL (one each with mycosis fungoides and unspecified peripheral T cell lymphoma). Both CTCL patients were treated at a dose of 10 mg on MWF. All patients had a performance status of ≤1 based on WHO criteria.

Treatment administration

Eleven patients (84.6%) were withdrawn from the study because of progressive disease. Two patients (15.4%) were withdrawn because they withdrew consent. As can be seen in Table 3, the median durations of exposure were 82.0, 51.0, and 71.5 days for the 10-, 15-, and 20-mg dose cohorts, respectively. The median duration of exposure was shorter in the 15-mg cohort than in the 10- and 20-mg cohorts, because two of the four patients at the 15-mg dose level discontinued treatment during cycle 1 due to disease progression.

Two patients (50.0%) in the 15-mg cohort and one patient (16.7%) in the 20-mg cohort required dose reductions because of AEs or laboratory test abnormalities. Seven of 13 patients required dose interruptions for the following reasons: 4 because of AEs, 3 because of laboratory test abnormalities, and 1 because of a dosing error. Among the seven patients required dose interruptions, one patient required two separate dose interruptions: one because of an AE and one because of a laboratory test abnormality. Two of these seven patients were in the 15-mg cohort, and five were in the 20-mg cohort.

DLT and MTD

Twelve patients were included in the MTD-determining population (3 patients each at the 10-mg and 15-mg dose levels and 6 patients at the 20-mg dose level). One patient in the 15-mg cohort experienced a decrease in the platelet count (grade 3) on day 15 of cycle 1. Per the protocol-specified criteria, the study drug should have been interrupted at this point; however, treatment continued until day 17, and the patient consistently experienced grade 3 thrombocytopenia for 9 days. In view of this protocol deviation, the Data Safety Monitoring Board considered this patient to be inevaluable, and the patient was therefore excluded from the MTD-determining population. A retrospective review of the data indicated that the interval from the onset of grade 3 thrombocytopenia to the nadir value of 26,000/mm^3 (grade 3) was 5 days, which would not have met DLT criteria had the protocol deviation not occurred. No DLT was observed in the MTD-determining population.

Table 2 Subject characteristics by initial dose cohort

Variable	10 mg on MWF (n=3)	15 mg on MWF (n=4)	20 mg on MWF (n=6)	Total (n=13)
Sex (n)				
Male	2	3	3	8
Female	1	1	3	5
Age (years)				
Median	62.0	61.0	61.5	62.0
Range	53–77	28–71	49–67	28–77
Weight (kg)				
Median	58.2	63.05	55.85	58.2
Range	56.0–63.9	52.9–69.5	45.4–82.0	45.4–82.0
Height (cm)				
Median	162.0	164.5	161.5	163.0
Range	156–171	143–176	147–175	143–176
Platelets (10^9/L)				
Median	376	185.5	257.5	252
Range	305–609	167–215	178–301	167–609
AST (U/L)				
Median	25	23.5	19	20
Range	14–72	16–31	16–25	14–72
ALT (U/L)				
Median	12	22	14.5	15
Range	11–59	12–37	7–21	7–59
Bilirubin (μmol/L)				
Median	6.84	12.825	11.115	10.26
Range	6.84–10.26	5.13–18.81	6.84–13.68	5.13–18.81
Creatinine (μmol/L)				
Median	53.04	65.86	66.74	62.76
Range	53.04–68.07	33.59–81.33	32.71–95.47	32.71–95.47
QT (ms)				
Median	345	360	410	390
Range	337–346	334–390	395–444	334–444
QTcF (ms)				
Median	394	394	413	403
Range	377–397	376–416	383–432	376–432
Primary site, histology/cytology [n (%)]				
Lung, adenocarcinoma	0 (0.0)	1 (25.0)	2 (33.3)	3 (23.1)
Rectum, adenocarcinoma	0 (0.0)	1 (25.0)	1 (16.7)	2 (15.4)
Non-Hodgkin lymphoma, CTCL	2 (66.7)	0 (0.0)	0 (0.0)	2 (15.4)
Colon, adenocarcinoma	0 (0.0)	0 (0.0)	1 (16.7)	1 (7.7)
Esophagus, squamous cell carcinoma	0 (0.0)	1 (25.0)	0 (0.0)	1 (7.7)
Small intestine, leiomyosarcoma	0 (0.0)	0 (0.0)	1 (16.7)	1 (7.7)
Larynx, squamous cell carcinoma	0 (0.0)	0 (0.0)	1 (16.7)	1 (7.7)
Pleura, mesothelioma	1 (33.3)	0 (0.0)	0 (0.0)	1 (7.7)
Thymus, squamous cell carcinoma	0 (0.0)	1 (25.0)	0 (0.0)	1 (7.7)
WHO performance status [n (%)]				
0	2 (66.7)	1 (25.0)	4 (66.7)	7 (53.8)
1	1 (33.3)	3 (75.0)	2 (33.3)	6 (46.2)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

ALT alanine transaminase, *AST* aspartate aminotransferase, *CTCL* cutaneous T-cell lymphoma, *MWF* Monday, Wednesday, and Friday, *WHO* World Health Organization

Table 3 Duration of exposure and duration of treatment by initial dose cohort

	10 mg MWF (n=3)	15 mg MWF (n=4)	20 mg MWF (n=6)	Total (n=13)
Duration of exposure[a] (days)				
Mean ± SD	72.7±29.14	52.8±34.56	106.0±85.92	81.9±64.12
Median	82.0	51.0	71.5	75.0
Range	40–96	22–87	26–253	22–253
Duration of treatment[b] (days)				
Mean ± SD	32.0±12.49	18.5±9.33	43.2±36.69	33.0±27.03
Median	36.0	18.0	27.5	26.0
Range	18–42	10–28	12–109	10–109

[a] Duration of exposure was defined as the time from the last known date the study drug was taken minus the time that the study drug was started + 1 (interruption periods were included). [b] Duration of treatment was defined as the total number of days that the study drug was taken (interruption periods were not included)

Safety and tolerability

All patients who received at least one dose of panobinostat experienced more than one AE. AEs occurring in at least 20% of the safety population, regardless of whether they were related to the study drug, are shown in Table 4. Grade 3 or 4 AEs occurred in 8 patients. Three grade 4 events were reported in 2 patients: thrombocytopenia for each patient, and decreased hemoglobin concentration.

The most frequently reported AEs, regardless of whether they were related to the study drug, were diarrhea and nausea (10 patients each, 76.9%), but most of the episodes were mild to moderate in degree. Thrombocytopenia was reported in 12 of 13 patients (92.3%); the exact MedDRA

Table 4 Adverse events (AEs), regardless of whether they were related to the study drug, by preferred terms, occurring in at least 20% of the population and in the initial dose cohort

Preferred terms	All grades				Grade 3/4			
	10 mg (n=3)	15 mg (n=4)	20 mg (n=6)	All (n=13)	10 mg (n=3)	15 mg (n=4)	20 mg (n=6)	All (n=13)
Patients with AEs, n (%)	3 (100.0)	4 (100.0)	6 (100.0)	13 (100.0)	1 (33.3)	2 (50.0)	5 (83.3)	8 (61.5)
Thrombocytopenia[a]	2 (66.7)	4 (100.0)	6 (100.0)	12 (92.3)	0 (0.0)	2 (50.0)	3 (50.0)	5 (38.5)
Hemoglobin decreased	0 (0.0)	0 (0.0)	3 (50.0)	3 (23.1)	0 (0.0)	0 (0.0)	1 (16.7)	1 (7.7)
Diarrhea	3 (100.0)	3 (75.0)	4 (66.7)	10 (76.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	3 (100.0)	3 (75.0)	4 (66.7)	10 (76.9)	1 (33.3)	0 (0.0)	0 (0.0)	1 (7.7)
Vomiting	2 (66.7)	2 (50.0)	4 (66.7)	8 (61.5)	1 (33.3)	0 (0.0)	0 (0.0)	1 (7.7)
Fatigue	0 (0.0)	1 (25.0)	4 (66.7)	5 (38.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	2 (66.7)	0 (0.0)	3 (50.0)	5 (38.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight decreased	2 (66.7)	2 (50.0)	1 (16.7)	5 (38.5)	0 (0.0)	1 (25.0)	0 (0.0)	1 (7.7)
Blood albumin decreased	0 (0.0)	0 (0.0)	3 (50.0)	3 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood thyroid-stimulating hormone increased	0 (0.0)	1 (25.0)	2 (33.3)	3 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
C-reactive protein increased	1 (33.3)	0 (0.0)	2 (33.3)	3 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anorexia	2 (66.7)	1 (25.0)	4 (66.7)	7 (53.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	0 (0.0)	1 (25.0)	2 (33.3)	3 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain in extremity	1 (33.3)	0 (0.0)	2 (33.3)	3 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	1 (33.3)	2 (50.0)	1 (16.7)	4 (30.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysgeusia	2 (66.7)	0 (0.0)	2 (33.3)	4 (30.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cough	0 (0.0)	2 (50.0)	1 (16.7)	3 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	1 (33.3)	0 (0.0)	2 (33.3)	3 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Thrombocytopenia including the MedDRA terms "thrombocytopenia" and "platelet count decreased"

(Medical Dictionary for Regulatory Activities) terms used were "thrombocytopenia" (7/13) and "platelet count decreased" (5/13). Thus, thrombocytopenia was the most frequently reported AE in this trial. Of the eight patients in whom grade 3/4 AEs occurred, five (62.5%) experienced thrombocytopenia. Although these patients required an interruption of the study drug, platelet counts recovered rapidly to grade 1 or less within 7 days in most cases.

The incidence of fatigue increased with increasing doses (0 of 3 patients at the 10-mg dose, 1 of 4 patients at the 15-mg dose, and 4 of 6 patients at the 20-mg dose), and this trend was the same as that observed in previous studies in a non-Japanese population [10].

Newly occurring or worsening abnormal electrocardiographic findings in the initial dose cohort are provided in Table 5. Absolute QT/QTcF prolongation was not observed in any of the patients. QT prolongation >60 ms was recorded in one patient in the 10-mg dose group, and QTcF prolongation >60 ms was recorded in another patient. Neither of these patients had any relevant symptoms. T wave abnormalities on the electrocardiogram, which were reported as AEs, were suspected to be related to the study drug in one patient (20-mg dose group).

Pharmacokinetics

Pharmacokinetic data were available for 13 patients. Plasma panobinostat concentration profiles on days 1 and 15 are shown in Fig. 1. After oral administration, panobinostat was rapidly absorbed, and the t_{max} was 1–2 h. The mean elimination $t_{1/2}$ of panobinostat ranged from 9 to 14 h on day 1 and from 17 to 18 h on day 15, respectively (Table 6). The plasma concentration of panobinostat at 48 h was below the lower limit of quantification on day 1 in most patients.

Pharmacodynamics

In five patients (three with colorectal cancer, one with non-small cell lung cancer, and one with esophageal cancer), the percentage of HBF increased over time during the study period. In the remaining patients, no suggestive trend in HBF was observed, and the differences in HBF from day 1 to the end of the study were ≤0.2%. No relation between panobinostat administration and HBF was observed.

Antitumor activity

Thirteen patients were evaluable for response. Tumor types and responses are shown in Table 7. Seven of 13 patients had stable disease. No complete responses or partial responses were observed. Two patients in the 15-mg cohort had progressive disease. Of 11 patients with solid tumors, 5 (1 in the 10-mg cohort and 4 in the 20-mg cohort) had stable disease. Two patients in the 20-mg cohort with stable disease had progression-free survival of 164 and 253 days, respectively. The two CTCL patients (both in the 10-mg cohort) had stable disease. The best PGA and CA responses indicated stable disease.

Discussion

This study showed that a dosing schedule of 20 mg oral panobinostat once daily for three noncontiguous days (MWF) weekly was well-tolerated in Japanese patients with advanced solid tumors or CTCL. No DLT was observed in patients in any cohort, and the MTD was not reached in the study. Panobinostat may be tolerable at higher doses; however, this possibility should be explored in future studies.

Table 5 Abnormal electrocardiographic findings by initial dose cohort

	10 mg on MWF (*n*=3)	15 mg on MWF (*n*=4)	20 mg on MWF (*n*=6)	Total (*n*=13)
Maximum absolute QT/QTcF [*n* (%)]				
QT >500 ms (CTCAE grade 3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QT >480 ms and ≤500 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QTcF >500 ms (CTCAE grade 3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QTcF >480 ms and ≤500 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maximum QT/QTcF increase from baseline [*n* (%)]				
>30 ms and ≤60 ms in QT	1 (33.3)	0 (0.0)	1 (16.7)	2 (15.4)
>60 ms in QT (CTCAE grade 2)	1 (33.3)	0 (0.0)	0 (0.0)	1 (7.7)
>30 ms and ≤60 ms in QTcF	1 (33.3)	0 (0.0)	0 (0.0)	1 (7.7)
>60 ms in QTcF (CTCAE grade 2)	0 (0.0)	0 (0.0)	1 (16.7)	1 (7.7)

CTCAE Common Terminology Criteria for Adverse Events, *MWF* Monday, Wednesday, and Friday

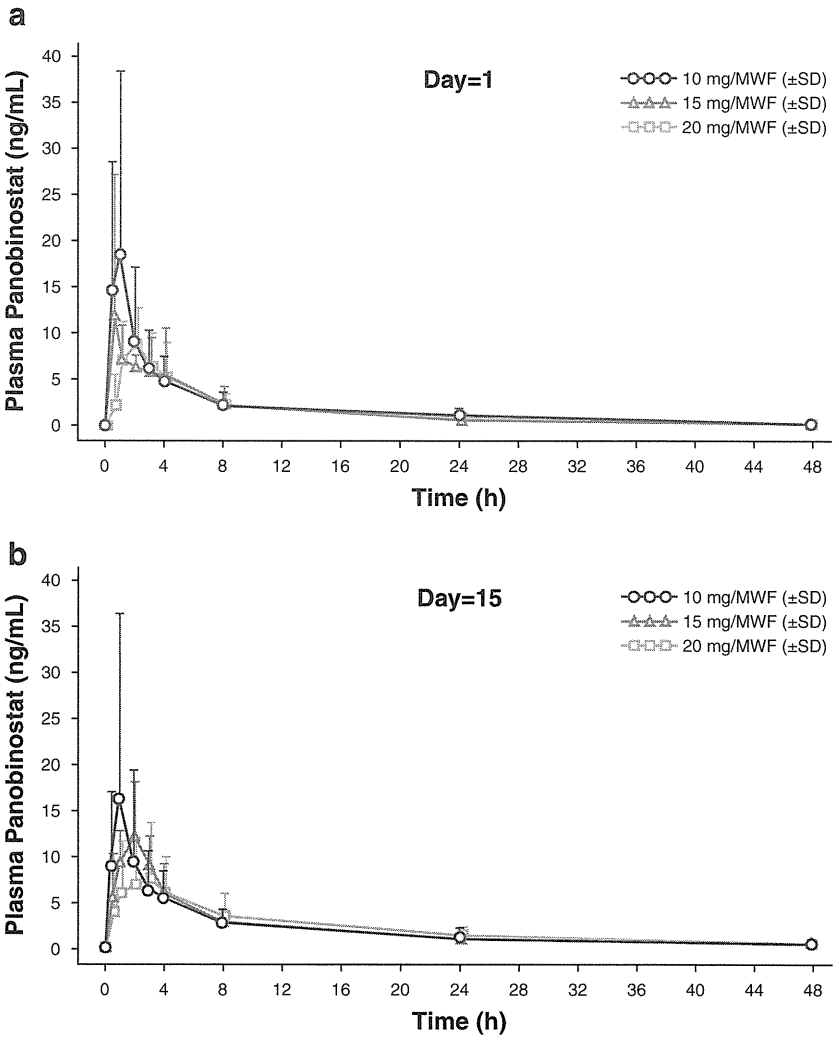

Fig. 1 **a** Panobinostat plasma concentrations on day 1 by initial dose cohort (mean + SD). Panobinostat was administered orally once daily on Monday, Wednesday, and Friday of each week. Pharmacokinetic data of panobinostat were obtained from 3, 4 and 6 patients in 10 mg, 15 mg and 20 mg cohorts, respectively. **b** Panobinostat plasma concentrations on day 15

The most frequently reported grade 3 or 4 AE was thrombocytopenia, but all such events were transient and resolved after the study drug was interrupted. No hemorrhage-related AEs were reported. Thrombocytopenia is a commonly reported AE and is a classic side effect of DACIs [11]. Recently, it was reported that DACIs inhibit GATA-1 gene expression in megakaryocytes by decreasing the transactivation function of GATA-1 itself. GATA-1 is a prototypic erythro-megakaryocytic transcription factor that plays an essential role in the differentiation of megakaryocytes and erythrocytes [12]. This GATA-1 reducing activity of DACIs may lead to a delay in megakaryocyte maturation and may cause thrombocytopenia. This proposed mechanism of action is supported by the in vivo result that administration of a potent HDACI (FR235225) to rats for 7 days resulted in a decrease in the peripheral platelet count and an increase in splenic megakaryocytes in a dose-dependent manner [13]. The rapid recovery of platelet counts seen in our study suggests that the mechanism of DACI-induced thrombocytopenia might be different from that of the typical cytotoxic agent–induced myelosuppression.

Because of the possible interaction of DACIs with the HERG K^+ channel, cardiac toxicity is a safety concern of DACIs [14, 15]. However, no serious cardiac toxicity was reported in our study. QTcF prolongation of 30 to 60 ms and of ≥60 ms was observed in 7.7% of the study population in our study, which was not greater than the results obtained in an integrated analysis of oral panobinostat in Western patients: QTcF changes of 30 to 60 ms and of ≥60 ms in 79 patients (27.1%) and 11 patients (3.8%), respectively, out of a total of 291 patients who received 20 mg panobinostat weekly on MWF [16].

The average exposure (C_{max} and AUC) did not increase with increasing dose, which may have been due to the large interindividual variability (coefficient of variation: 20–90% for C_{max} and AUC) and the limited number of pharmacokinetic profiles. Therefore, we were unable to draw any conclusions regarding the dose proportionality, or the lack thereof, of panobinostat pharmacokinetics in the Japanese

Table 6 Pharmacokinetic parameters by initial dose cohort

Time and pharmacokinetic parameter[a]	10 mg on MWF (n=3)	15 mg on MWF (n=4)	20 mg on MWF (n=6)
Day 1			
t_{max} (h)[b]	1.0 (0.5–2.0)	1.2 (0.5–4.0)	1.5 (0.5–3.0)
C_{max} (ng/mL)	20.5±18.9	16.6±11.4	10.8±3.0
$AUC_{0\text{-}24\ h}$ (h · ng/mL)	91.2 (36.5, 146)[c]	67.4±30.6	66.5±28.7
$AUC_{0\text{-}inf}$ (h · ng/mL)	129 (44.6, 214)[c]	79.0±44.8	91.3±43.5[d]
$t_{1/2}$ (h)	15.8 (9.27, 22.3)[c]	9.2±3.9	12.8±5.1
Vz/F (L)	2249 (1500, 2998)[c]	2633±894	3878±2061[d]
CL/F (L/h)	135 (46.7, 224)[c]	230±101	263 ±144[d]
Day 15			
t_{max} (h)[b]	1.0 (0.5–4.0)	1.5 (0.4–2.0)	2.0 (0.5–8.0)
C_{max} (ng/mL)	19.4 ±18.3	14.4±4.3	11.6±6.1
$AUC_{0\text{–}24}$ (h · ng/mL)	89.1±60.0	88.5±25.7	87.9±40.8
$AUC_{0\text{-}inf}$ (h · ng/mL)	177 (107, 247)[c]	133±35.1[d]	153±57.5[e]
$t_{1/2}$ (h)	18.4±6.3	17.8±5.5	18.4±5.0[f]
Vz/F (L)	2094 (1334, 2854)[c]	2548±540[d]	3598±1086[e]
CL/F (L/h)	67.0 (40.4, 93.6)[c]	118±27.2[d]	150±68.6[e]

[a] Values are means ± SDs, unless otherwise noted. [b] Values are medians (ranges). [c] n=2; values are mean (individual values). [d] n=3. [e] n=4. [f] n=5. AUC, area under the curve; CL/F, apparent clearance; Vz/F, volume of distribution during the terminal phase

subjects. Additional research is necessary to address this issue properly. When plasma concentrations of panobinostat after oral administration were compared between Japanese and non-Japanese subjects in a previous study [10], the average concentration appeared to be somewhat lower in the Japanese subjects. However, the range of individual values between the two populations largely overlapped. This apparent difference may have been attributable to the large interindividual variability and limited number of patients; therefore, these data did not conclusively indicate an ethnic difference in the pharmacokinetic profile of panobinostat. A meta-analysis including other ongoing studies will enable us to clarify the cause of the large interindividual variability, including potential ethnic factors.

HBF is the predominant hemoglobin in the fetus, but it is gradually replaced by adult hemoglobin after birth. Experi-

Table 7 Tumor response to panobinostat

Tumor type	Dose level (mg/day)	Prior medication use		PFS (days)	Best response
		No. of regimens	Antineoplastic drugs used		
CTCL	10	2	Predonine, cyclosporine	–	Stable disease
CTCL	10	4	Etoposide, INF-γ, nidran	–	Stable disease
Mesothelioma	10	4	Cisplatin, gemcitabine, irinotecan	78	Stable disease
Esophagus	15	3	Fluorouracil, cisplatin, nedplatin, docetaxel	85	Unknown
CRC	15	5	Irinotecan, fluorouracil, doxorubicin, mitomycin c, cisplatin, oxaliplatine, s-1	78	Unknown
Thymus	15	1	Paclitaxel, carboplatin	24	Progressive disease
NSCLC	15	5	Paclitaxel, carboplatin, gefitinib, gemcitabine, irinotecan	23	Progressive disease
Larynx	20	5	Cisplatin, fluorouracil, carboplatin, paclitaxel, s-1, docetaxel	≥25	Unknown
CRC	20	3	Oxaliplatine, s-1, fluorouracil, irinotecan	51	Unknown
CRC	20	3	Tegafur uracil, irinotecan, s-1, fluorouracil, oxaliplatine	79	Stable disease
Leiomyosarcoma	20	1	Imatinib	164	Stable disease
NSCLC	20	6	Vinorelbine, cisplatin, gefitinib, s-1, gemcitabine, docetaxel	71	Stable disease
NSCLC	20	2	Gemcitabine, cisplatin, docetaxel	253	Stable disease

CRC colorectal cancer, *CTCL* cutaneous T-cell lymphoma, *INF-γ* interferon gamma, *NSCLC* non-small cell lung cancer, *PFS* progression-free survival

mental studies have shown that DACIs can induce the re-expression of HBF [17]. We measured HBF to evaluate whether it could be used as a pharmacodynamic biomarker of DACIs; however, no apparent relation was observed between panobinostat administration and HBF. In our study, an absolute increase in HBF over time was observed in all three colorectal cancer patients. This finding supports recent evidence of HBF-containing red blood cells within colorectal tumor tissues, which suggests that the colonic microenvironment may stimulate extra-medullary fetal-type hematopoiesis [18].

Unfortunately, despite promising preclinical evidence, little clinical activity was observed in this trial. No objective responses were observed, although one patient with leiomyosarcoma and one with non-small cell lung cancer achieved progression-free survival of >5 months. However, encouraging activity at higher doses was recently reported. Panobinostat induced clinical responses in CTCL patients who received doses of 20 or 30 mg on MWF, although in the trial a dose of 30 mg on MWF was considered excessively toxic [7] Additionally, clinical responses have been observed in heavily pretreated patients with Hodgkin lymphoma who received panobinostat at doses ≥30 mg on MWF weekly or ≥45 mg on MWF every other week [19].

Panobinostat should be explored at higher doses than evaluated in this trial. Based on the patient population evaluated in this trial (i.e. advanced solid tumors or CTCL), and emerging global clinical data at that time the decision was made to stop dose escalation at 20 mg. Of note, in a preliminary report of a trial in Western patients (conducted in Australia, Germany, and the United States) with solid tumors or Non-Hodgkin lymphoma receiving oral panobinostat on a MWF schedule, dose-limiting toxicities of grade 3 diarrhea and grade 4 thrombocytopenia were observed at 30 mg and grade 3 fatigue at 20 mg [8]. However, the results obtained here suggest that single-agent treatment with panobinostat at 20 mg on MWF might be suboptimal and that greater clinical benefit might be observed at higher doses.

Panobinostat is likely to have greater therapeutic potential when administered in combination with other therapeutic agents. Recently, panobinostat in combination with bortezomib showed antitumor activity against relapsed or refractory multiple myeloma in a phase Ib trial. Clinical efficacy was observed in 18 (14 partial or better responses and 4 minor responses) of 28 evaluable patients (64%). Responses were also seen in patients refractory to prior bortezomib treatment, which suggests synergy of the combination [20]. Furthermore, from a theoretical standpoint, many anticancer agents have the potential to synergize with the epigenetic regulation mediated by panobinostat; e.g., drugs that have an overlapping mechanism of action or drugs that affect the same target through a complementary mechanism of action, which needs to be confirmed in future clinical trials.

In conclusion, a dose of 20 mg of panobinostat administered orally on MWF has been confirmed to be safe and tolerable for patients with advanced solid tumors or cutaneous T-cell lymphoma, although further studies should be conducted to establish the MTD. Given the promising data concerning the efficacy of panobinostat in Western patients with Hodgkin lymphoma and multiple myeloma, studies in Japanese patients with hematologic tumors should also be undertaken.

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ORIGINAL PAPER

Development of Fundamental Infrastructure for Nationwide EHR in Japan

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Abstract The movement of create medical information systems that is now taking place involves both progress in EMR (Electronic Medical Records)—computerization of records at hospitals and clinics, and also in EHR (Electronic Health Records) in which information is shared with individual regions. However, the geographical coming and going of people in modern society is extremely active. Naturally the places these people move to are not necessarily within the same region. For this reason, even if the basic unit for the health care supply system is in practical terms limited to the local level, if services are restricted to only one region, many persons may be unable to receive the benefits of health care cooperation. In this study, we constructed a mechanism for a medical cooperation system which links the EHR systems of individual regions and is able to create a one-patient, one-record system on the national level. In this paper, we will provide a report of this mechanism and of the 4-year operational trial.

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Introduction

The movement of create medical information systems that is now taking place involves both progress in EMR (Electronic Medical Records) computerization of records at hospitals and clinics, and also in EHR (Electronic Health Records) in which information is shared with individual regions. A variety of trials have been carried out worldwide for this purpose, primarily in developed countries, and informatics is also receiving attention as an effective means of improving the efficiency of medical services in newly industrialized and developing countries as well. For example under the leadership of the state, Canada and England have invested at least 1.6 billion U.S. dollars [1] and 20 billion U.S. dollars [2] respectively. It is said that the United States will invest 20 billion U.S. dollars in switching to electronic medical documents. For EHR, many successful examples in sharing medical information within regions continue to be reported from around the world, and several EHR projects have been carried out in Japan as well [3].

However the geographical coming and going of people in modern society is extremely active. In the United States, 35 million people change their place of residence each year [4], and it is said that on average a person in Japan moves 5 times in his or her life [5]. Naturally the places these people move to are not necessarily within the same region. For this reason, even if the basic unit for the health care supply system is in practical terms limited to the local level, if services are restricted to only one region, many persons may be unable to receive the benefits of health care

cooperation. In this study, we constructed the actual fundamental infrastructure needed for local medical EHR, and carried out EHR projects in several regions of Japan [6], and during this study we found that it will be impossible to gain a comprehensive grasp of patient medical information at the national level only because no solution to the problems caused by movement of patients. Of course, we cannot use national identified number in Japan, so it make the solving problems more difficult.

Therefore when considering the future development of EHR, a mechanism for consolidating local-level medical information on the national level, as well as functions for data compatibility and other purposes, will be needed.

In this study, we constructed a mechanism for a medical cooperation system which links the EHR systems of individual regions and is able to create a one-patient, one-record system on the national level. In this paper, we will provide a report of this mechanism and of the 4-year operational trial.

Methods

As we discuss a mechanism for medical cooperation between regions, we will first describe the current conditions of inter-regional medical cooperation in Japan.

Local-level EHR

Many regions in the world have created EHR systems for managing patient medical data within that region, and many projects have been launched using these systems as hubs for coordinated health care and the provision of medical record [1, 7, 8]. For these purposes, it is necessary to ensure safe routes of information between the medical institutions and the system, and also to create a mechanism that allows patients to safely view medical data via the internet, which penetration rate is 78.0% in Japan [9]. The formulation and operation of an open standard for exchanging medical data from a wide variety of medical records are also important [10]. In Japan as well, there are many EHR systems operating in individual regions. In these cases, the systems are operated in a way that makes best use of the unique characteristics of each region. Data exchange is accomplished in a variety of ways, including direct connections to the hospital information systems of large scale hospitals, and exchange using MML (Medical Markup Language) [11, 12] or HL7 (Health Level 7) [13]. Because it is the local governments which are directly faced with a need for health care cooperation in the region, in many cases the systems are operated under the leadership of the local governments, and currently it is difficult to carry out activities that span multiple regions.

Construction of a mechanism for wide-area medical cooperation

As described above, attempts to integrate local EHR systems and carry out services over a wide area face a number of problems. One is data-level integration. Although some believe that collecting data using a single unified format is sufficient, this approach is not practical when one considers the current conditions in which many independent local EHR systems are operating, using various formats. The solution is data conversion (mapping) on the content level between different data structures.

Another problem is fragmentation among EHRs because of lack of national level patient's identification. It is thought that this problem can be resolved by assigning an internal upper-level ID at upper-level sites in place of the unique IDs used on the local level, and to assign the local IDs to these upper-level IDs (essentially assigning them to an upper-level directory structure) [14]. Following is a description of data mapping and the upper-level directory structure.

Data mapping

Absorbing differences in data structures can be accomplished by constructing a mechanism for XML (eXtensible Markup Language) data mapping. Figure 1 shows a concept diagram of XML data mapping. A document has a format showed in the left-hand side while another document has a format showed in the right-hand side. For example, the document on the left-hand side in Fig. 1 defines the patient ID as <ID>, while the document on the right-hand side defines it as <SocNum>. If these two are considered equivalent, they can be mapped so that they can be converted back and forth. In the same way, <given name> and <first name> is another example that is often seen. If the XML label and the data indicated by that label have the same code system, they can also be mapped. For example, if <disease> in the left-hand document contains an ICD-10 code, then it can be converted to the <ICD code> in the right-hand document.

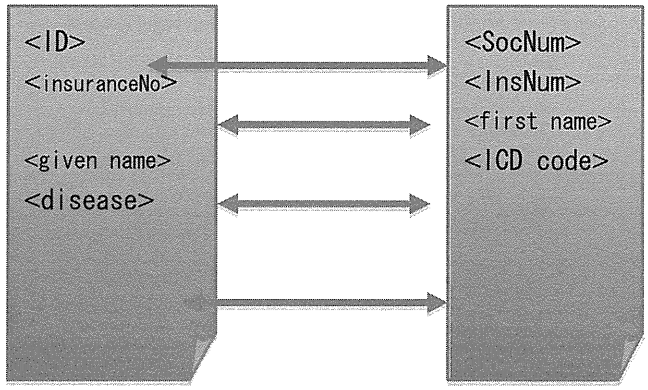


Fig. 1 XML data mapping

There have been reports of cases in which XML data mapping is used for bidirectional data conversion between EMR and EHR [15], and commercially products such as Asteria from the Infoteria Corporation (Japan) [16] and Rhapsody™ from Orion Health (New Zealand) [17] have been marketed as middleware intended for medical use. Use of these sorts of products makes data compatibility possible.

Upper-level directory structure

On the national level, if it is possible to issue and use a unique patient ID to each citizen on the national level, then such IDs can be used. However in many countries including Japan, use of these IDs in EHR is difficult. If a person is issued different patient IDs by multiple local EHR systems, it is necessary to understand that these different patient IDs actually indicate the same person. For this purpose, when a certain local EHR system issues a patient ID, an authorized organization can issue an upper-level patient ID for the national level, and can manage the links between patient IDs in multiple local EHR systems [18]. Using this mechanism, when a search for user data is performed using any local EHR system patient ID, it is possible to send a search request to other local EHR systems by means of the upper-level patient ID and return complete and integrated search results. Figure 2 shows a concept diagram of this process.

Actual system

In this study, we constructed a nationwide-capable EHR directory service (super site), with named "Super Dolphin" that includes the XML data mapping and upper-level directory structure described earlier, and verified that it is possible to link multiple local EHR systems together. Specifically, the subjects were two regions of Japan (Miyazaki and Kyoto) where EHR systems are actually operating. These two local EHR systems were connected to the super site that we constructed, and this super site was given the name "Super Dolphin". The NPO Japan Medical Network Association, which was established since 2005 to implement nationwide EHR manages this super site [19].

Table 1 is an overview of the two local EHR systems which were the subjects of this test.

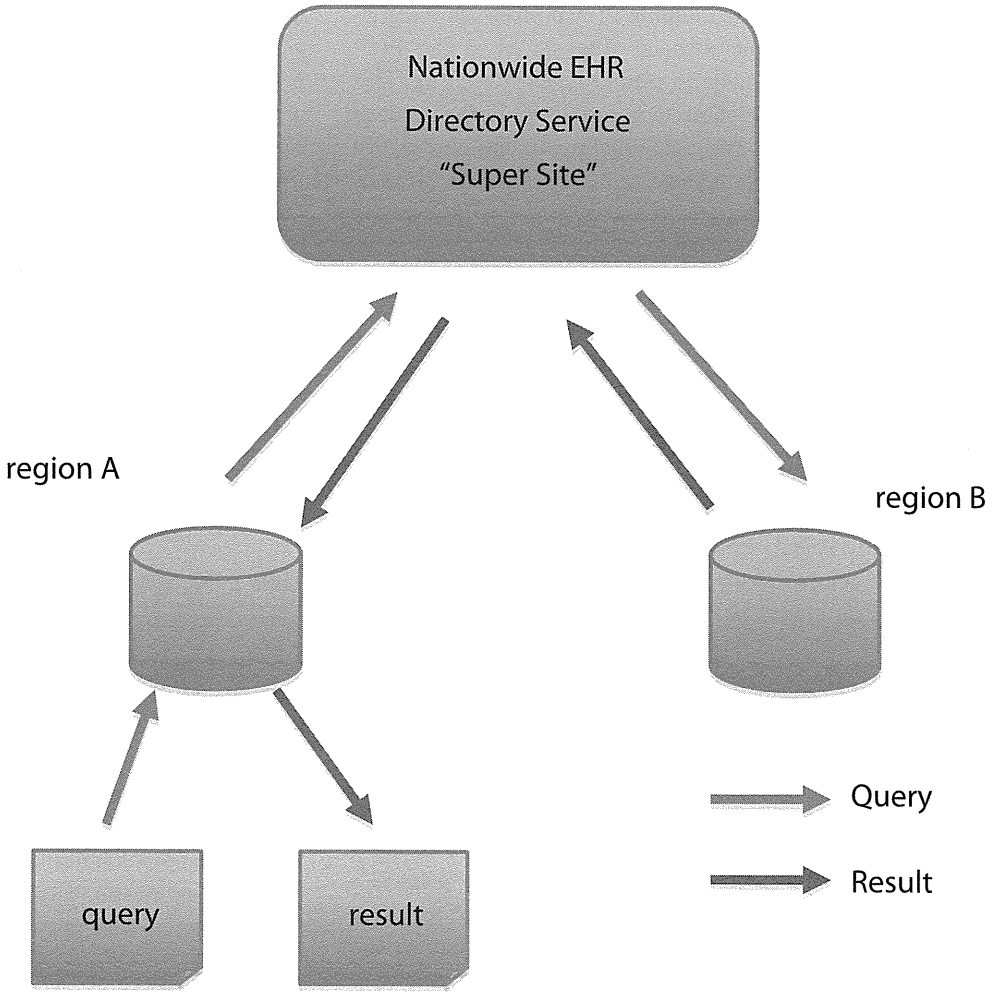


Fig. 2 Concept diagram of upper-level directory structure

Table 1 Test conditions

1) Local EHR systems and using data formats
Miyazaki EHR system (haniwa): Using MML2.3
Kyoto EHR system (maiko): Using MML3.0 (CDA* rel.1 compliant)
2) Upper-level site: Super Dolphin
3) Paths: The two local EHR systems and Super Dolphin were connected by Japan Gigabit Network version2 (JGN2**)
The internet is used for the communications route from the medical institutions to the center server

*CDA** clinical document architecture

JGN2** is research and development testbed network operated by the National Institute of Information and Communications Technology (NiCT) in Japan

Both the Miyazaki and Kyoto EHR systems are EHR systems that were constructed within the framework of the Dolphin Project [2]. The Dolphin Project was proposed by Yoshihara et al. in 1997 [11], and took its first step toward becoming reality in 2000 as a R&D project of the Ministry of Economy, Trade and Industry, Japan. Subsequently, experimental EHR services were launched in two regions, Kumamoto [20] and Miyazaki [21], in December 2001 and remain in use today. Later, full-scale projects aimed at providing practical services were launched in Tokyo [22], Kyoto [23], and other major cities.

The framework of the Dolphin Project involves integrated management of the medical data stored in the EHR system central server under a certain level of security. This allows medical practitioners to centrally view the medical data of patients who have concluded treatment agreements, and allows coordinated medical care. Patients can also view their own medical data (electronic record disclosure) and can enter symptoms and other information into their own records. The central server is connected to clinics, hospitals, laboratory test services, pharmacies, home nursing-care stations, and other facilities, which can send information such as past histories, laboratory results, letters of introduction, and discharge summaries. This information is all integrated and stored for each patient. In addition to sharing of local treatment data, this information is also used as a backup for the record data of each medical institution. In the Dolphin Project, the data of each medical institution is sent to the central server using MML, HL7, or other data format and is stored by the server in a database. A web interface is provided to the patients and medical practitioners. At present, each region is currently operating an original system utilizing the above basic design but making use of the local characteristics. The scale of each local project is as shown below (Table 2).

In this study, each patient is issued a unique patient ID in the local EHR system where person wants to receive service. Using this ID, the patient is able to view pateient's own medical information within the region. When a patient wants to view his/her own medical information from another region, by linking the patient IDs from multiple local EHR systems, Super Dolphin allows medical information from different regions to be viewed.

When a search for medical information is performed on the Miyazaki or Kyoto system, first a query is sent to the database of that local EHR system using the patient ID as the key. At the same time, the local EHR system sendsa query to Super Dolphin to check whether or not that patient ID is linked with patient IDs in other regions. As a result of this query, if the patient ID is found to be linked to an EHR system patient ID in another system, Super Dolphin uses this link information to request a search. The obtained data is converted to the data structure used by the data center which sent the request, and displayed. Communications between each EHR system and the super site utilize a local area network that uses the JGN2 network (Japan Giga Network version2) [24] provided jointly by the Ministry of Internal Affairs and Communications (MIC) and by NiCT. For local EHR systems and users, communication uses SSL with security functions utilizing Certification Authorities. The overall configuration is shown in Fig. 3.

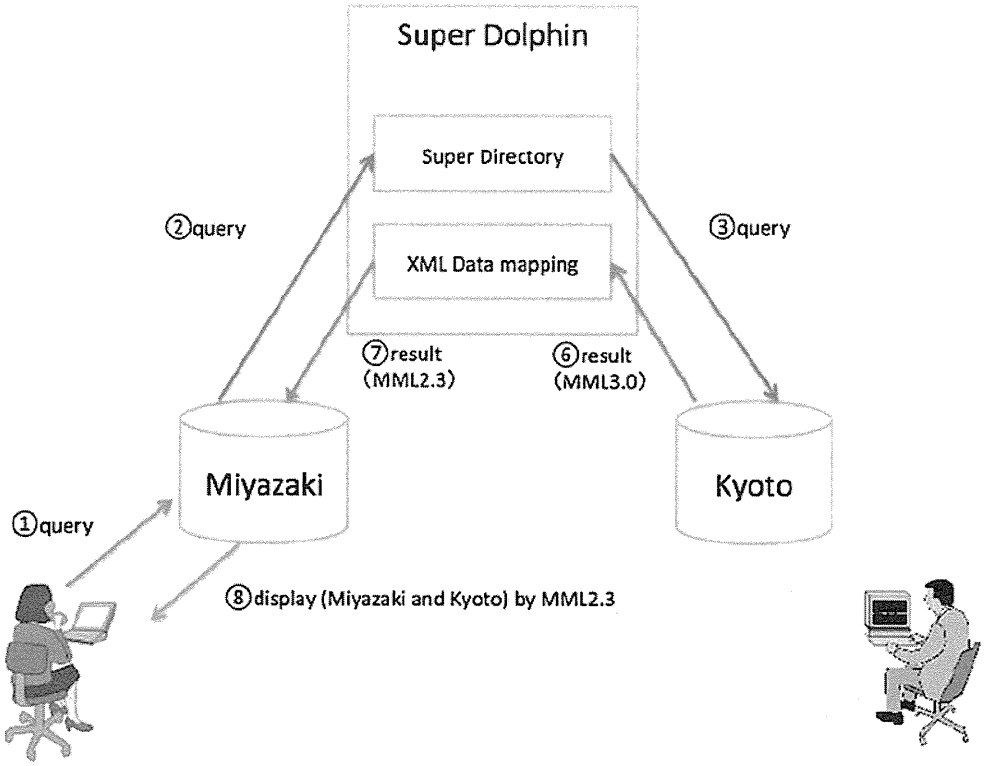
Results

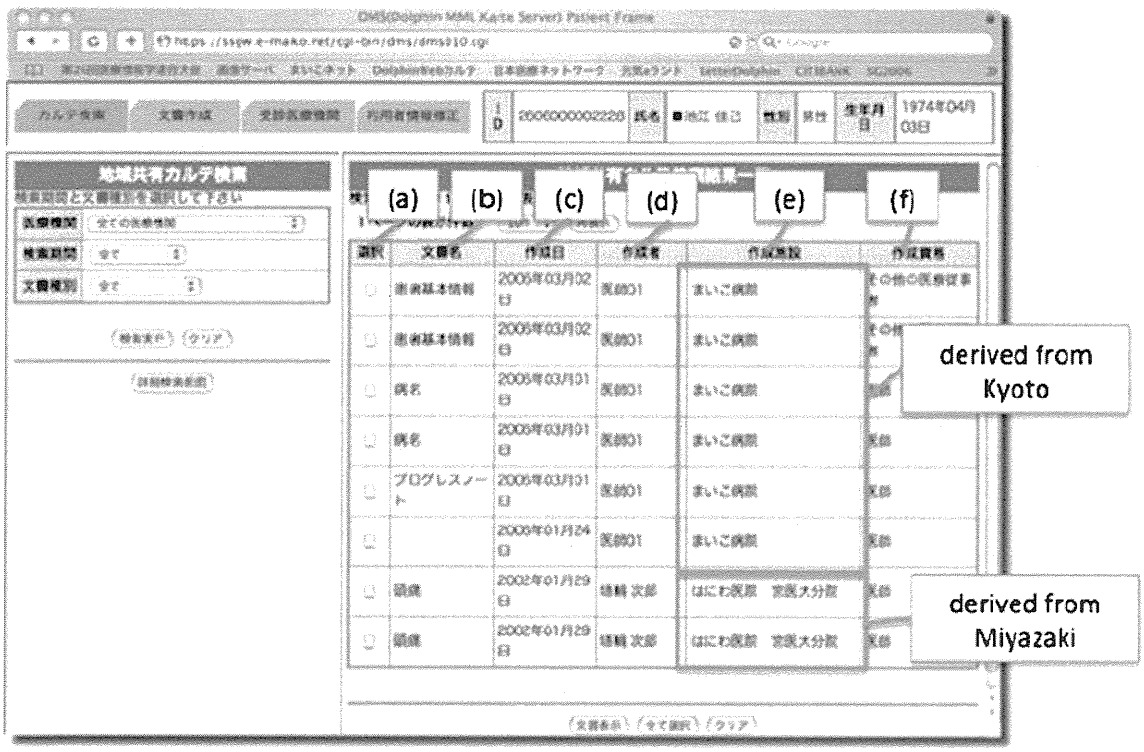
Figure 4 shows an example of the results from display of patient medical data.

Table 2 The scale of each local project

	Miyazaki	Kyoto
Registered patients	1078	1,100
Registered medical institutions	84	5
Registered physicians	478	2,000
Monthly views (physicians)	185	100
Monthly views (patients)	60	2,000
No. of documents sent (text)	1,600,000	7,000,000
No. of documents sent (images)	85,000	86,000
Year started	2002	2007

Measurement date is 30 Oct 2010





(a): check box,(b): medical document name, (c): document date,
(d): document author name, (e): medical institution name,
(f): author category(doctor, nurse, etc)

Fig. 3 Overall super dolphin configuration

Fig. 4 Patient medical data