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

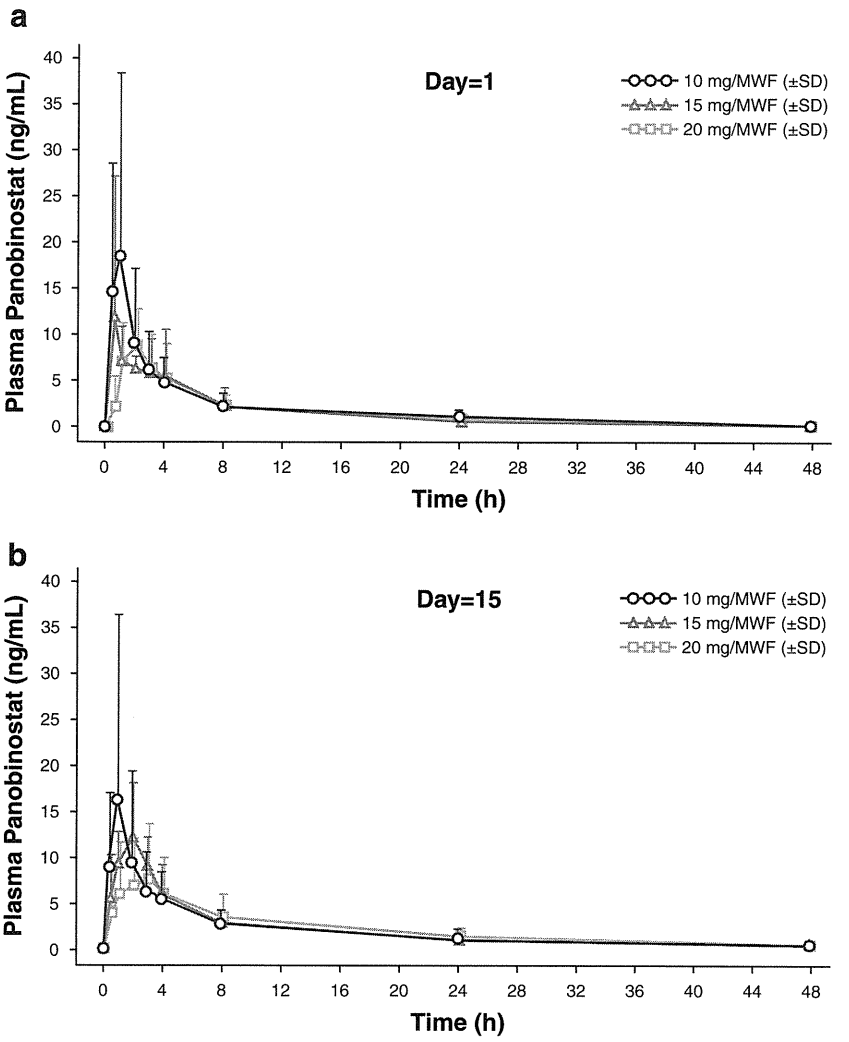

Fig. 1 **a** Panobinostat plasma concentrations on day 1 by initial dose cohort (mean + SD). Panobinostat was administered orally once daily on Monday, Wednesday, and Friday of each week. Pharmacokinetic data of panobinostat were obtained from 3, 4 and 6 patients in 10 mg, 15 mg and 20 mg cohorts, respectively.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

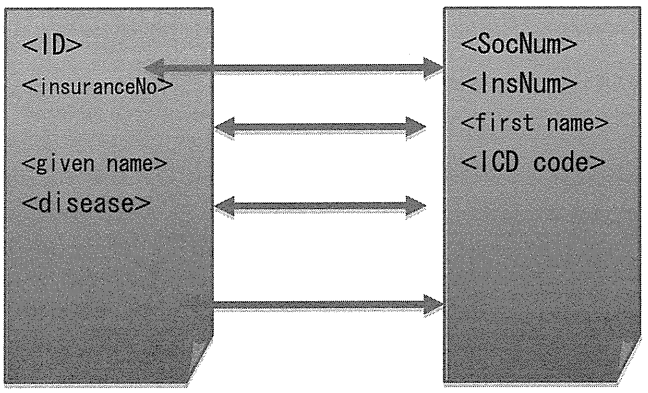


Fig. 1 XML data mapping

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.

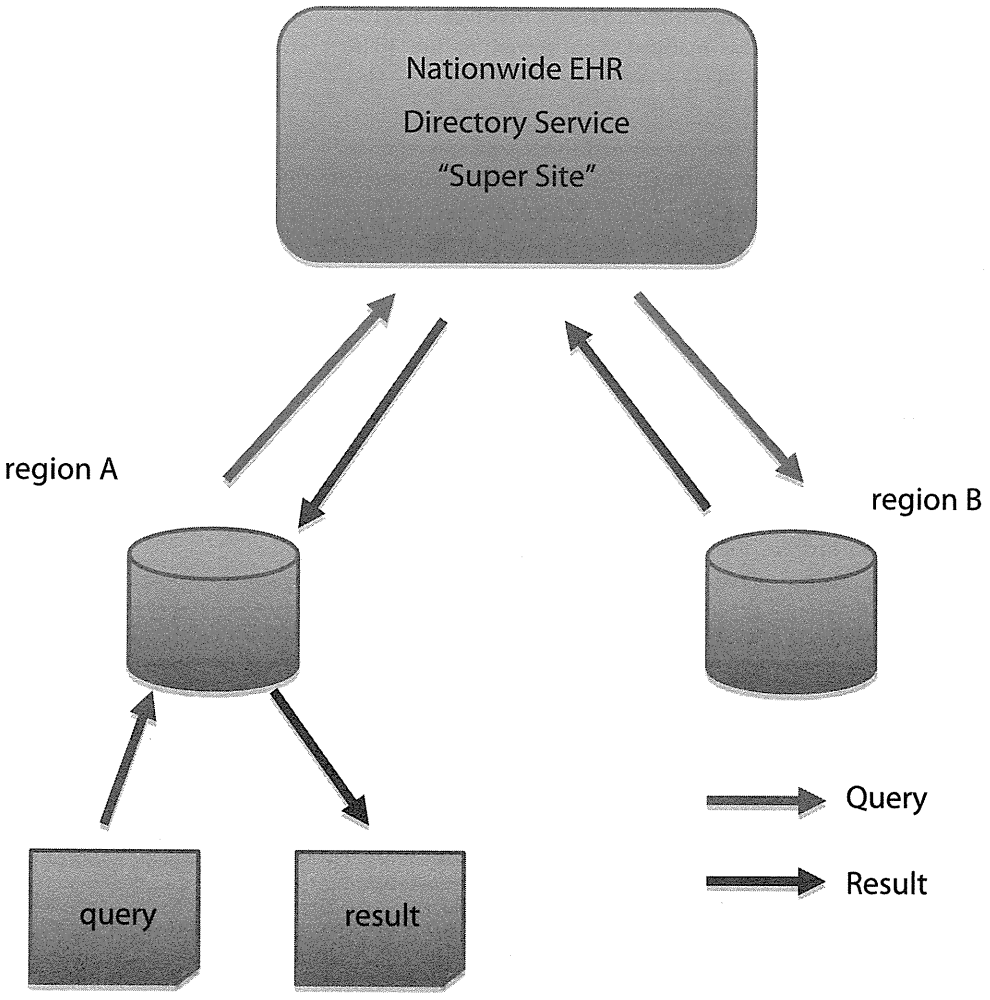


Fig. 2 Concept diagram of upper-level directory structure

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.

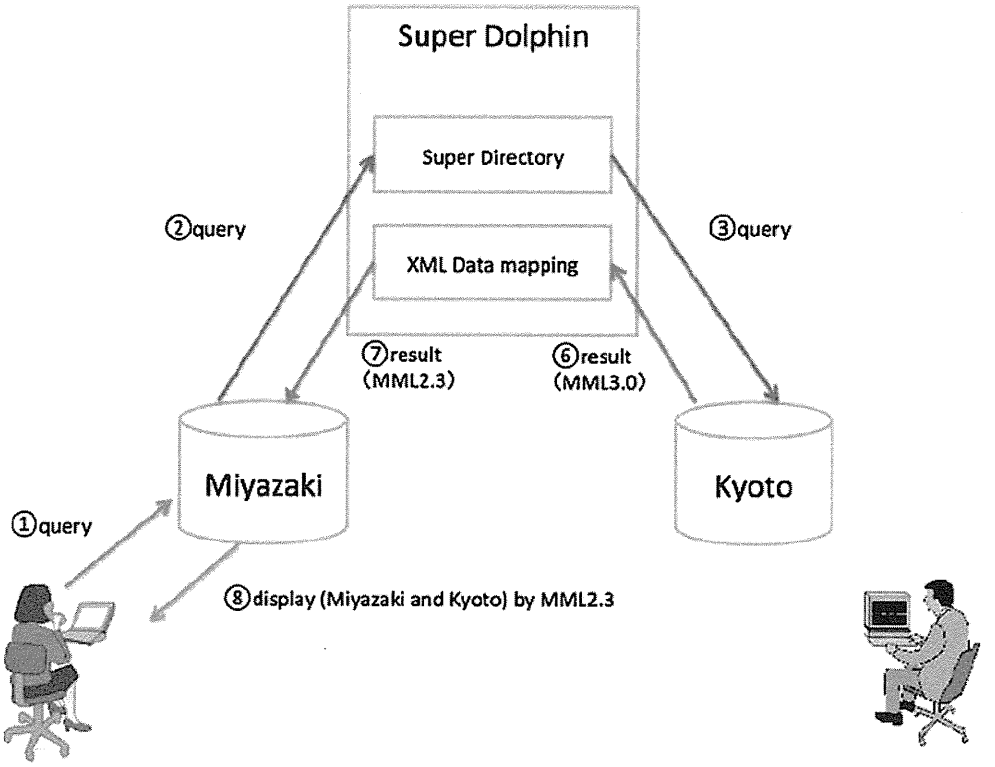
Results

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



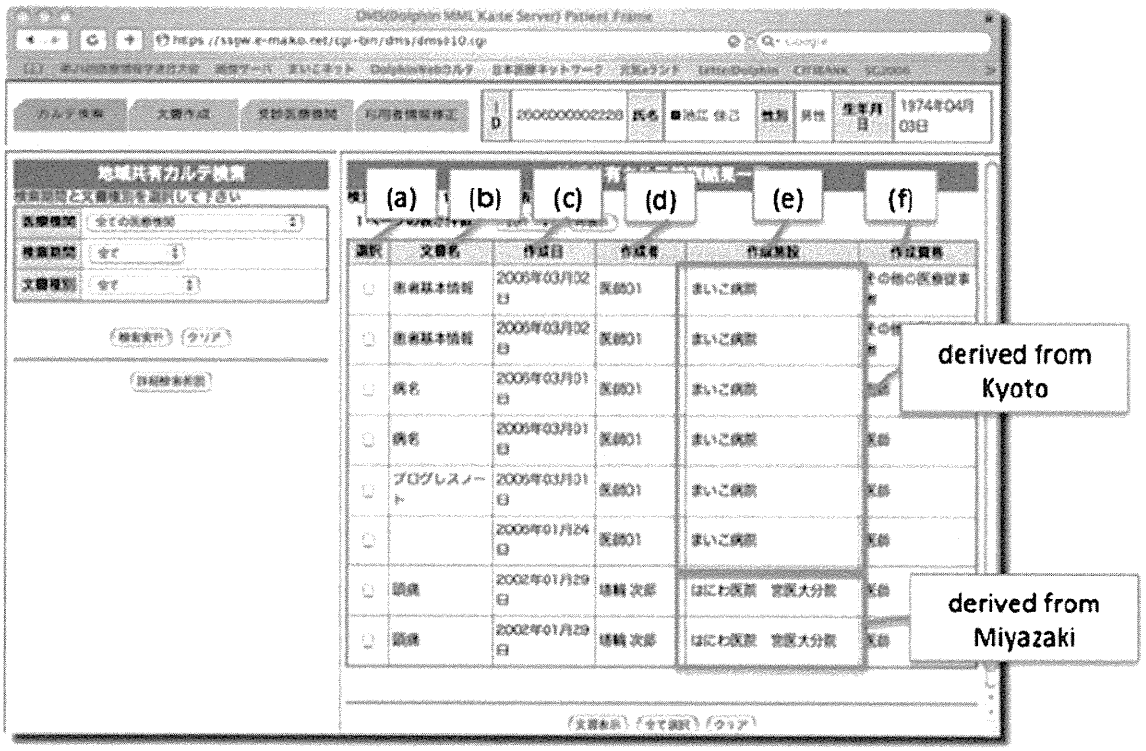


Fig. 3 Overall super dolphin configuration

Fig. 4 Patient medical data

The medical data is organized into lists that are based on the MML structure and that include disease name information, laboratory information, and progress reports. The fifth column in the list indicates the medical institution where the patient was treated. "Maiko Hospital" in this column indicates a Kyoto area medical institution and data which was uploaded to the Kyoto EHR system in CDA rel.1 (MML3.0) format. On the other hand the data of "Haniwa hospital" was uploaded to Miyazaki EHR system in MML2.3 format. In this way, this super site is able to merge and display data from EHR systems in different regions.

Observations

In this study, we considered, and verified by testing, a mechanism for integrating local EHR systems and providing medical cooperation that spans multiple regions. We constructed a super site (Super Dolphin) with data mapping functions for the purposes of matching patient IDs from different regions using an upper-level directory structure, and of compatibility between different data structures. Japan Medical Network Association was established as the operating body for operation of this super site. Although the upper-level directory structure is simple, it is highly universal and is expected to provide large benefits for medical cooperation between regions within a country and with regions where a unique national-level ID cannot be used. In this study, we also succeeded in mapping between different data structures. As described before, in this case conversions were only performed in one-to-one combinations (MML2.3 and CDA rel.1(MML3.0)). Naturally in order to use this mechanism to handle a broad range of clinical data in a versatile manner, the development of a correspondence table for the various standards will be necessary. In this case, determining how to coordinate the different levels of detail in the information may be a larger problem than mapping. However, the structures of the minimum necessary data that needs to be recorded for medical purposes do not differ greatly, and we believe that there will be no serious problems. In the future, we intend to increase the number of local EHR systems which participate in this super site and verify the effectiveness of this fundamental infrastructure, working towards achieving a national-level EHR.

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Controlled-Release Basic Fibroblast Growth Factor for Peripheral Artery Disease: Comparison with Autologous Bone Marrow-Derived Stem Cell Transfer

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Objective: We examined the safety and efficacy of controlled-release basic fibroblast growth factor (b-FGF) for peripheral artery disease (PAD), compared with autologous bone marrow mononuclear cell implantation (BMCI).
Background: We recently developed a b-FGF-incorporated biodegradable hydrogel that enables slow-releasing drug delivery system.
Methods: PAD patients were divided into a b-FGF group ($n=10$) and BMCI group ($n=15$). Injection of gelatin hydrogel containing 600 μg b-FGF or BMCI ($0.4–5.1\times10^{10}$ cell) was performed. Visual analog pain scale (VAS), ^{99m}technetium-tetrofosmin (Tc-TF) scintigraphy, transcutaneous oxygen tension ($TcPO_2$), and ankle-brachial index (ABI) were evaluated before and 4 weeks after each treatment, and 2-year prognosis was determined.
Results: VAS (b-FGF 67±15 to 4±5, $p<0.01$, BMCI 67±42 to 5±9 mm, $p<0.01$) and $TcPO_2$ (b-FGF 16±14 to 47±17, $p<0.01$, BMCI 13±13 to 37±21 mmHg, $p<0.01$) were significantly improved in both groups. Tc-TF and ABI were not changed. Prognosis was similar between the groups (b-FGF 91%, BMCI 80%, NS).
Conclusion: Controlled-release b-FGF is as safe as BMCI, and its efficacy appears to be comparable. Thus, this therapy may be an alternative to BMCI.

Introduction

THE DEVELOPMENT OF NEW vessels from an existing network of vessels, a process referred to as angiogenesis, contributes to various pathological processes such as tumor progression and chronic inflammation.[1–3] On the other hand, neovascularization (angiogenesis) in response to ischemia is a desirable response against tissue hypoxia.[4–7] Therapeutic angiogenesis is a promising strategy for the treatment of many occlusive vascular diseases, such as myocardial and limb ischemia. To date, clinical studies on promoting angiogenesis in ischemic tissues have focused exclusively on the use of angiogenic growth factors, delivered using two main strategies.[8,9] One strategy has been to deliver recombinant proteins directly to the ischemic tissue by intramuscular or intraarterial injection. The alternate strategy has been to use gene therapy, by direct transfer of expression vectors with either virus or naked plasmid. An optimal delivery strategy has not been established, and the approach of using a large amount of protein or gene as a therapeutic agent has several disadvantages. Also, the outcome of early-phase clinical trials with a particular molecule has been less than encouraging, possibly because of factors such as selection and formulation of the growth factor, duration of exposure, route of administration, and selection of patients.[8,9] A cell-based approach, such as autologous bone marrow mononuclear cell implantation (BMCI), has more potential because bone marrow secretes variable cytokines in response to ischemia[10,11] and promotes angiogenesis.[12] However, in this cell-based therapy, it is difficult to standardize the amount, quality, and purification of cells, because the patients (cell donor) are not in identical condition. Also, it is difficult to confirm the type and amount of dominant angiogenic substance released from cells in the clinical situation.

Thus, to establish therapeutic regenerative medicine, there remains a clear need for research on an effective approach and the precise mechanisms by which to establish therapeutic angiogenesis. Recently, Tabata *et al.* designed a novel approach with a drug-delivery system (DDS) that enabled controlled release of a single growth factor *in vivo* and thus improved efficacy of growth factor therapy.[13] This DDS was

This project was published as an abstract in American Heart Association 2006 annual scientific sessions.
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incorporated with the potent growth factor, basic fibroblast growth factor (b-FGF), which has a strong angiogenic property and is a potent cytokine expressed in bone marrow in response to ischemia.[10,11] The present clinical study was designed to determine the effectiveness and safety of the use of a DDS-guided single angiogenic cytokine, b-FGF, which improved above disadvantage, for peripheral artery disease (PAD), and to confirm the mechanisms and whether a single cytokine can possess angiogenic property or not. In addition, the effect was compared with that of cell-based therapy utilizing BMCI.[14]

Methods

Patients

From April 2005 to May 2008, we enrolled 28 consecutive patients with arteriosclerosis obliterans or Buerger's disease with Fontaine class 3 or 4, aged 27–73 years. All the patients were indicated as limb amputation at previous hospital before visit to Nippon Medical School. With the approval of the ethics committee of Nippon Medical School, written informed consent was obtained from each patient. The advisory committee (consisting of cardiologists, vascular/plastic surgeons, radiologists, and an anesthesiologist) reviewed these patients, and 25 of them were selected as having no indication for vascular surgery or peripheral catheter intervention. Administration of the b-FGF into the muscle is off-label use; thus, we avoid other technical or hemodinamics affects to single-dose therapy. According to this concern, all of the patients who require surgical debridement or who on hemodialysis are allocated to BMCI group. The remaining patients were allocated to b-FGF group, which is not a randomized trial. Because patient selection is condition based, this study was not performed using sample size power analysis. Also, the procedures were totally different between treatments, and open label study was selected: 10 patients were allocated to b-FGF treatment and 15 to BMCI. Because these patients' condition was determined as severe limb ischemia requiring limb amputation, it was not possible to include control subjects from the ethics standpoint. Also, because the aim of this study was observation of the safety and efficacy of b-FGF therapy, patients who required additional interventions such as surgical treatment (including minor debridement or skingrafting) or who were treated with hemodialysis (which may affect hemodynamics) were allocated to the BMCI group. Exclusion criteria were (1) no evidence of angiological stenosis confirmed by digital subtraction angiography, (2) history of vascular surgery (within 30 days), (3) presence of any malignant disease or history of its treatment within 5 years (determined by fiberscopy, tumor marker, or fecal occult blood), (4) untreated proliferative diabetic retinopathy, (5) smoker unable to quit smoking, (6) drug addiction of any kind (including alcohol), (7) evidence of viral infection (HBV, HCV, and HIV), (8) infectious osteomyelitis, and (9) complication of any serious disease affecting the patient's general condition (heart, lung, kidney, or liver failure) (Fig. 1).

Endpoints

The primary endpoint of this project was the occurrence of an adverse event, such as death, life-threatening state, functional disturbance, or other severe condition. Secondary endpoints were pain relief, ulcer healing, and avoidance of amputation at 4 weeks' follow-up.

b-FGF therapy

Gelatin hydrogel microspheres (20 μm in diameter) incorporating b-FGF (Kaken Pharmaceutical) were prepared according to the method previously reported.[15–17] Briefly, 600 μg human recombinant b-FGF with an isoelectric point of 9.6 was mixed with hydrogel microspheres with an isoelectric point of 5.0 prepared from bovine gelatin (Nitta Gelatin) through an alkaline process. Gelatin microspheres incorporating b-FGF can release b-FGF for 2–3 weeks.[17] Microspheres were carefully prepared under clean conditions. To confirm the safety of gelatin microspheres, culture test and endotoxin level were examined according to the Japanese Pharmacopoeia regulations and found to be negative. To maintain enough local concentration in the tissue, gelatin

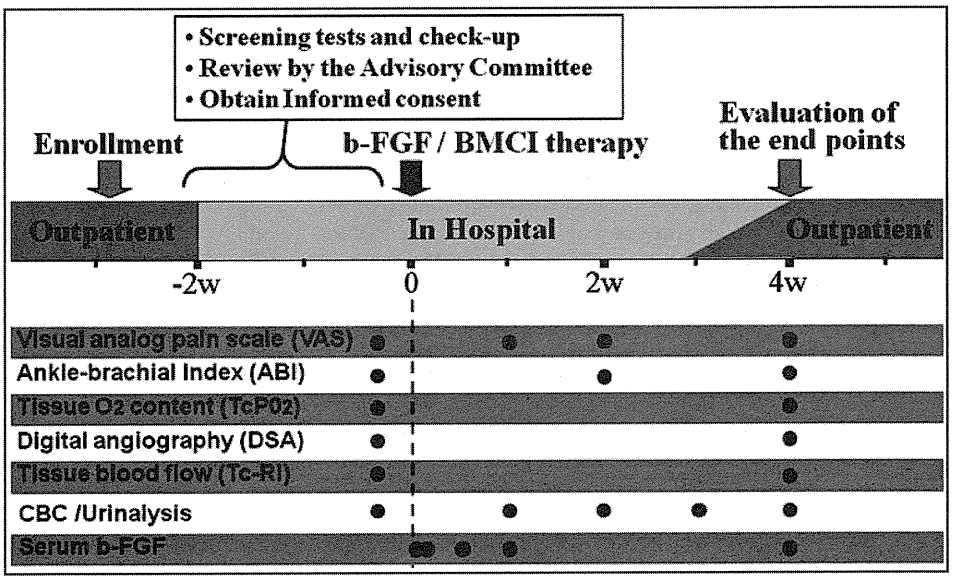

FIG. 1. Study schedule. VAS, visual analog pain scale; ABI, ankle-brachial index; DSA, digital subtraction angiography; Tc-RI, ^{99m}Technetium tetrofosmin scintigraphy; CBC, complete blood count; b-FGF, controlled-release basic fibroblast growth factor therapy; BMCI, bone marrow mononuclear cell implantation; $TcPO_2$, transcutaneous oxygen tension.

hydrogel microspheres incorporating b-FGF were dispersed in 20 mL saline. To avoid local edema associated with injected fluid, injection amount was standardized as 1 mL/site. Based on the ultrasound procedure, 20 sites to be injected were pre-determined with reference to the vasculature of the calf muscles, and marked in advance. Echo-guided intramuscular direct injection (1 mL/site) was performed on calf and foot muscles under general or epidural anesthesia.

BMCI therapy

This method was described previously.[14] Briefly, bone marrow (400–600 mL, $2.6–6.5 \times 10^9$ cells in total) was collected from the bilateral iliac bones under general anesthesia. The mononuclear cell fraction was sorted, and 60–100 mL of cell suspension was processed by a cell separator (AS-TEC 204; Fresenius). Injection points were marked beforehand using transparent sheets with a 3×3 cm grid. To avoid local edema associated with injected fluid, injection amount was standardized as 1 mL/site as mentioned above. Thus, total point for intramuscular injection was about 70 points/leg.

Examinations

The following parameters were evaluated. Pain scale (visual analog pain scale [VAS]), which indicated maximum pain as 100 mm and minimum as 0 (Ankle-brachial index [ABI]; Omron Healthcare) (Fig. 1). ABI was measured by standard methods, and calculated as the ratio of the ankle to brachial pressure. Tissue oxygen content was measured by TCM 400 (transcutaneous oxygen tension [$TcPO_2$]; Radiometer). The sampling site was cleaned with alcohol. The positioning did not overlie a bony prominence, superficial vessel, or pulse site. Then, the transducer was placed on the dorsum of the ischemic limb, and warmed up to 43.5°C to increase the permeability of the skin to oxygen molecules at the measurement site. With the patients resting in supine position, data were acquired in room air for about 20 min. Digital subtraction angiography was performed using the standard technique with 4F catheter. Tissue blood flow was determined by ^{99m}technetium tetrofosmin (^{99m}Tc-TF) scintigraphy.[14] ^{99m}Tc-TF (555–740 MBq) was injected intravenously. Approximately 10 min after injection of the radiotracer, whole-body scintigraphy was performed in the prone position both in the anterior and posterior projection with a dual-head large field-of-view gamma camera (Vertex, ADAC). Image acquisition time was approximately 15 min. For quantitative analysis, regions of interest of equal size were drawn around the appropriate muscle group (e.g., calf muscles) in anterior and posterior projections. Additionally, intra cranial uptake (brain uptake) was calculated as the background. The muscle-to-brain ratio was defined as average counts per pixel in each muscle/average counts per pixel in the brain. Evaluation was performed before and 4 weeks after therapy.

Table 1. Study Patient Population

	b-FGF (n=10)	*BMCI (n=15)*
Age	53±17	61±13
Male	10 (100%)	13 (87%)
Fontaine classification	3.6±0.5	3.9±0.3[a]
ASO/Buerger disease	6/4	12/3
Previous smoker	9 (90%)	9 (60%)
Diabetes mellitus	5 (50%)	10 (67%)

[a] $p < 0.05$.
ASO, arteriosclerosis obliterance; b-FGF, basic fibroblast growth factor; BMCI, bone marrow mononuclear cell implantation.

Safety evaluation

To evaluate the possible side effects of b-FGF, blood concentration was measured immediately after injection, 1 day, 1 week, 2 weeks, and 4 weeks after administration. Also, urinalysis was performed at 3 days, 1 week, 2 weeks, and 4 weeks after administration. For the long-term prognosis analysis, Kaplan–Meier analysis was performed 2 years after administration.

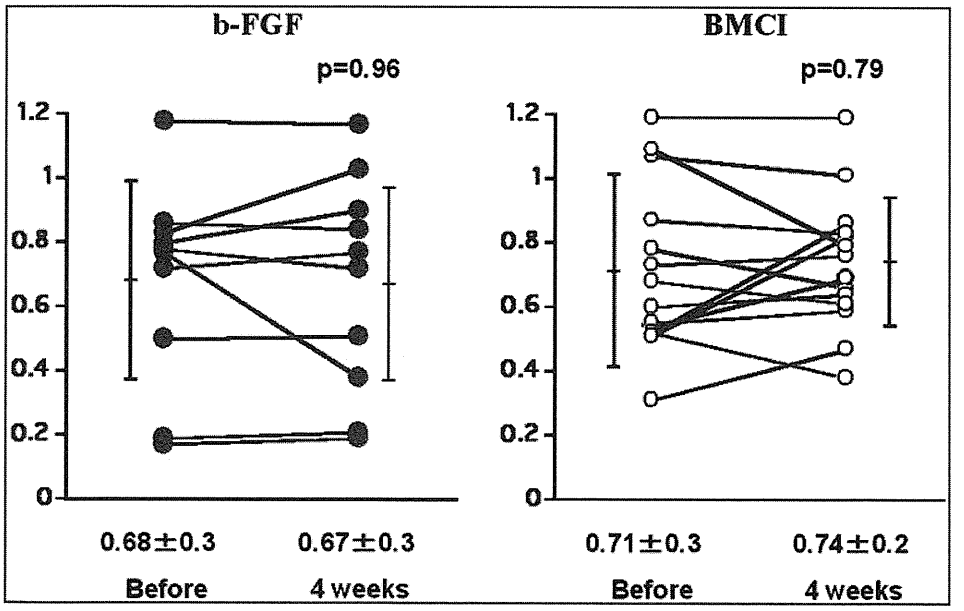

FIG. 2. The effect of controlled-release b-FGF therapy to ABI. b-FGF therapy (left) and BMCI therapy (right).

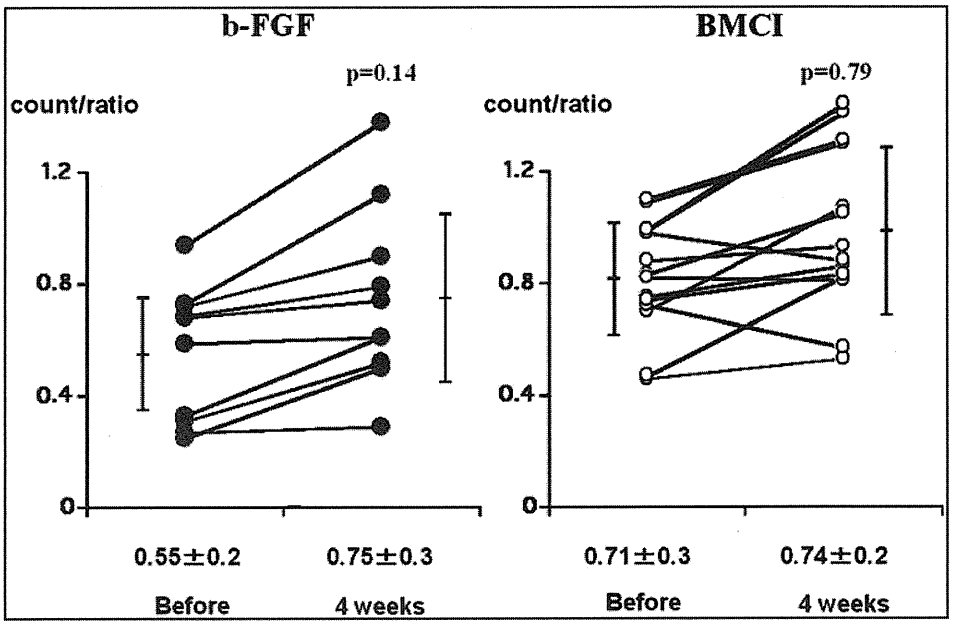

FIG. 3. The effect of controlled-release b-FGF therapy to ^{99m}Technetium-tetrofosmin scintigraphy. b-FGF therapy (left) and BMCI therapy (right).

Statistical analysis

All data are presented as mean±SD. Repeated measure analysis of variance was used to test for treatment-group baseline differences for continuous variables. Within-treatment analyses of changes were performed using a Student's *t*-test. Time to all cause mortality was compared between the two groups using Kaplan–Meier analysis with log-rank test. A value of $p<0.05$ was taken as the minimum level of significance.

Results

Baseline characteristics are shown in Table 1. Age, sex, original disease, smoking history, and diabetes mellitus prevalence were similar between two groups. Because all the patients with an ischemic ulcer requiring a skin graft or minor debridement were allocated to the BMCI group, Fontaine classification was worse in the BMCI group than in the b-FGF group. Regarding the primary end point, no adverse event occurred during the 4-week period in both groups. Also, no amputation was required during this period. Figure 2 shows the effect of therapy on ABI. ABI was not significantly increased 4 weeks after treatment in both groups (b-FGF 0.7±0.3 to 0.7±0.3, $p=0.96$, BMCI 0.7±0.3 to 0.7±0.2, $p=0.79$). ^{99m}Tc-TF scintigraphy was performed to evaluate tissue blood flow. There was a tendency for ^{99m}Tc-TF to increase in both groups; however, it did not reach statistical significance 4 weeks after treatment (b-FGF 0.5±0.2 to 0.8±0.2, $p=0.14$, BMCI 0.7±0.3 to 0.7±0.2 count ratio/pixel, $p=0.79$; Fig. 3). Figure 4 shows the time course of

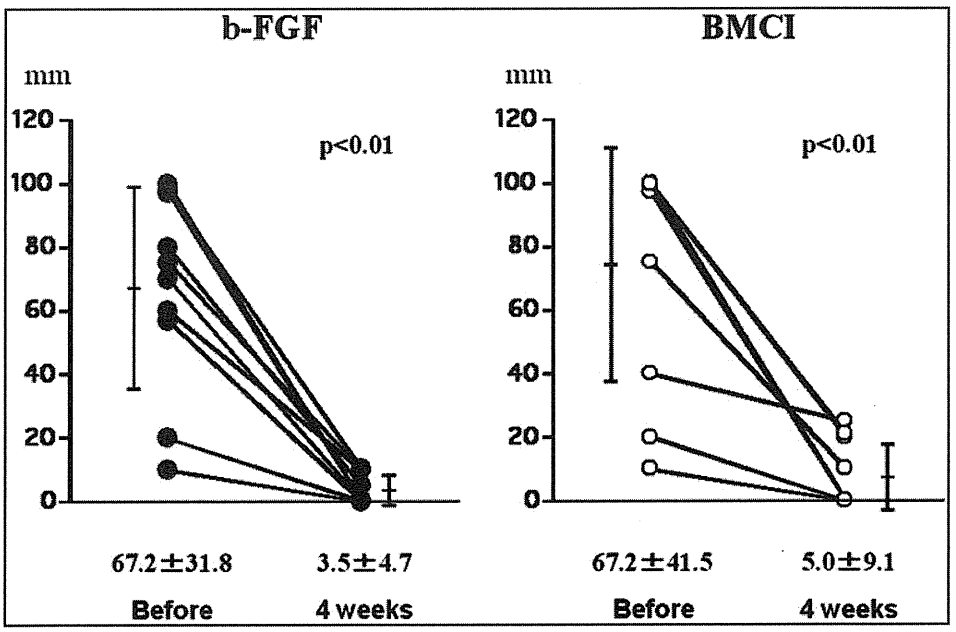

FIG. 4. The effect of controlled-release b-FGF therapy to pain scale (VAS). b-FGF therapy (left) and BMCI therapy (right).

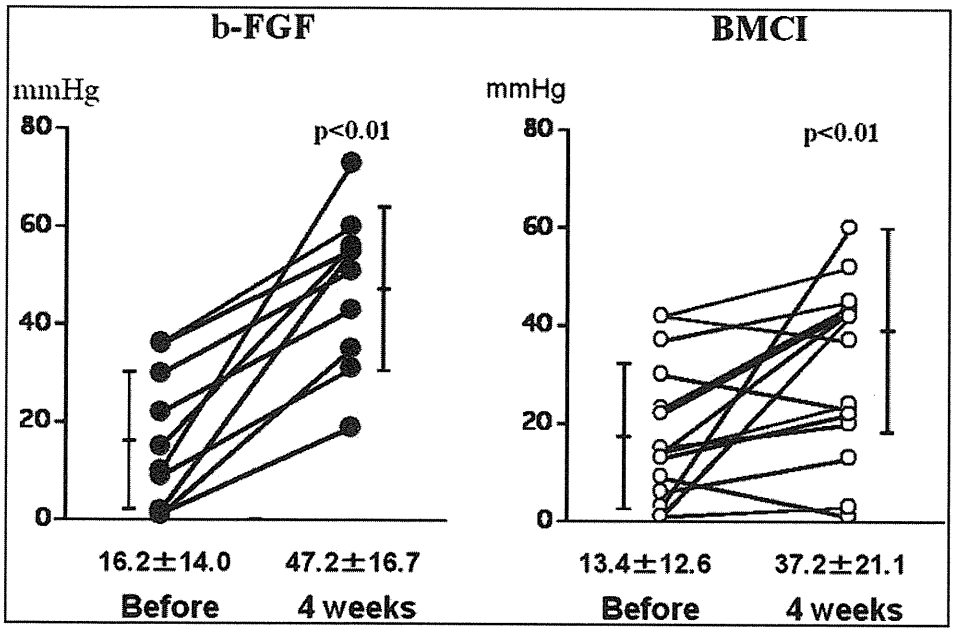

FIG. 5. The effect of controlled-release b-FGF therapy to transcutaneous oxygen tension. b-FGF therapy (left) and BMCI therapy (right).

pain scale (VAS). It was significantly decreased in both groups after treatment (b-FGF 67±32 to 4±5, $p<0.01$, BMCI 67±42 to 5±9 mm, $p<0.01$). Also, skin perfusion, determined by $TcPO_2$, was significantly increased 4 weeks after b-FGF treatment in both groups (b-FGF 16±14 to 47±17, $p<0.01$, BMCI 13±13 to 37±21 mmHg, $p<0.01$; Fig. 5). Serum b-FGF level was slightly elevated immediately after injection in two patients (Fig. 6, left), but it then returned to the normal range in the b-FGF group until 4 weeks. Urine protein level was not elevated after b-FGF treatment (Fig. 6, right). Figure 7 indicates the representative picture of foot ulcer before and after the therapy.

Two-year prognosis after administration was not different between the groups (b-FGF 91%, BMCI 80% $p=0.502$; Fig. 8). One patient died because of ischemic heart disease, but there was no amputation case in the b-FGF group. Three patients died because of pneumonia ($n=2$) and sepsis ($n=1$), including three amputation cases in the BMCI group. No limb amputation was found in survived patients in the BMCI group. Rest pain scale remains zero for 2 years in all patients except for event cases in both groups.

Discussion

Even though recent medical progress has achieved effective vascular regenerative therapy, the underlying ischemic condition or disease status is not simple and sometimes results in an undesirable clinical outcome. For example, on clinical observation, intractable ischemic ulcers occur in patients with vasculitis or auto-immune disease. The effects of BMCI for ischemic condition were confirmed; however, it is unknown whether this autologous bone marrow, which containing immune-related cells, may worsen auto-immune related ischemia by immune modulation. Thus, one of the

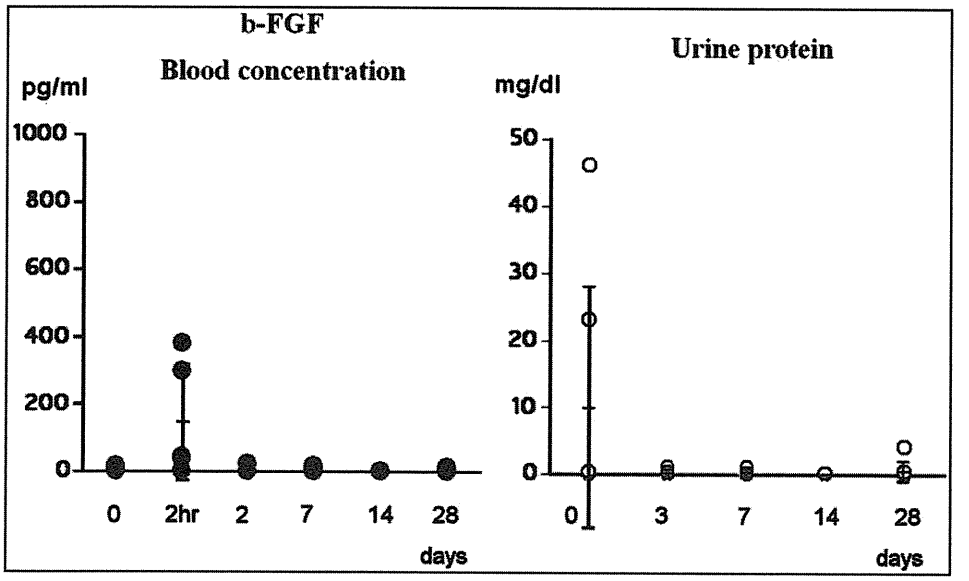

FIG. 6. Serum b-FGF concentration and urine protein level: b-FGF blood concentration (left) and urine protein level (right).

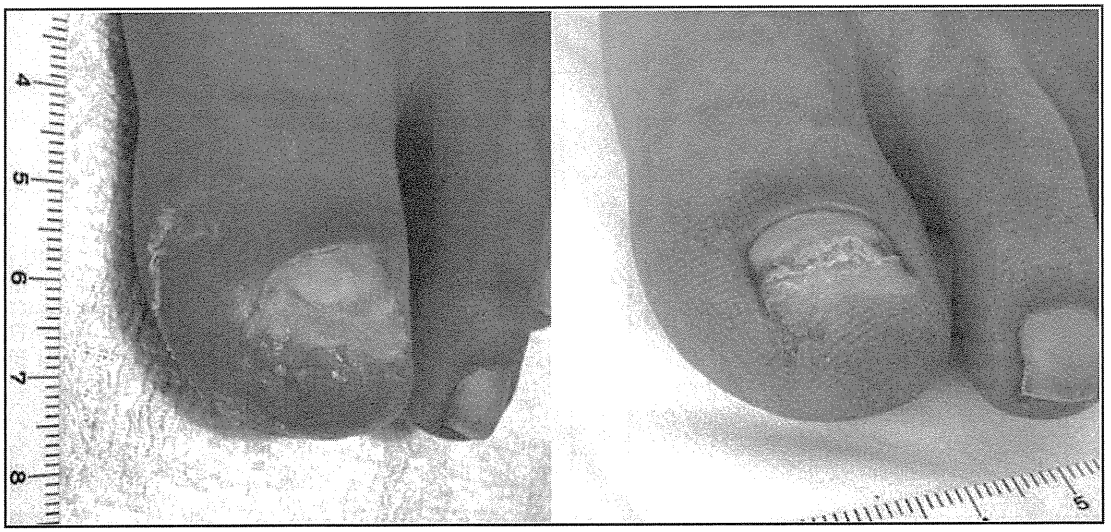

FIG. 7. Representative picture. Digitus primus ulceration of the left leg. Before treatment on the left and after treatment on the right.

new concepts is to establish alternative angiogenesis therapy for many disease states. We experienced a case in which this controlled-release b-FGF protein had potential clinical benefit, in a patient with allergic vasculitis due to Churg-Strauss syndrome under no systemic immune modulation.[15] To examine this concept, a phase I to II study in arteriosclerosis obliterans or Buerger's disease was designed as a pilot study at this investigation. We also achieved standardization, the purification profile, and a controlled delivery system of b-FGF protein as a therapeutic angiogenesis. The major findings of this study were restoration of blood flow by b-FGF, confirmed by skin perfusion examinations in the ischemic area, and safety, confirmed until 4 weeks after administration, resulted in better 2 years prognosis. Also, the effectiveness showed the same tendency as that of BMCI. A clinical study utilizing b-FGF showed that bolus administration was preferable in terms of efficacy.[18–23] On the other hand, because b-FGF is water soluble, unbound free b-FGF, administered directly into the artery, resulted in an extremely high b-FGF blood concentration such as 60,000 pg/mL.[23] It has also been reported that intra-arterial injection was associated with the development of glomerulosclerosis in an experimental model.[24–27] A clinical double-blind placebo-controlled trial reported that gross proteinuria occurred after b-FGF administration.[28] To resolve this problem, Tabata *et al.* developed a novel technique, which incorporated a variety of substances with biodegradable gelatin hydrogel enabling b-FGF to be released at the site of action for 2–4 weeks.[29,30] When this gelatin incorporated with bFGF was administered intramuscularly, it minimized side effects, avoided loss to the systemic circulation, and yielded a higher local concentration and maintained it compared with arterial administration,[31] maximizing clinical effectiveness. Our results indicated that b-FGF blood concentration was very low (< 10 pg/mL). Thus, our data support the safety and efficacy of controlled-release b-FGF administration in clinical situations even in small sample size. A recent basic science report suggested that controlled-release b-FGF combined with stem cells is an effective approach.[32] Thus, this investigation may provide important clinical information to progress future vascular regenerative therapy.

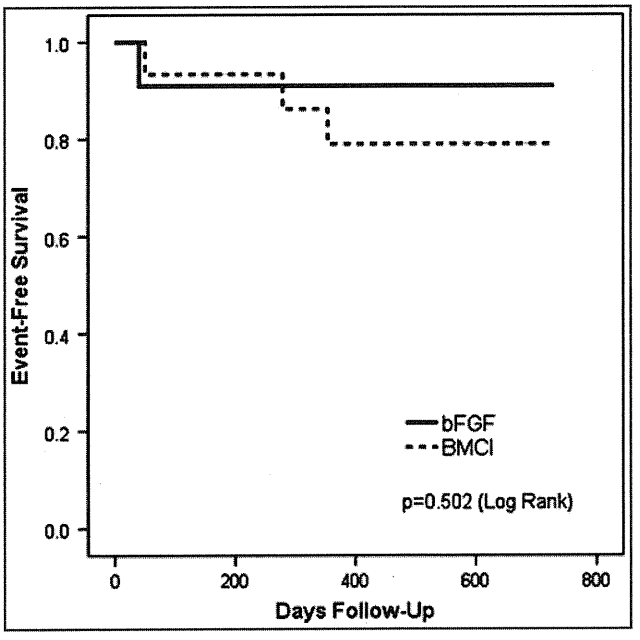

FIG. 8. Event-free survival. Data represent Kaplan–Meier curves for all cause mortality during 2-year follow-up in each group.

Limitations

Because of ethical and clinical considerations, treatment was not randomized, and this bias reflects to worse Fontaine classification in BMCI group and the data favor of b-FGF group. Also, from the methodological aspect, the study was open labeled, which reflects to the VAS value, but not to ABI, $TcPO_2$, and Tc-TF value, because automated scoring was made by equipments. Because injection amount was standardized between the groups, different injection points may affect the result. Even with careful injection, the injection needle hit vessels on administration in two patients, which

was confirmed by the b-FGF blood concentration at first pass (Fig. 2). Thus, technical failure may occur.

In summary, controlled-release b-FGF protein therapy was performed in 10 patients with PAD. Four weeks after therapy, pain scale and $TcPO_2$ were significantly improved to similar extent as that with BMCI, and 2-year prognosis was similar to BMCI.

Conclusion

Controlled-release b-FGF protein therapy was found to be safe, and its efficacy appeared to be comparable to that of BMCI. Thus, this therapy may be able to become an alternative to BMCI.

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Disclosure Statement

There is no disclosure except the **above funding source.** This investigation was an academia-initiated exploratory phase I–IIa study. There was no external sponsor involved in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in this study and had final responsibility for the decision to submit the article for publication.

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