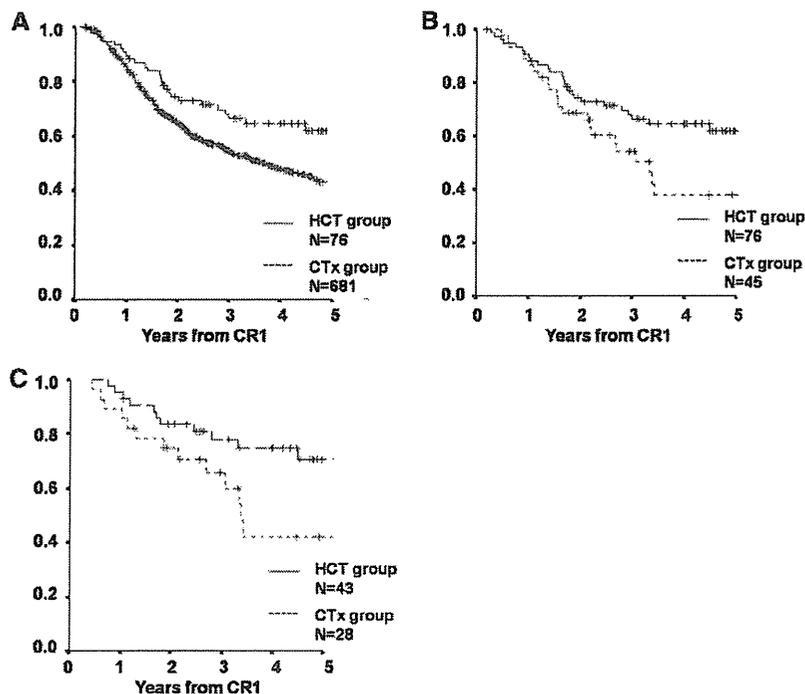value: results from a prospective clinical trial. *Br J Haematol.* 2007;136:96-105.

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APPENDIX: PARTICIPATING CENTERS

National Cancer Center Hospital (Tokyo), Toranomon Hospital (Tokyo), Saiseikai Maebashi Hospital (Gunma), NTT Kanto Medical Center (Tokyo), Fujita Health University (Aichi), Metropolitan Komagome Hospital (Tokyo), Kanagawa Cancer Center (Kanagawa), Metropolitan Bokutoh Hospital (Tokyo), Ehime Prefectural Central Hospital (Ehime), Jikei University (Tokyo), Nihon University (Tokyo), Kurume University (Fukuoka), St. Marianna University Yokohama Seibu Hospital (Kanagawa), Matsushita Memorial Hospital (Osaka), Tokyo Medical Center (Tokyo), University of Tokyo (Tokyo), Sasebo City General Hospital (Nagasaki), Nagasaki University (Nagasaki), Tsukuba University (Ibaraki), Jichi Medical University (Tochigi), Gunma University (Gunma), Teikyo University (Tokyo), Shimane Prefectural Central Hospital (Shimane), Rinku General Medical Center (Osaka), Oakayama Medical Center (Okayama), Miyagi Prefectural Cancer Center (Miyagi), Yokohama City University (Kanagawa), Dokkyo Medical University (Tochigi), Kobe University (Hyogo), Yokohama City University Medical Center (Kanagawa), National Defense Medical College Hospital (Saitama), Sapporo Medical University (Hokkaido), Osaka City University (Osaka), Fukuoka University Hospital (Fukuoka), Saga

Prefectural Hospital Koseikan (Saga), Osaka University (Osaka), Iwate Prefectural Central Hospital (Iwate), Tokushima Red Cross Hospital (Tokushima), Toyama Prefectural Central Hospital (Toyama), Akita University (Akita), Musashino Red Cross Hospital (Tokyo), Kyoto Prefectural University of Medicine (Kyoto), Kawasaki Medical School Hospital (Okayama), University of Yamanashi (Yamanashi), Kyushu Kosei Nenkin Hospital (Fukuoka), Northern Fukushima Medical Center (Fukushima), Okayama University (Okayama), Kagawa University (Kagawa), National Kyushu Cancer Center (Fukuoka), Hirosaki University (Aomori), Hamanomachi Hospital (Fukuoka), Shinshu University (Nagano), Tenri Hospital (Nara), Gifu University (Gifu), Niigata University (Niigata), Hokkaido University (Hokkaido), Tokyo Hitachi Hospital (Tokyo), Kanazawa University (Ishikawa), Yamaguchi University (Yamaguchi), Kumamoto Medical Center (Kumamoto), Mie University (Mie), Koga General Hospital (Miyazaki), St. Luke's International Hospital (Tokyo), Tohoku University (Miyagi), Tokushima University (Tokushima)

Appendix 1. Overall survival from CR1 are compared between the patients who received allogeneic transplantation in first complete remission and those who did not among the group of patients who had a suitable related donor. (A) Comparison of the two groups when 622 patients who did not have their HLA typed (those who were not known to have a suitable related donor) were included in the chemotherapy group (66% versus 54%, $P = .011$). (B) Comparison of the two groups when landmark was extended to 5 months from CR1 (66% versus 54%, $P = .068$). (C) Comparison of the two groups limited to intermediate-risk AML patients (78% versus 63%, $P = .048$).
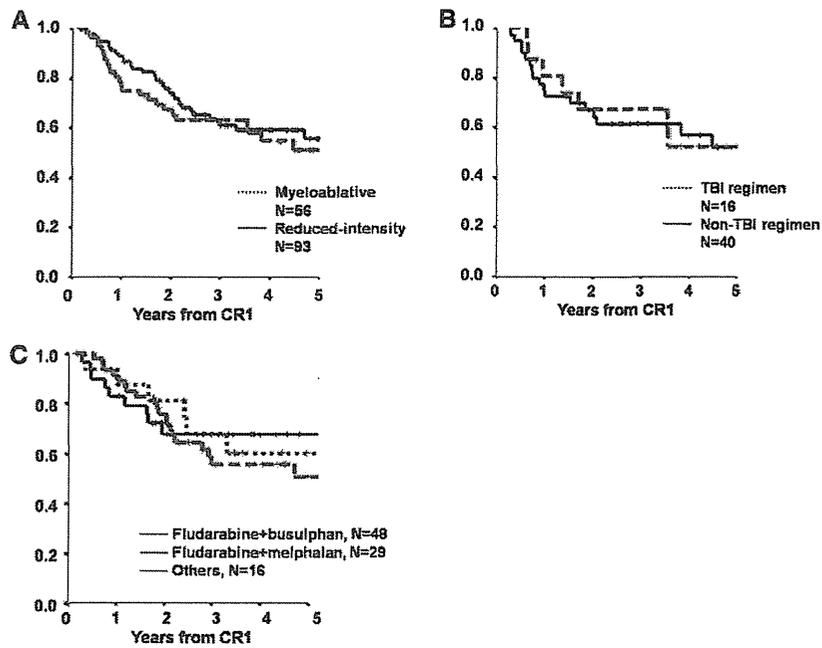
Appendix 2. (A) Overall survival (OS) rates from CR1 are compared between myeloablative and reduced-intensity conditioning regimens. There were no significant differences between myeloablative and reduced-intensity conditioning regimens (63% versus 61%, $P = .571$). (B) OS did not differ significantly according to the application of total-body irradiation among patients who received myeloablative regimen (TBI regimen versus non-TBI: 67% versus 61%, $P = .932$). (C) Among patients who received reduced-intensity conditioning regimen, OS from CR1 did not differ significantly among different regimens (fludarabine + busulfan-based, 56%; fludarabine + melphalan-based, 67%; others, 68%, $P = .862$).

ORIGINAL ARTICLE

Clinical efficacy and safety of biapenem for febrile neutropenia in patients with underlying hematopoietic diseases: a multi-institutional study

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Abstract A multi-institutional study was conducted to assess efficacy and safety of biapenem (BIPM), a carbapenem antibiotic, as an initial-stage therapeutic agent for febrile neutropenia (FN) in patients with hematopoietic diseases. A total of 216 patients from 25 medical institutions were enrolled in this study; of these, 204 were included in the safety analysis and 178 in the efficacy analysis. The combined (excellent and good) response rate was 67.9%, and antipyretic effect (subsidence + tendency to subsidence) was achieved within 3 and 5 days of treatment in 67.3 and 75.9% of patients, respectively. Thus, the clinical responses were gratifying. A response rate of 61.7% (37/60) was observed even in high-risk FN patients in whom neutrophil counts prior to and at 72 h after the start of BIPM were $\leq 100/\mu l$. BIPM is considered to be a highly promising drug, with prompt onset of clinical benefit, as an initial-stage therapeutic agent for the treatment of FN in patients with hematopoietic diseases.

For the Study Group for Infectious Disease involved in hematopoietic diseases.

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Introduction

Neutropenia associated with intensive chemotherapy, radiation therapy, or hematopoietic stem cell transplantation for acute leukemia and other hematopoietic diseases or solid cancers is often accompanied by discomforting fever and precipitates serious exacerbation in several instances. The disease state associated with neutropenia has come to be referred to by the term febrile neutropenia (FN). Guidelines for treating FN were first issued in 1990, primarily by the Infectious Diseases Society of America (IDSA) [1], and have been revised on two occasions [2, 3]. In Japan, a guideline for treating FN was first published in 1998 by Masaoka and colleagues [4]. FN was also listed in the Japanese national health insurance reimbursement list in 2004. The guideline for FN recommends early-stage treatment with broad-spectrum antimicrobial agents. Cefepime and carbapenems are often administered for empirical treatment of FN in Japan. Biapenem (BIPM) is a carbapenem antibiotic endowed with broad-spectrum antibacterial activity and a quick bactericidal effect and is remarkably stable against renal dehydropeptidase-1 (DHP-1) [5]. It was launched into the market in March 2002. Treatment with BIPM has been shown to yield high response rates of 86.4–100% in patients with respiratory tract, urinary tract, intraperitoneal, and obstetric/gynecologic infections, with a response rate as high as 91.7% (data at the time of approval) in patients with sepsis, so that "sepsis" was approved as an additional indication for the drug in February 2004. Its widespread use in clinical settings is expected. However, there is still limited information on the usefulness of this drug in managing FN [6, 7], and our multi-institutional study was conducted to assess the clinical responses to treatment with BIPM and confirm efficacy and safety in the treatment of FN in patients with hematopoietic diseases.

Patients and methods

Patients

Patients from the participating institutions who had hematopoietic diseases and developed complicating FN and gave informed consent for participation between June 2006 and September 2007 were enrolled in this study. Definition of FN in patients with hematopoietic diseases (patients meeting the conditions specified below, with the exception of those whose clinical condition was rated as low-risk by the attending physician[1]) were (1) neutropenia: peripheral blood neutrophil count of <1000/μl at the start of the treatment, even if the count appeared likely to decrease to <500/μl; and (2) fever: axillary temperature ≥37.5°C and oral temperature ≥38.0°C in the measurements obtained once.

Exclusion criteria

1. Patients in whom significant effectiveness of the drug against the potential causative organisms cannot be expected
2. Patients with serious cardiac, hepatic, and/or renal dysfunction
3. Patients with a history of hypersensitivity to β-lactam antibiotics
4. Patients with a predisposition to allergies
5. Patients strongly affected by aging and unsuitable for drug evaluation
6. Pregnant and possibly pregnant women and lactating mothers
7. Patients with convulsive disorders, e.g., epilepsy
8. Patients under treatment with valproic acid
9. Other patients judged by the attending physician as being unsuitable for the study

Method of drug administration

Dosage and administration

BIPM (Meiji Seika Kaisha Ltd, Tokyo, Japan) was administered at the dosage of 0.6 or 1.2 g in two divided doses, each given, in principle, by intravenous drip infusion over 2 h or (over 30–60 min. Treatment was initially started at the above dosage and administration schedule and was continued in accordance with the FN guideline (Fig. 1: see the flowchart of treatment in this study).

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[1] Patients with fever obviously not attributable to infection were excluded.
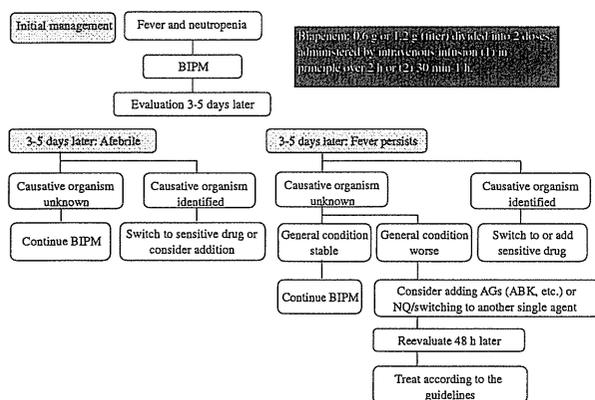
Fig. 1 Summary of treatment algorithm for managing febrile neutropenic (FN) patients. Treatment with biapenem (BIPM) was initially administered at 0.6 or 1.2 g (titer) in two divided doses, each dose given, in principle, by intravenous drip infusion over 2 h or 30–60 min. It usually takes 3–5 days after onset of therapy for a significant improvement in FN to occur. Unless the patient's condition deteriorates rapidly, close follow-up while the same antibiotics are administered is warranted. Defervescence within 3–5 days: When the patient becomes afebrile within 3–5 days of treatment, therapy is continued. If a causative microorganism has been identified, therapy can be adjusted accordingly while a broad-spectrum coverage is maintained. The *panel* suggests that as long as the patient remains in good condition, the initial antibiotic can be continued, regardless of isolated microorganisms. Persistent fever after 3–5 days: If the patient continues to be febrile 3–5 days after treatment with antibiotics begins, he or she should be reevaluated with a thorough physical examination. When cultures of infectious foci or blood yield positive results, and susceptibility of the isolated microorganism is known, specific antimicrobials are added to the ongoing therapy for patients with severe neutropenia. If causes of fever are not identified but the patient is otherwise in a good condition, the same regimen can be continued. If a causative microorganism is unknown, an aminoglycoside should be added, or it can be changed to a broad-spectrum cephalosporin. A 48-h observation period and another reevaluation should follow the change in antimicrobials

Case enrollment procedure

Patient enrollment was performed using the FAX-based centralized enrollment scheme.

Therapeutic response rating

Antipyretic effect on days 3 and 5 (criteria)

Subsidence of fever: Patient's temperature consistently remains at $\leq 37.0^\circ$C, and the drop in body temperature is not due to exacerbation of infection.

Tendency of the fever to subside: Patient's temperature is $<38.0^\circ$C and decreases by 0.5°C or more on day 3 or day 5 compared with the temperature measured prior to the start of the study medication; the drop in temperature is not due to exacerbation of infection.

Persistence of fever: Any condition other than the above.
Unassessable: Difficult to rate the antipyretic effect of the drug because of overlap with the response to drug(s) used for treatment of the underlying disease, adverse reaction(s) eventually leading to discontinuation of the study medication, or death.

Efficacy (antipyretic effect/clinical response) on day 7 (criteria)

Excellent: Fever subsides within 3–5 days of the start of the administration of BIPM, the patient's temperature remaining normal ($\leq 37.0^\circ$C) for 2 days or more thereafter, with improvement of symptoms and laboratory findings associated with the infection.
Good: Fever recedes within 3–5 days of the start of BIPM administration, the patient's temperature returning to normal within 7 days while still on the same medication, with improvement of symptoms and laboratory findings associated with the infection.
Poor: Any condition other than the above.
Unassessable: Adverse event(s) reaction(s) eventually leading to discontinuation of BIPM administration or marked influence of concurrently administered medication (for treatment of the underlying disease).

Bacteriological response (criteria)

Eradicated: The causative organism (including suspected causative organisms) has been eradicated or marked symptomatic improvement at the conclusion of the study, resulting in unfeasibility of specimen collection.
Diminution or partial elimination: Causative organism (including suspected causative organisms) has definitely diminished in infection density or a plurality of causative organisms can be demonstrated with evidence of partial elimination.
Persistence: Indefinite, no diminution, or increase in infection density of the causative organisms (including suspected causative organisms).
Microbial substitution: Substituting organism causes inflammation.
Unassessable: No causative organism can be identified or changes in infection density of the causative organism over time remain unclear.

Statistical analysis

Statistical comparisons were performed using Fisher's exact test. P value of <0.05 was considered statistically significant.
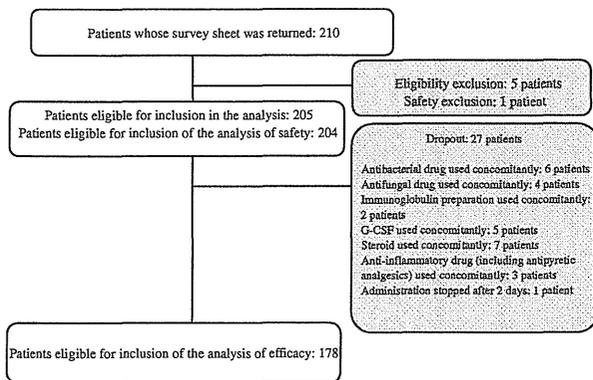
Fig. 2 Safety and efficacy analysis of biapenem (BIPM) carried out based on intention to treat in 178 patients

Results

Distribution of patients

In all, 216 patients from 25 hospitals were enrolled in the study. Survey forms with study data were retrieved from 210 of the 216 patients, of whom 204, excluding six who failed to meet the enrollment criteria, were subjected to the safety analysis. Of these 204 patients, 178 (excluding 26 who had been started on any of other restricted anti-microbial agents, immunoglobulin preparations, granulo-cyte-colony-stimulating factor (G-CSF) preparations, or corticosteroids on the same day as the start of the study medication) were included for efficacy evaluation (Fig. 2).

The decision as to whether any given patient may be enrolled in the study and whether he or she should be included in the analysis was made by the Case Conference constituted by the members of the Response Evaluation Committee.

Patient background characteristics

Demographic and baseline clinical characteristics of the 178 patients included in the efficacy analysis population are summarized in Table 1. There were 113 male and 65 female patients, ranging broadly in age from 18 to 90 years. The underlying disease was acute myelogenous leukemia in 72 patients and non-Hodgkin's lymphoma in 59 patients, together accounting for 73.5% of all patients (Table 2).

BIPM was administered in doses of 0.3 g b.i.d. in 85 patients and 0.6 g b.i.d. in 83 patients, of whom only 33 received the 2-h intravenous infusions as advocated, taking into consideration the pharmacokinetics/pharmacody-namics (PK-PD) of the drug. Table 3 shows the numbers of patients classified by dosage and administration schedule. Mean duration of BIPM administration was 10.1 days (Table 3).

Table 1 Patient background

Background factors	Number of patients: 178	Composition rate (%)
Stage		
Initial	121	68.0
Recurrence	55	30.9
Unknown	2	1.1
Gender		
Male	113	63.5
Female	65	36.5
Age	18–90 (median 54.4) years	
Body weight	34–100 kg (median 58.5 kg)	
PS		
0	81	45.5
1	64	36.0
2	21	11.8
3	10	5.6
4	1	0.6
Unknown	1	0.6

PS Performance status

Table 2 Patient background (underlying diseases)

Underlying diseases	No. of patients: 178	Composition rate (%)
Acute myelogenous leukemia	72	40.4
Acute lymphoblastic leukemia	14	7.9
Chronic myelocytic leukemia	3	1.8
Myelodysplastic syndrome	9	5.1
Non-Hodgkin's lymphoma	59	33.1
Hodgkin's lymphoma	2	1.1
Multiple myeloma	1	0.6
Aplastic anemia	1	0.6
Other	8	0.4

Clinical response

Clinical responses were evaluated in 162 of the 178 patients; 16 of the 178 were judged to be unassessable in terms of clinical response. The therapeutic response during the first 7 days of treatment with BIPM was excellent in 71 (43.8%), good in 39 (24.1%), and poor in 52 (32.1%); hence a response rate (percentage of combined excellent and good responders) of 67.9% (Fig. 3).

In patients obtaining relief from fever within 3–5 days of the start of BIPM administration, subsidence of fever was achieved in 61 and the fever tended to subside in 48 within 3 days of start of the study medication (67.3%). Subsidence of fever was achieved in 86 patients and fever showed a tendency toward subsidence in 37 patients within 5 days (75.9%) (Table 4).

Table 3 Dosage method and duration of administration

Item	No. of patients	Composition rate (%)
Dosage		
0.3 × 2	85	47.8
0.6 × 2	83	46.6
Other	10	5.6
IV drip time		
120 min	33	18.5
30–60 min	138	77.5
Unknown	7	3.9
No. of days administered	Mean: 10.1 (minimum 2; maximum 30)	

Efficacy rate (marked efficacy + efficacy) by administration day 7 = 67.9%

(Tabulation of 162 patients after excluding 16 patients incapable of being evaluated)
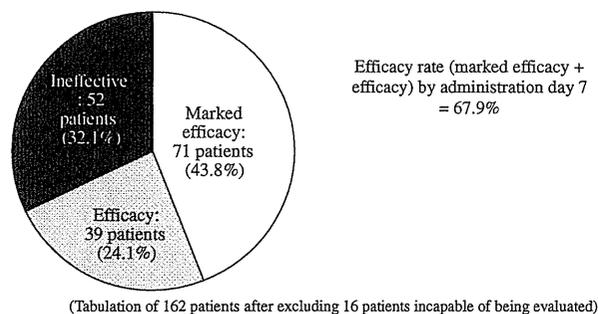
Fig. 3 Clinical efficacy shown in the *circle*. Clinical responses were evaluated in 162 of the 178 patients included in the efficacy analysis population; 16 of the 178 were judged to be unassessable in terms of the clinical response

As for clinical responses classified by the underlying hematopoietic disease, the response rate was 65.2% in patients with acute myeloid leukemia, 62.7% in patients with non-Hodgkin's lymphoma, 61.5% in patients with acute lymphocytic leukemia, and 66.7% in patients with myelodysplastic syndrome (MDS). There was no significant difference in response rates among disease categories (Table 5).

Clinical response by the neutrophil count

Data were analyzed with patient stratification according to neutrophil count, which is considered one of the background factors, in particular, exerting influence on clinical response to treatment. For FN patients whose baseline (i.e., before the start of BIPM administration) neutrophil counts were ≤100/μl and whose neutrophil counts at 72 h after the start of the study medication were still ≤100/μl (reflective of a severely myelosuppressed status) the response rate was 61.7% (37/60). In patients with a baseline neutrophil count of ≤100/μl in whom neutrophil count at 72 h after the start of the study medication was 101–500 or ≥501/μl, response rates were 83.3 (5/6) and 85.7% (6/7), respectively. The response rate tended to increase with progressive recovery of neutrophil count (Table 6).

Table 4 Antipyretic effect

Defervescence rate	No. (%)
Within 3 days	
Subsidence of fever + tendency toward subsidence of fever[a]	109 (67.3)
Subsidence of fever	61 (37.7)
Within 5 days	
Subsidence of fever + tendency toward subsidence of fever	123 (75.9)
Subsidence of fever	86 (53.1)

[a] Tabulation of 162 patients after excluding 16 who were incapable of being evaluated

Clinical response by dosage and administration

Response rates of patients treated with BIPM at 0.3 g b.i.d. and 0.6 g b.i.d. were 64.0 and 73.1%, respectively. Furthermore, in patients administered BIPM by 2-h intravenous infusions in consideration of the PK-PD of the drug, the response rate was 62.5%, which was not significantly different from that in patients administered the drug over the usual duration of intravenous infusion (30–60 min) (Table 7). Stratification of response rates by dose level and infusion time revealed that the response rate in patients administered BIPM at 0.6 g b.i.d. by a 2-h intravenous infusion, although few, was as high as 83.3% (5/6) (Table 8).

Bacteriological response

As regards bacteriological responses, pathogenic organisms were isolated by blood culture from 24 patients (30 isolates), including methicillin-sensitive *Staphylococcus epidermidis* (MSSE) (six patients), methicillin resistant coagulase-negative staphylococci (MRCNS) including methicillin-resistant *S. epidermidis* (MRSE) (5 patients), methicillin-resistant *S. aureus* (MRSA) (three patients), and methicillin-sensitive *S. aureus* (MSSA) (two patients) in gram-positive bacteria, and *Escherichia coli* (four patients) in gram-negative bacteria. The bacteriological responses classified by the genus/species of the isolated organisms are presented in Table 9. The relationship between bacteriological responses and clinical responses in 24 patients with isolated pathogenic organisms is shown in Table 10. Of the 24 patients, 13 were responders (marked efficacy + efficacy) and 11 were nonresponders; from five nonresponders, the resistant bacteria, such as MRSA and MRSE, were isolated.

Adverse reactions

Of the 204 patients included in the safety analysis population, 13 (6.4%) experienced adverse reactions, which

Table 5 Clinical response according to underlying disease

	Marked efficacy	Effective	Ineffective	Unable to evaluate	Total	Efficacy rate (marked efficacy + efficacy)/number of evaluable patients (%)
Acute myelogenous leukemia	24	19	23	6	72	43/66 (65.2)
Acute lymphoblastic leukemia	7	1	5	1	14	8/13 (61.5)
Chronic myelocytic leukemia	3	–	–	–	3	3/3 (100.0)
Myelodysplastic syndrome	3	3	3	–	9	6/9 (66.7)
Non-Hodgkin's lymphoma	22	10	19	8	59	32/51 (62.7)
Hodgkin's lymphoma	1	1	–	–	2	2/2 (100.0)
Multiple myeloma	4	4	1	–	9	8/9 (88.9)
Aplastic anemia	1	–	–	–	1	1/1 (100.0)
Other	6	1	1	1	9	7/8 (87.5)
Total	71	39	52	16	178	110/162 (67.9)

Table 6 Clinical response according to neutrophil count

No. of effective cases/no. of patients[a] (efficacy rate)	Neutrophil count 72 h after administration				Total (%)
	≤100/μl (%)	101–500/μl (%)	≥501/μl (%)	Unknown (%)	
Neutrophil count before administration					
≤100/μl	37/60 (61.7)	5/6 (83.3)	6/7 (85.7)	17/21 (81.0)	65/94 (69.1)
101–500/μl	11/13 (84.6)	12/17 (70.6)	4/4 (100.0)	4/10 (40.0)	31/44 (70.5)
≥501/μl	1/2 (50.0)	2/4 (50.0)	4/5 (80.0)	7/13 (53.8)	14/24 (58.3)
Total	49/75 (65.3)	19/27 (70.3)	14/16 (87.5)	28/44 (63.6)	110/162 (67.9)

[a] Tabulation of 162 patients after excluding 16 who were incapable of being evaluated

included liver-function-related events (13), rash/drug eruption (four), paroxysmal supraventricular tachycardia (one), abdominal pain (one), and fever (one) (Table 11). The incidence of adverse reactions among patients aged ≥65 years and those with depressed renal function are presented in Table 12. There were no deaths that were judged to be causally related to BIPM administration.

Discussion

It is of vital clinical importance to provide appropriate therapy for infections complicating hematopoietic disorders, as infections reportedly rank first among the causes of death in these patients, particularly those with acute leukemias and MDS [8]. FN occurring as a complication in patients with hematopoietic disorders may be associated with serious outcomes, and the patient prognosis can be profoundly affected by appropriate investigation, precise diagnosis, and prompt institution of empirically proven effective antimicrobial agents. BIPM has been demonstrated to have a broad-spectrum antibacterial activity against gram-positive and gram-negative organisms,

including *Pseudomonas aeruginosa*, and exerts a rapid bactericidal effect. Satisfactory antimicrobial activity of this antibiotic has been maintained since it was first launched into the market in 2002 [9]. As a unique clinical feature of this drug, it was proved to have an earlier effect than imipenem/cilastatin in a comparative trial, particularly for the treatment of lower respiratory tract infections [10].

This study was conducted in patients treated at the institutions listed in Table 13 with the objective of assessing the efficacy and safety of BIPM in patients with acute myeloid leukemia, non-Hodgkin's lymphoma, or other hematopoietic disorders. Response rate in the efficacy analysis population was 67.9%, being comparable with response rates reported from other studies of drugs belonging to a similar class for similar indications in patients with the same disorders [11–13]. According to the 2004 Guideline for Management of FN, subsequent therapy should be selected on the basis of the response evaluated 3–5 days after the start of initial treatment in initial management. Assessment of therapeutic response in the early stage is a point of great importance, and, in this context, the excellent response rate of 43.8% and the antipyretic rate of 67.3% within 3 days and 75.9% within 5 days of start of

Table 7 Clinical response according to administration and dosage (1)

	No. of patients[a]	Effective	Ineffective	Efficacy rate (%)	Statistical test (Fisher)
Dosage					
No. of patients[a]	162	110	52	67.9	$p = 0.296$
0.3 g × 2	75	48	27	64.0	
0.6 g × 2	78	57	21	73.1	
Other	9	5	4	55.6	
Intravenous infusion time					
No. of patients[a]	162[a]	110	52	67.9	$p = 0.527$
30–60 min infusion	123	85	38	69.1	
2 h infusion	32	20	12	62.5	
Unknown	7	5	2	71.4	

[a] Tabulation of 162 patients after excluding 16 who were incapable of being evaluated

Table 8 Clinical response according to administration and dosage (2)

	No. of patients[a]	Effective	Ineffective	Efficacy rate (%)	Statistical test (Fisher)
0.3 g × 2 group					
No. of patients[a]	75	48	27	64.0	$p = 0.797$
30–60 min IV infusion	46	30	16	65.2	
2-h IV infusion	25	15	10	60.0	
Unknown	4	3	1	75.0	
0.6 g × 2 group					
No. of patients[a]	78	57	21	73.1	$p = 1.000$
30–60 min IV infusion	71	51	20	71.8	
2-h IV infusion	6	5	1	83.3	
Unknown	1	1	–	100.0	

[a] Tabulation of 162 patients after excluding 16 who were incapable of being evaluated

Table 9 Antimicrobial efficacy

	No. isolated	Eradicated	Diminution	Persistence	Substitution	Unknown
MSSE	6	2				4
MRCNS (including MRSE)	5	1		1		3
MRSA	3			1	2	
MSSA	2	1	1			
Streptococcus spp.	3	1				2
Enterococcus spp.	2				1	1
Total gram-positive bacteria	21	5	1	2	3	10
Escherichia coli	4	2			1	1
Enterobacter cloacae	1					1
Serratia marcescens	1	1				
Stenotrophomonas maltophilia	1			1		
Proteus vulgaris group	1					1
Capnocytophaga spp.	1					1
Total[a]	30	8	1	3	4	14

MSSE methicillin-sensitive *Staphylococcus epidermidis*, *MRCNS* methicillin resistant coagulase-negative staphylococci, *MRSE* methicillin-resistant *S. epidermidis*, *MRSA* methicillin-resistant *S. aureus*, *MSSA* methicillin-sensitive *S. aureus*

[a] Total number of isolates, 30 (microbial detection 24 patients)

Table 10 Relationship between bacteriological and clinical responses

	Clinical efficacy ($N = 24$)		
	Marked efficacy ($N = 6$)	Effective ($N = 7$)	Ineffective ($N = 11$)
Bacterial response			
Eradicated	3	2	3
Diminution	1	0	2
Persistence			3
Substitution		1	1
Unknown	2	4	2

Table 11 Breakdown of adverse events

Adverse event	No. of events[a]
Liver-function-related	13
Rash/drug eruption	4
Paroxysmal supraventricular tachycardia	1
Abdominal pain	1
Fever	1
Total	20 events/13 patients (6.4%)

[a] Patients eligible for evaluation of safety: 204

the administration observed in this series following treatment with BIPM are worthy of good appraisal.

Decrease in neutrophil count is a factor of prime importance in the treatment of FN, and it is generally recognized that the risk of development and rate of progression of infections vary with duration of sustained FN, rate and severity of decrease of neutrophil count, and recovery status. In fact, it has been reported that the incidence of infection rises when the neutrophil count is ≤500/µl, and the incidence of a fatally severe infection, including sepsis, is markedly elevated when the neutrophil count is ≤100/µl [14]. The data presented in this report represent remarkably gratifying

clinical responses, with a response rate of 61.7% (37/60) even in high-risk FN patients in whom the neutrophil counts prior to and at 72 h after the start of BIPM were ≤100/µl.

In recent years, appropriate use of antimicrobial agents based on the PK-PD theory has been recommended and has become widespread in the treatment of infections in patients with immune deficiency states such as FN, because responses to β-lactam antibiotics, including carbapenems, have been shown to be correlated with the time above the minimum inhibitory concentration (T > MIC%), and such correlation with T > MIC% has also been reported for BIPM [15–19]. In view of this, we adopted a protracted 2-h intravenous infusion schedule to obtain greater T > MIC%. Results revealed no significant difference in the response rate between a cohort administered the drug by 2-h intravenous infusion (62.5% [20/32]) and that administered infusion over the usual 30–60 min [69.1% (85/123)]. However, when response rates were compared by dose and infusion time, a high clinical efficacy with a response rate up to 83.3% (5/6) was observed in patients who were administered BIPM at 0.6 g b.i.d. by 2-h intravenous infusion. Further study is therefore needed to establish the optimal method BIPM administration.

The causative microorganisms often remain unclear in patients with FN. The reported percentage of FN patients with a positive blood culture is ≤10%, whereas clinically overt infections such as stomatitis or pneumonia and fever of unknown etiology are said to account for 10–20 and 70–80% of FN patients, respectively [20, 21]. In our study, causative organisms were isolated from 24 (13.5%) of 178 patients studied, and gram-positive bacteria mainly comprising *S. epidermidis*, including MRSE, and *S aureus*, including MRSA, accounted for 70% of the isolates. These results support a recent report concerning clinical bacterial isolates [22], and the current trend of an increasing rate of isolation of gram-positive organisms as the causative pathogens is considered to be attributable to prolonged use of central venous catheters and prophylactic use of oral

Table 12 Safety evaluation

	No. of patients	Adverse events	Incidence of adverse events (%)	Statistical test (Fisher)
Incidence of adverse reactions in elderly patients				
No. of patients	204	13	6.40	$p = 1.000$
<65 years	138	9	6.50	
≥65 years	66	4	6.10	
Incidence of adverse reactions according to renal function (creatinine clearance) prior to the start of administration				
No. of patients	204	13	6.4	$p = 1.000$
<50 years	12	1	8.3	
50–79 years	31	2	6.5	
≥80 years	115	9	7.8	
Unknown	46	1	2.2	

Table 13 Case registration institutions

Institutions (in alphabetical order according to the Japanese syllabary)	
Iwate Medical University School of Medicine	NTT Kanto Medical Center
The Cancer Institute Hospital of JFCR	Kitasato University Hospital
Gunma Prefectural Cancer Center	Gunma University Hospital
Showa General Hospital	Saitama Red Cross Hospital
Jichi Medical University Hospital	Showa University Hospital
Showa University Fujigaoka Hospital	Tokai University Hospital
Tokyo Medical University Hospital	Tokyo Medical and Dental University Hospital Faculty of Medicine
Tokyo Women's Medical University Hospital	Tokyo Women's Medical University Medical Center East
Tokyo Metropolitan Fuchu Hospital	Toranomon Hospital
Nagaoka Red Cross Hospital	Niigata Cancer Center Hospital
Niigata University Medical and Dental Hospital	Japanese Red Cross Medical Center
University of Yamanashi Hospital	Yokohama City University Medical Center
Yokohama Rosai Hospital	

antibiotic administration prior to onset of pyrexia [23]. In fact, as many as 98 patients in our series had an indwelling catheter.

With regard to safety, adverse reactions (20 events) were reported in 13 patients (6.4%). Most of these were expected reactions and mild, such as liver-function-related events and rash and drug eruptions and did not pose any particular safety concern. Thus, BIPM appears to be promising as an initial-stage therapeutic agent in patients with FN complicating hematopoietic disease, as it was demonstrated to afford prompt clinical benefit in these patients.

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ORIGINAL ARTICLE

An open-label extension study evaluating the safety and efficacy of romiplostim for up to 3.5 years in thrombocytopenic Japanese patients with immune thrombocytopenic purpura (ITP)

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Abstract Long-term use of the thrombopoietin mimetic romiplostim was examined in Japanese patients with chronic immune thrombocytopenic purpura (ITP) in this open-label extension. The starting dose of romiplostim was the previous trial dose or 3 μg/kg/week, which was titrated up to 10 μg/kg/week to maintain platelet counts between 50 and 200 × 10^9/L. As of April 2010, 44 patients had enrolled; 71 % women, median age 55.5 years, with five patients discontinuing romiplostim due to patient request (2), administrative decision (2), or not achieving study-defined platelet response (1). Median treatment duration was 100 weeks; median average weekly dose was 3.8 μg/kg.

Twenty-eight patients (64 %) self-injected romiplostim. The most frequent adverse events were nasopharyngitis and headache. Nine patients (20 %) had a total of 14 serious adverse events (0.31/100 patient-weeks); of these, only oral hemorrhage was considered treatment related. Fifty hemorrhagic adverse events were reported in 20 patients (46 %) (1.12/100 patient-weeks). Ninety-six percent of patients had a platelet response (doubling of baseline platelet count and platelet count ≥50 × 10^9/L). Of the 25 patients receiving concurrent ITP therapy at baseline, all reduced or discontinued the therapy. Eight patients (18 %) received rescue medications. Administration of up to

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3.5 years of romiplostim increased platelet counts and was well tolerated in Japanese patients with chronic ITP.

Keywords Immune thrombocytopenic purpura (ITP) · Romiplostim · Thrombopoietin receptor agonists · Thrombopoietin mimetic

Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by isolated thrombocytopenia (i.e., no other hematologic abnormality) with platelet counts below 100×10^9/L, due to both increased platelet destruction and a relatively low level of platelet production [1–5]. Incidence of ITP in Japan is 2.16/100,000/year, with approximately 70 % of cases occurring in patients older than 50 years [6, 7]. Treatment is typically not recommended for patients with platelet counts >50 $\times 10^9$/L [2, 8, 9]. When treatment is necessary, options include corticosteroids and other immunosuppressive agents, splenectomy, and immunoglobulins [8, 9]. However, a significant proportion of ITP patients either will not respond to or will not have a sustained platelet response with these agents, many of which are accompanied by significant side effects [8, 15, 16]. For those ITP patients who have active *Helicobacter pylori* infection, *H. pylori* eradication therapy appears to improve thrombocytopenia in some [6, 10–14].

While, traditionally, options such as those listed above aim to limit platelet destruction, a new class of agents addresses the now understood relative deficiency in platelet production. Romiplostim, a thrombopoietin (TPO) mimetic with no structural overlap with TPO, increases platelet production by a mechanism similar to that of endogenous TPO [5, 17, 18]. Romiplostim, which has been shown to be effective for the treatment of chronic ITP with good tolerability, has been approved in many countries for the treatment of chronic ITP in adult patients with an insufficient response to previous treatments [19]. Specifically, romiplostim (Nplate®) is indicated in the United States for the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy [20]. Romiplostim should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding, but not to normalize platelet counts [20]. In Europe, romiplostim is indicated for the treatment of splenectomized adult chronic ITP patients who are refractory to other treatments and may be considered as second-line treatment for adult non-splenectomized ITP patients for whom surgery is contraindicated [21]. As of January 21, 2011, the Japanese regulatory agency, the Ministry of

Health, Labour, and Welfare, approved romiplostim (brand name Romiplate®) for the treatment of thrombocytopenia in adult chronic ITP in patients who have had an inadequate response to or are intolerant of other therapies for ITP [22]. Romiplostim should be used only in those patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding [22].

Disease presentation, pharmacokinetics, pharmacodynamics, and safety may be affected by ethnic background [23, 24]. Therefore, the use of romiplostim in Japanese patients with ITP was assessed in clinical studies in Japanese patients with ITP. Similar to early phase studies in other populations, romiplostim was found to be well tolerated and effective at increasing platelet counts in a dose-dependent manner with good tolerability in Japanese patients with ITP [25–27]. Likewise, romiplostim significantly increased and maintained platelet counts and was well tolerated in a phase 3 study of 34 Japanese patients with ITP, with similar dosing to that seen in non-Asian patients [27, 28]. However, there are few reports of the long-term safety and efficacy of romiplostim in clinical trials. We describe here the results of patients from the phase 2 and phase 3 studies who then continued into an open-label extension study for up to 3.5 years of romiplostim treatment.

Materials and methods

Study design

This was an open-label extension study designed to assess the safety and efficacy of long-term romiplostim dosing in thrombocytopenic Japanese patients with ITP (Fig. 1). If patients entered the extension study within 12 weeks of receiving the last romiplostim dose in the previous study and had shown an increase in platelet counts $\geq 20 \times 10^9$/L from baseline at least once during the 13-week treatment period of the original trial (excluding 4 weeks after rescue medication), they were treated with romiplostim at the same weekly dose last received in the previous study. Otherwise, patients were treated with romiplostim at a starting dose of 3 μg/kg. Romiplostim was administered by subcutaneous (SC) injection once per week. Dose adjustment based on platelet counts was permitted throughout the treatment period to allow patients to maintain platelet counts in the target range of $50–200 \times 10^9$/L, up to a maximum permitted dose of 10 μg/kg. Patients who achieved a stable dose of romiplostim for at least 3 consecutive weeks were allowed to self-inject romiplostim away from the clinic. The study began in October 2006 and is ongoing.
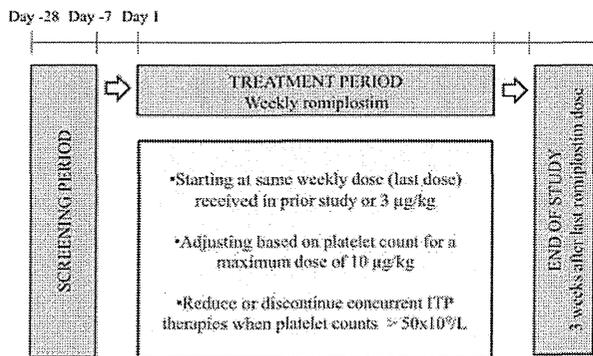
Day -28 Day -7 Day 1

Fig. 1 Study design. This was an open-label extension study of long-term romiplostim dosing in thrombocytopenic Japanese patients with ITP

Eligibility

Patients who had completed any previous romiplostim ITP study in Japan (a phase 2 open-label study and a phase 3 randomized study) were eligible to screen for this study. Additionally, patients were required to provide written informed consent before any study-specific procedures were performed and must have had a platelet count at screening of <50 × 10^9/L. Patients were excluded from the study if they had any significant change in medical history since completion of the previous romiplostim ITP study, including bone marrow stem cell disorders or new active malignancies; tested positive for neutralizing antibodies to romiplostim in the previous romiplostim ITP study; were receiving any treatment for ITP except oral corticosteroids, azathioprine, and/or danazol administered at a constant dose and schedule for at least 4 weeks prior to the screening visit; were pregnant, breastfeeding, or of reproductive potential and not using adequate contraception; had a known severe drug hypersensitivity; or were unlikely to comply with the protocol.

Study endpoints

The primary endpoint of this study was to determine the safety of romiplostim as a long-term treatment in thrombocytopenic Japanese patients with ITP, as measured by the incidence of adverse events, including clinically significant changes in laboratory values. Additional endpoints included incidence of anti-romiplostim antibody formation, incidence of platelet response (doubling of the baseline platelet count at study entry of the previous study and platelet counts ≥50 × 10^9/L), and proportion of patients able to reduce or discontinue their concurrent ITP therapies (for patients who were receiving oral corticosteroids at a constant dose and schedule at the screening visit). Anti-romiplostim antibodies were assayed at week 1, every

12 weeks during the study and at end of study. Specifically, two validated assays were used: a Biacore 3000 (Biacore International, AB, Uppsala, Sweden) immunoassay and a cell-based bioassay to detect neutralizing or inhibitory effects in vitro [29–31]. If a sample was positive in both assays, a subject was defined as positive for neutralizing antibodies. Throughout the study, investigators could perform a bone marrow biopsy when deemed medically appropriate.

Statistics

The statistical analyses in this open-label extension study were descriptive in nature. Categorical endpoints were summarized by the number and percentage of patients in each category. Continuous endpoints were summarized by number in an eligible subset (*n*), mean, standard deviation, median, Q1 (25th percentile), Q3 (75th percentile), and minimum and maximum values.

Results

Patient characteristics, disposition, and exposure

As of April 2010, 44 patients who had previously completed either a phase 2 or phase 3 study in Japan [25, 27] enrolled in this open-label extension study. These patients had baseline characteristics of 71 % women, median age 55.5 years (ranging from 25 to 81 years), and median (Q1, Q3) platelet count of 16.5 (6.0, 23.0) × 10^9/L (Table 1). Past treatments included corticosteroids (98 %), IVIg (57 %), *H. pylori* eradication (48 %), splenectomy (39 %), azathioprine (25 %), danazol (23 %), cyclophosphamide (11 %), vincristine/vinblastine (7 %), and rituximab (7 %). Two patients had a past medical history of hepatitis B virus (HBV), three of hepatitis C virus (HCV), and one of HBV and HCV. As of this data cutoff, 5 patients (11 %) discontinued romiplostim due to patient request (2, after 85 and 183 days of treatment, respectively), administrative decision secondary to platelet counts >200 × 10^9/L (2, after 281 and 583 days of treatment, respectively) and platelet counts ≤20 × 10^9/L after 4 weeks of dosing with 10 µg/kg (1, after 247 days of treatment). The patients who discontinued romiplostim completed an end of study visit 3 weeks after the last administration of romiplostim. All patients received at least one dose of romiplostim, with the mean (SD) treatment duration being 102 (47) weeks (ranging from 12 to 184 weeks) and the mean (SD) average weekly dose being 4.3 (2.7) µg/kg (ranging from 0 to 10 µg/kg). The overall mean weekly dose increase around week 150 corresponds to when the study population consisted of patients from the phase 2 study only (i.e., none

Table 1 Baseline characteristics

	Phase 2 (N = 11)	Phase 3 (N = 33)	Total (N = 44)
Age (years)			
Mean ± SD	55.5 ± 9.8	54.7 ± 13.9	54.9 ± 12.9
Median (min, max)	62.0 (32, 63)	54.0 (25, 81)	55.5 (25, 81)
Sex, n (%)			
Female	7 (63.6)	24 (72.7)	31 (70.5)
Male	4 (36.4)	9 (27.3)	13 (29.5)
Baseline platelet count (×10⁹/L)[a]			
Mean ± SD	11.5 ± 10.1	17.7 ± 8.5	16.1 ± 9.2
Median (min, max)	5.5 (3, 31)	19.5 (3, 32)	16.5 (3, 32)
Platelet count prior to the treatment of this study (×10⁹/L)[b]			
Mean ± SD	10.7 ± 8.6	16.3 ± 11.9	14.9 ± 11.3
Median (min, max)	6.0 (3, 25)	11.0 (3, 53)	11.0 (3, 53)

Baseline platelet count $(\times 10^9/L)^a$

Platelet count prior to the treatment of this study $(\times 10^9/L)^b$

[a] Baseline platelet count in this study was baseline platelet count obtained in the previous study

[b] Platelet count of week 1 or pre-treatment platelet count closest to the first dose of romiplostim in this study if platelet count of week 1 was missing
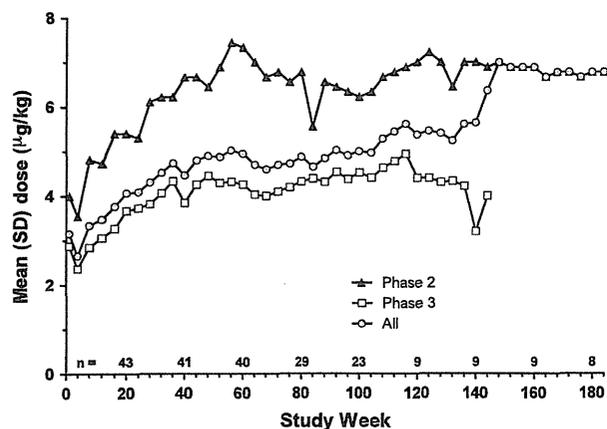

Fig. 2 Mean dose over time. Mean doses for all of the patients, as well as for those who were originally from the phase 2 trial or the phase 3 trial prior to entering the extension, are shown

from the phase 3 study) (Fig. 2). The patients in the phase 2 study had received higher doses throughout this extension. Twenty-eight patients (64 %) received romiplostim by self-injection, beginning after a median (Q1, Q3) of 21 (8.5, 29.0) weeks on study and continuing self-injection for a median (Q1, Q3) duration of 60.0 (28.5, 87.5) weeks. The median (Q1, Q3) percent of weeks these patients were self-injecting was 65 % (42, 81 %). Twelve of these 28 patients (43 %) discontinued self-injection.

Safety

All patients reported at least 1 adverse event after beginning treatment with romiplostim, with 27 patients (61 %) reporting adverse events that were considered by the investigator to be related to the treatment with romiplostim (Table 2). The most frequent adverse events were nasopharyngitis (2.1/100 patient-weeks), headache (0.7/100 patient-weeks), back pain (0.3/100 patient-weeks), contusion (0.3/100 patient-weeks), and malaise (0.3/100 patient-weeks). All nasopharyngitis cases were considered by investigators to not be related to romiplostim, and they were generally mild common upper respiratory tract infections; 6 cases (of 101) were rated as moderate in severity. The most frequently reported treatment-related adverse events were headache (0.52/100 patient-weeks), back pain (0.13/100 patient-weeks), malaise (0.13/100 patient-weeks), and vertigo (0.09/100 patient-weeks).

Nine patients (20 %) reported serious adverse events (duration-adjusted rate of 0.31/100 patient-weeks), with one serious adverse event, mouth hemorrhage, considered by the investigator to be related to the treatment with romiplostim. Other reported serious adverse events included one event each of hemorrhagic anemia, thrombocytopenia, appendicitis, grand mal convulsion, transient ischemic attack, epistaxis, intracranial aneurysm, lumbar spinal stenosis, allergic transfusion reaction, melena, mouth hemorrhage, subcutaneous hematoma, wound, and spinal compression fracture (Table 3). The event of mouth hemorrhage occurred 17 months after initiation of romiplostim in this study. Platelet counts in this patient during romiplostim treatment fluctuated greatly, and thus the dose was frequently adjusted. During one of the times of low platelet counts, the mouth hemorrhage occurred, thus the investigator indicated that there was a reasonable possibility that the hemorrhage was due to romiplostim. As the investigator judged the romiplostim as being effective, treatment with romiplostim was continued. The event of transient ischemic attack occurred 59 days after initiation of romiplostim in this study. The patient had a history of paroxysmal atrial fibrillation, hyperlipidemia, and hyperbilirubinemia. Three days prior to the event, the platelet count was 206 × 10⁹/L. The patient went to the emergency room, where the platelet count was measured at 135 × 10⁹/L. He was not hospitalized, returned home, and the event resolved the next day. Platelet count 4 days after the event was 70 × 10⁹/L. As the investigator judged that the event was caused by transient cerebral hypoperfusion and cerebrovascular spasm, it was considered to not be due to romiplostim, and romiplostim treatment continued. Each of these serious adverse events occurred at a rate of 0.02/100 patient-weeks. There were

Table 2 Overall summary of safety

	N (%)	Rate
Any adverse events (AE)	44 (100)	11.15
Serious AE (SAE)	9 (21)	0.31
Any treatment-related AE	27 (61)	1.70
Any treatment-related SAE	1 (2)	0.02
Death	0 (0)	0
Withdrawal due to AE	0 (0)	0

Rate events per 100 patient-weeks

Table 3 Serious adverse events (SAE)

	N (rate)
All SAE	14 (0.31)
Hemorrhagic anemia	1 (0.02)
Thrombocytopenia	1 (0.02)
Appendicitis	1 (0.02)
Grand mal convulsion	1 (0.02)
Transient ischemic attack	1 (0.02)
Epistaxis	1 (0.02)
Intracranial aneurysm	1 (0.02)
Lumbar spinal stenosis	1 (0.02)
Allergic transfusion reaction	1 (0.02)
Melena	1 (0.02)
Mouth hemorrhage[a]	1 (0.02)
Subcutaneous hematoma	1 (0.02)
Wound	1 (0.02)
Spinal compression fraction	1 (0.02)

Rate events per 100 patient-weeks

[a] Considered by the investigator to be related to romiplostim

no life-threatening adverse events, and no patients died or withdrew from the study.

A total of 50 hemorrhagic adverse events were reported in 20 patients (46 %), with a duration-adjusted rate of 1.12/100 patient-weeks. The most common hemorrhagic adverse events were contusion (0.29/100 patient-weeks), epistaxis (0.16/100 patient-weeks), purpura (0.11/100 patient-weeks), and conjunctival hemorrhage (0.09/100 patient-weeks). Three patients (7 %) had a total of 5 serious hemorrhagic adverse events; one with epistaxis and hemorrhagic anemia, one with melena and subcutaneous hematoma, and one with mouth hemorrhage.

Regarding adverse events of interest, no cases were reported of hematopoietic malignancy, myelodysplastic syndrome, thrombocytosis, or bone marrow reticulin/collagen fibrosis (bone marrow biopsies were performed at investigator discretion). A total of 14 biopsies were performed on 8 patients over a wide range of time, from before the study (1), within the first year (8), to more than 1 year up to over 2 years (5). All biopsies were negative

for reticulin and collagen. However, after this data cutoff (on study day 735), one patient experienced a mild non-serious adverse event of increased reticulin that was considered by the investigator to be related to treatment with romiplostim. The only thromboembolic event was a serious adverse event of transient ischemic attack. Additionally, no patients tested positive for neutralizing antibodies to romiplostim or TPO in the antibody assays that were performed every 12 weeks.

Efficacy

Overall, 96 % of patients had a platelet response (doubling of the baseline platelet count at study entry of the previous study and platelet counts $\geq$50 $\times$ 10^9/L) (response rate over time shown in Fig. 3). Median platelet counts stayed above 50 $\times$ 10^9/L each week from week 2 onward (Fig. 4). Of the 25 patients receiving concurrent ITP therapy at baseline, all were able to reduce or discontinue that therapy: 11 (44 %) had a >25 % reduction in at least 1 concurrent therapy, 5 (20 %) had a >50 % reduction in at least 1 concurrent therapy, and 9 (36 %) discontinued all concurrent therapies. There was an overall decrease over time in the proportion of patients with bleeding events (Fig. 5). Eight patients (18 %) received rescue medications for ITP at some point during the study. These included prednisolone (6 patients), platelet transfusion (5 patients), immunoglobulins (3 patients), dexamethasone and red blood cell transfusion (each 1 patient). Details on individual patients are provided in Table 4.

Discussion

Results of this study indicate that romiplostim administration for up to 3.5 years was well tolerated in Japanese patients with ITP. The reported incidence of adverse events did not increase over time during long-term exposure to romiplostim and were similar to those seen in other romiplostim studies, such as the long-term open-label extension in ITP patients of other ethnic origins (N = 292) [32]. In addition, both studies had similar proportions of patients having a platelet response (96 % in this study, 95 % in the other), similar median doses (3.8 vs. 4.0 μg/kg), and a majority of patients initiating self-injection (64 vs. 82 %). In this study, the safety and tolerability of romiplostim self-injection was generally satisfactory; however, please note that self-injection of romiplostim is not approved in Japan. During self-injection, patients continued to have regular platelet count assessments, and, if platelet counts were greater than the target range (50–200 $\times$ 10^9/L), romiplostim was discontinued. This discontinuation rule applied to those who received romiplostim from a healthcare provider

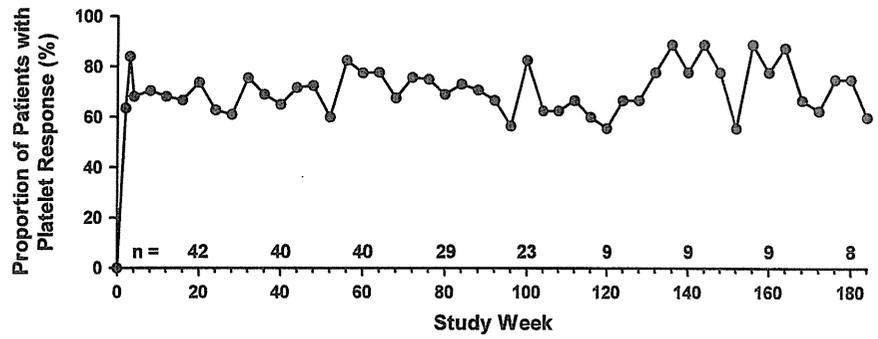Fig. 3 Platelet response over time
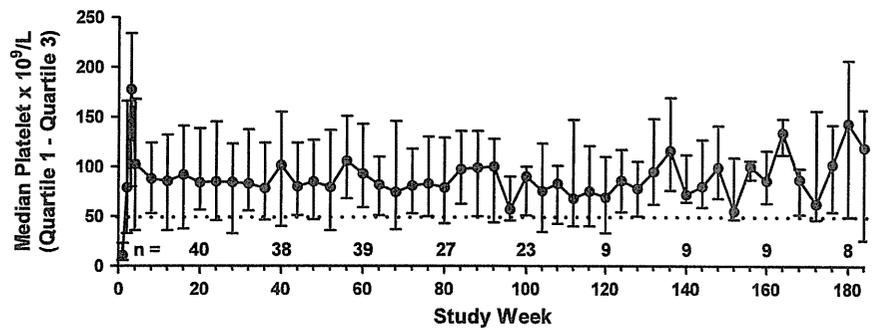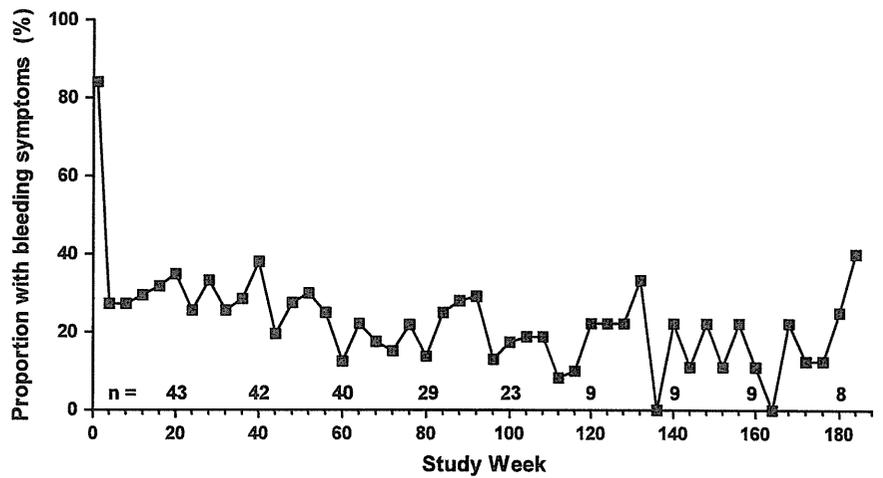

Fig. 4 Platelet count over time

Fig. 5 Bleeding symptoms over time

as well. Concurrent ITP medications at baseline were reduced or discontinued in most patients in both studies (100 vs. 81 %). Overall, the efficacy and safety profile is consistent in these two study populations [28, 33, 34].

During the study, one thromboembolic event of transient ischemic attack was reported. The event occurred in a patient who had a history of paroxysmal atrial fibrillation, hyperlipidemia, and hyperbilirubinemia. Although the transient ischemic attack was not judged to be related to romiplostim by the investigator based on the patient's medical history, this kind of thromboembolic event should be noted and followed carefully during romiplostim

treatment. Thus, the benefit:risk ratio of romiplostim should be carefully considered in patients with significant risk factors for thromboembolic events, and platelet counts should be closely monitored. Other reported serious adverse events were mouth hemorrhage, hemorrhagic anemia, thrombocytopenia, appendicitis, grand mal convulsion, epistaxis, intracranial aneurysm, lumbar spinal stenosis, allergic transfusion reaction, melena, mouth hemorrhage, subcutaneous hematoma, wound, and spinal compression fracture, each occurring at a rate of 0.02/100 patient-weeks. Eight patients received rescue medications for ITP, including prednisolone, platelet transfusion,

Table 4 Rescue medication use

Patient	Rescue medication	Number of incidents	Notes[a]
1	Prednisolone	1	
2	Platelet transfusion	2	
3	Prednisolone	3	
4	Prednisolone	2	
	IVIg	1	
5	Dexamethasone	1	
	IVIG	2	GI hemorrhage leading to anemia
	Platelet transfusion	7	One was due to epistaxis, the other 6 due to GI hemorrhage leading to anemia
	Prednisolone	2	
6	Platelet transfusion	1	Mouth hemorrhage
	Prednisolone	5	
	IVIg	3	1 was due to mouth hemorrhage
7	Platelet transfusion	22	2 were due to subcutaneous hematoma
	RBC transfusion	11	All were due to anemia
	Prednisolone	3	
8	Platelet transfusion	4	

GI gastrointestinal

[a] Unless otherwise indicated, use was for thrombocytopenia, not any other specific cause

immunoglobulin, dexamethasone and red blood cell transfusion. There were no deaths and no neutralizing antibodies to romiplostim or TPO. A total of 14 bone marrow biopsies were performed on 8 patients over a wide range of time, with no findings of bone marrow reticulin or collagen as of this data cutoff. Subsequently, there was a mild nonserious adverse event of increased reticulin considered related to romiplostim (study day 735).

A higher romiplostim dose was consistently seen with patients originally from the phase 2 study as compared with those from the phase 3 study. It was thought that this may reflect that the patients from the phase 2 study had a longer history of ITP (median 11.8 vs. 5.8 years for the phase 3 study), and hence likely more advanced disease. To explore this possibility, we performed a post hoc analysis and found that higher romiplostim doses were related to lower platelet count at study entry ($p = 0.0003$)(i.e., inversely related) and inversely related to *H. pylori* eradication prior to study start ($p < 0.0001$), and positively associated with starting dose in this extension study ($p = 0.006$). Of note, the association of ITP duration with romiplostim dose was

not statistically significant ($p = 0.1$). Rather, the higher dose in patients originally in the phase 2 study was due to lower platelet count at study entry ($p = 0.01$) and higher starting dose ($p = 0.02$) compared with the phase 3 study, as per study design.

One limitation of this study is the relatively small size (44 patients). Therefore, it is difficult to make conclusions regarding different patient subgroups (such as splenectomized vs. non-splenectomized, etc.). As of this data cutoff, there have been 86 patient-years of romiplostim exposure in this extension study; as this study is ongoing, analyses at future dates will be based on longer exposure time. Another possible limitation is self-selection, as often patients who respond to a medication are more likely to enter an extension study. As a high proportion of patients from earlier studies (44/46, or 96 %) enrolled into this study, it is unlikely that selection bias influenced the results of this extension trial.

In conclusion, similarly to non-Japanese patients, long-term administration of romiplostim was well tolerated in Japanese patients with ITP, with the vast majority of patients achieving a platelet response and no new safety concerns. With the approval of romiplostim in Japan, Japanese patients with ITP will now have access to another option for second-line therapy.

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