学 会 等 発 表 実 績

委託業務題目「 成人T細胞性白血病／リンパ腫（ATLL）に対するNY-ESO-1+AS15 ASCIのモガムリズマブ併用での安全性と有効性探索のための医師主導治験（第Ⅰ／Ⅱ相）」

機関名　公益財団法人慈愛会 今村病院分院

1．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別

2．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Mogamulizumab, an anti-CCR4 antibody, targets human T-lymphotropic virus type 1-infected CD8+ and CD4+ T cells to treat associated myelopathy.	Yamauchi J, Coler-Reilly A, Sato T, Araya N, Yagishita N, Ando H, Kunitomo Y, Takahashi K, Tanaka Y, Shibagaki Y, Nishioka K, Nakajima T, Hasegawa Y, Utsunomiya A, Kimura K, Yamano Y	J Infect Dis	2015. Jan	国外
Recent advances in treatment of adult T-cell leukemia- lymphomas.	Utsunomiya A, Choi I, Chihara D, Seto M	Cancer Science	in press	国内
Clinical outcomes of a novel therapeutic vaccine with Tax peptide-pulsed dendritic cells for adult T cell leukaemia/lymphoma in a pilot study.	Suehiro Y, Hasegawa A, Iino T, Sasada A, Watanabe N, Matsuoka M, Takamori A, Tanosaki R, Utsunomiya A, Choi I, Fukuda T, Miura O, Takaishi S, Teshima T, Akashi K, Kannagi M, Uike N, Okamura J	Br J Haematol	in press	国外

学 会 等 発 表 実 績

委託業務題目「 成人T細胞性白血病／リンパ腫（ATLL）に対するNY-ESO-1+AS15 ASCIのモガムリズマブ併用での安全性と有効性探索のための医師主導治験（第Ⅰ／Ⅱ相）」

機関名　福岡大学

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Is watch and wait still standard for indolent ATL?（口演）	石塚賢治	7Th annual T-cell lymphoma forum	2015.1.29-31	国外

２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Japan Clinical Oncology Group (JCOG) prognostic index and characterization of long-term survivors of aggressive adult T-cell leukaemia-lymphoma (JCOG0902A).	Fukushima T, Nomura S, Shimoyama M, Shibata T, Imaizumi Y, Moriuchi Y, Tomoyose T, Uozumi K, Kobayashi Y, Fukushima N, Utsunomiya A, Tara M, Nosaka K, Hidaka M, Uike N, Yoshida S, Tamura K, Ishitsuka K, Kurosawa M, Nakata M, Fukuda H, Hotta T, Tobinai K, Tsukasaki K.	Br J Haematol.	2014. Sep	国外
Human T-cell leukaemia virus type I and adult T-cell leukaemia-lymphoma.	Ishitsuka K, Tamura K.	Lancet Oncol.	2014. Oct	国外
Promise of combining a Bcl-2 family inhibitor with bortezomib or SAHA for adult T-cell leukemia/lymphoma.	Kunami N, Katsuya H, Nogami R, Ishitsuka K, Tamura K.	Anticancer Res.	2014. Oct	国外

学 会 等 発 表 実 績

委託業務題目「 成人T細胞性白血病／リンパ腫（ATLL）に対するNY-ESO-1+AS15 ASCIのモガムリズマブ併用での安全性と有効性探索のための医師主導治験（第Ⅰ／Ⅱ相）」

機関名　国立がん研究センター東病院

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Hierarchical clustering analysis of surface antigens on ATL cells and search for AT- initiating cell marker.（ポスター）	Ishigaki T, Kobayashi S, Nakano N,Utsunomiya A, Uchimaru K , Tojo A	第73回日本癌学会学術総会	2014.9.25-27	国内
A nationwide survey of patients with adult T cell leukemia/lymphoma (ATL) in Japan: 2010-2011.（口演）	野坂生郷、岩永正子、石澤賢一、石田陽治、内丸薫、石塚賢治、天野正宏、石田高司、今泉芳孝、鵜池直邦、宇都宮與、大島孝一、河井一浩、田中淳司、戸倉新樹、飛内賢正、渡邉俊樹、塚崎邦弘	第76回日本血液学会学術集会	2014.10.31-11.2	国内
Clinical features of adult T-cell leukemia/lymphoma (ATL) in Okinawa Prefecture（口演）	Nishi Y, Fukushima T, Nomura S, Tomoyose T, Nakachi S, Morichika K, Tedokon I, Tamaki K, Shimabukuro N, Taira N, Miyagi T, Karimata K, Yohama M, Yamanoha A, Tamaki K, Hayashi M, Arakaki H, Uchihara J, Ooshiro K, Asakura Y, Tanaka Y, Masuzaki H	第76回日本血液学会学術集会	2014.10.31-11.2	国内
Is watch and wait still standard for indolent ATL?（口演）	Ishitsuka K	7Th annual T-cell lymphoma forum	2015.1.29-31	国外

Comprehensive Analysis of Surface Antigens on Adult T-Cell Leukemia/Lymphoma (ATL) Cells and Search for ATL-Initiating Cell Markers.（ポスター）	Ishigaki T, Kobayashi S, Ohno N, Nakano N, Utsunomiya A, Yamazaki S, Watanabe N, Uchimaru K, Tojo A, Nakauchi H.	The 56th ASH Annual Meeting and Exposition.	2014.12.6-9	国外

2．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Human T-cell lymphotropic virus type I-associatedadult T-cell leukemia-lymphoma.	Tsukasaki K,Tobinai K.	Clin Cancer Res	2014.Oct	国外
Molecular Characterization of Chronic-type Adult T-cell Leukemia/Lymphoma.	Yoshida N, Karube K, Utsunomiya A, Tsukasaki K, Imaizumi Y, Taira N, Uike N, Umino A, Arita K, Suguro M, Tsuzuki S, Kinoshita T, Ohshima K, Seto M.	Clin Cancer Res	2014.Oct	国外
Japan Clinical Oncology Group prognostic index and characterization of long-term survivors of aggressive adult T-cell leukemia-lymphoma (JCOG0902A).	Fukushima T, Nomura S, Shimoyama M, Shibata T, Imaizumi Y, Moriuchi Y, Tomoyose T, Uozumi K, Kobayashi Y, Fukushima N, Utsunomiya A, Tara M, Nosaka K, Hidaka M, Uike N, Yoshida S, Tamura K, Ishitsuka K, Kurosawa M, Nakata M, Fukuda H, Hotta T, Tobinai K, Tsukasaki K.	Cancer Res	2014.Sep	国外

IV. 研究成果の刊行物・別刷

Int J Hematol (2015) 101:37–45
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ORIGINAL ARTICLE

Impact of early use of lenalidomide and low-dose dexamethasone on clinical outcomes in patients with relapsed/refractory multiple myeloma

Tsutomu Kobayashi · Junya Kuroda · Shin-ichi Fuchida · Hitomi Kaneko · Hideo Yagi · Hirohiko Shibayama · Hirokazu Tanaka · Satoru Kosugi · Nobuhiko Uoshima · Masayuki Kobayashi · Yoko Adachi · Kensuke Ohta · Kazuyoshi Ishii · Hitoji Uchiyama · Mitsuhiro Matsuda · Eiji Nakatani · Mitsuru Tsudo · Chihiro Shimazaki · Akifumi Takaori-Kondo · Shosaku Nomura · Itaru Matsumura · Masafumi Taniwaki · Yuzuru Kanakura · KMF investigators

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Abstract We retrospectively investigated the prognostic factor of lenalidomide plus low-dose dexamethasone (Rd) in Japanese patients with refractory or relapsed multiple myeloma (RRMM) registered in the Kansai Myeloma Forum from January 2006 to December 2013. A total of 140 patients were analyzed. The median age was 66 years. The overall response rate was 68.6 %, including 33.1 % with a better than very good partial response. At 13.0 months median follow-up, the median overall survival (OS) and progression-free survival (PFS) were 34.2 and 17.0 months, respectively. In univariate analyses, patients with one or two prior therapies had significantly longer OS (41.2 vs. 21.5 months; $P = 0.002$) and PFS (29.0 vs. 13.0 months; $P = 0.006$) than patients treated with three or more prior therapies. Prior use of thalidomide was associated with significantly shorter PFS (19.0 vs. 16.0 months; $P = 0.045$). The prior use of bortezomib or high-dose therapy with stem cell transplantation, and the International

T. Kobayashi (✉) · J. Kuroda · M. Taniwaki
Division of Hematology and Oncology, Graduate School of Medicine, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kamigyo-ku, Kyoto 602-8566, Japan
e-mail: t-koba@koto.kpu-m.ac.jp

S. Fuchida · C. Shimazaki
Department of Hematology, Japan Community Health Care Organization Kyoto-Kuramaguchi Medical Center, Kyoto, Japan

H. Kaneko · M. Tsudo
Department of Hematology, Osaka Red Cross Hospital, Osaka, Japan

H. Yagi
Department of Hematology, Nara Hospital Kinki University Faculty of Medicine, Nara, Japan

H. Shibayama · Y. Kanakura
Department of Hematology and Oncology, Osaka University Graduate School of Medicine, Osaka, Japan

H. Tanaka · I. Matsumura
Division of Hematology and Rheumatology, Department of Internal Medicine, Faculty of Medicine, Kinki University, Higashiosaka, Japan

S. Kosugi
Department of Hematology, Toyonaka Municipal Hospital, Toyonaka, Japan

N. Uoshima · H. Uchiyama
Department of Hematology, Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan

N. Uoshima
Department of Hematology, Matsushita Memorial Hospital, Moriguchi, Japan

M. Kobayashi · A. Takaori-Kondo
Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Y. Adachi
Department of Internal Medicine, Japan Community Health Care Organization Kobe Central Hospital, Kobe, Japan

K. Ohta
Department of Hematology, Osaka Saiseikai Nakatsu Hospital, Osaka, Japan

K. Ishii · S. Nomura
First Department of Internal Medicine, Kansai Medical University, Hirakata, Japan

M. Matsuda
Department of Hematology, PL General Hospital, Tondabayashi, Japan

Staging System had no impact on long-term outcome. Multivariate analysis showed that only the number of prior therapies was a significant predictor of both OS and PFS. Our findings suggest that greater benefit may occur when Rd therapy is used at the first or second relapse in RRMM.

Keywords Lenalidomide · Multiple myeloma · Relapse · Refractory

Introduction

Multiple myeloma (MM), the second most common hematologic cancer, is mostly incurable. Newer agents, such as bortezomib, thalidomide, and lenalidomide, have improved treatment outcomes of patients with MM [1, 2]. The immunomodulatory drug thalidomide has efficacy in relapsed or refractory MM (RRMM) and exerts a greater effect when used in combination with dexamethasone or chemotherapy [3–6]. Lenalidomide is a thalidomide derivative that is more potent than thalidomide [7]. Two phase III trials (MM-009 and MM-010) demonstrated that lenalidomide plus dexamethasone was more effective than dexamethasone alone in patients with RRMM [8, 9]. Namely, in the pooled analysis from the MM-009 and MM-010 trials, it was demonstrated that treatment with lenalidomide plus dexamethasone significantly improved the overall response (OS), complete response rate, time to progression, and duration of response compared with dexamethasone plus placebo [10].

In Japan, the efficacy and safety of treatment with lenalidomide plus dexamethasone have only been demonstrated in a small cohort study [11]. In this study, we retrospectively analyzed the outcome and the prognostic factor of 140 RRMM patients treated with lenalidomide plus low-dose dexamethasone (Rd).

Materials and methods

Patients

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and approved by the institutional review boards of all institutes participating in the Kansai Myeloma Forum (KMF). We retrospectively analyzed 140 RRMM patients treated with Rd from January 2006 to December 2013 in the KMF, which was founded for the purpose of registering patients with myeloma-related disease in the Kansai area, Japan. Patients who had received Rd as the planned treatment prior to high-dose therapy or maintenance therapy were excluded.

Treatment schedule

The patients enrolled in this study had been treated with at least one previous anti-myeloma regimen. Patients generally received lenalidomide 25 mg on days 1–21 plus dexamethasone 40 mg on days 1, 8, 15, and 22 of a 28-day cycle [12], and the doses of lenalidomide and dexamethasone were reduced at the doctor's discretion, based on the patients' renal function, the onset of adverse effects and the patients' condition [13]. The choice of a later anti-myeloma regimen after disease progression was not specified.

Response criteria

The International Myeloma Working Group (IMWG) criteria were used for the assessment of treatment response [14]. Disease stage was assessed according to the International Staging System (ISS) [15]. After initiation of Rd therapy, patients were followed up until discontinuation of Rd therapy, due to progression, or the date of death from any cause. PFS was defined as the time from initiation of Rd therapy to discontinuation of Rd therapy, due to progression, or the date of death from any cause, whichever occurred first. OS was calculated from initiation of Rd therapy to death from any cause. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Statistical analysis

Analysis was performed using a data cutoff date: February 28, 2014. OS and PFS curves were estimated using the Kaplan–Meier method. The log-rank test was performed to compare curves. Cox proportional-hazards regression model was used to identify prognostic variables for OS and PFS. Extraction of candidate prognostic factors was performed in univariate analysis with $P < 0.2$ and identification of prognostic factors was performed in multivariate analysis with $P < 0.05$. The variables assessed included age, gender, number of prior therapies, time to Rd therapy from the initiation of myeloma treatment, treatment response to Rd, prior treatment with thalidomide, bortezomib, or high-dose chemotherapy with autologous stem cell transplantation (HDT/ASCT), and other baseline disease characteristics such as the ISS disease stage at diagnosis and type of M-protein. Student's t test and Chi-square test were used to compare baseline characteristics between patients with one or two prior therapies and those with more than 3 prior therapies. The confidence interval was 95 % for all analyses and $P < 0.05$ was considered to be statistically significant.

E. Nakatani
Translational Research Informatics Center, Foundation for Biomedical Research and Innovation, Kyoto, Japan

Statistical analyses were performed using SPSS statistical software (version 19; IBM, Armonk, NY, USA).

Results

Patients' background

A total of 140 patients were investigated in this study. The patients' demographics are summarized in Table 1. International Staging System classification was available for 133 patients, while age, gender, the number of prior therapies, the type of paraprotein, and history of treatment with bortezomib, thalidomide, or HDT/ASCT were evaluable for all patients. Of the 133 evaluable patients, 40, 61, and 32 were classified in the ISS stage I, II, and III, respectively. All patients had been treated with at least one prior chemotherapeutic regimen other than Rd therapy. Previous treatments included radiotherapy ($n = 16$), HDT/ASCT ($n = 35$), and various combination chemotherapies, i.e., bortezomib and dexamethasone (VD) ($n = 73$); melphalan and prednisolone (MP) ($n = 58$); vincristine, doxorubicin, and dexamethasone (VAD) ($n = 41$); bortezomib, cyclophosphamide, and dexamethasone (VCD) ($n = 20$); MP and bortezomib (MPV) ($n = 16$); thalidomide and dexamethasone (TD) ($n = 11$); dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) ($n = 9$); MP and thalidomide (MPT) ($n = 9$); ranimustine, vincristine, melphalan, and dexamethasone (ROAD) ($n = 4$); lenalidomide and high-dose dexamethasone (RD) ($n = 4$); cyclophosphamide and prednisolone (CP) ($n = 3$); bortezomib, thalidomide, and dexamethasone (VTD) ($n = 2$); vincristine, cyclophosphamide, doxorubicin, and steroid (VCAP or CVAD) ($n = 2$); thalidomide and prednisolone ($n = 1$); melphalan, thalidomide, and dexamethasone (MTD) ($n = 1$); and cyclophosphamide, doxorubicin, and dexamethasone (CAD) ($n = 1$). Among them, 33 patients had a prior history of thalidomide treatment and 97 had undergone prior treatment with bortezomib.

To compare the background factors between patients who had undergone two or less prior therapies and three or more prior therapies, Table 2 is shown. Age, treatment history with thalidomide, or bortezomib and the time from the initiation of anti-myeloma therapy were significantly different between patients with one or two prior therapies and those with three or more prior therapies (Table 2).

Table 1 Demographics of the 140 RRMM patients analyzed in this study

Patient background ($n = 140$)	
Age	
Median	66.5
Range	39–88
Gender	
Male/female	72/68
Prior therapy, no. (%)	
Number of therapies	
Median (range)	2 (1–9)
≤ 2	92 (65.7)
≥ 3	48 (34.3)
Type of therapy	
HDT/ASCT	35 (25.0)
Bortezomib	97 (69.3)
Thalidomide	33 (23.6)
M-protein, no. (%)	
IgG	77 (55.0)
IgA	33 (23.6)
IgD	5 (3.6)
BJP	25(17.8)
ISS no. (%)	
I	40 (28.6)
II	61 (43.6)
III	32 (22.8)
NA	7 (5.0)

Response

Among 121 evaluable patients, 22 (18.2 %) achieved complete response (CR), 18 (14.9 %) achieved very good partial response (VGPR), 43 (35.5 %) achieved partial response (PR), 24 (19.8 %) exhibited stable disease (SD), and 14 patients (11.6 %) exhibited progressive disease (PD). The overall response rate (ORR; CR + VGPR + PR) was 68.6 %. The median number of treatment cycles was 7 (range 1–43) in the entire study period, and 53.7 % of patients received Rd therapy for more than 7 cycles. The median number of treatment cycles until the occurrence of best response was 4 (range 1–34).

Long-term outcome with Rd therapy and the impact of prior treatment

At a median follow-up of 13.0 months, the median OS was 34.2 months, and the estimated OS at 2 years was 61.1 %; the corresponding values for PFS were 17.0 months and 38.0 %, respectively (Fig. 1). Eighty-seven (62.1 %) in 140 patients discontinued Rd therapy in the study period because of disease progression (43.7 %), adverse events (27.6 %), death (14.9 %), switching to a different regimen as maintenance therapy (6.9 %), disease stabilization (4.6 %), and others. As observed in the MM-009 and MM-010 trials, disease progression was the major cause of death during Rd therapy in our cohort.

In univariate analyses, both OS and PFS were significantly longer in patients with two or less prior therapies than in patients with three or more prior lines of therapy (median OS 41.2 vs. 21.5 months; $P = 0.002$, median PFS 29.0 vs. 13.0 months; $P = 0.006$, respectively) (Fig. 2a). Similarly, patients who received Rd therapy within 24 months after the start of anti-myeloma therapy showed significantly longer OS and a trend toward longer PFS compared with patients who received Rd therapy 24 months after the start of anti-myeloma therapy (Fig. 2b). Older age (over 65 years old) was associated with shorter OS (median 35.6 vs. 21.7 months; $P = 0.031$), while it was not associated with PFS. Importantly, among the evaluable 133 patients, ISS stage did not predict long-term outcome after Rd among the RRMM patients (Fig. 2c).

Table 2 Baseline characteristics, treatment history, and outcomes in patients according to the number of prior therapies

	1 or 2 prior therapies ($n = 92$)	≥3 prior therapies ($n = 48$)	P value
Age			
Median (range)	69 (39–88)	65 (44–78)	0.004
Gender			
Male/female	44/48	28/20	0.238
Type of prior therapies, no. (%)			
HDT/ASCT	20 (21.7)	15 (31.3)	0.217
Bortezomib	57 (62.0)	40 (83.3)	0.009
Thalidomide	10 (10.9)	22 (45.8)	<0.001
M-protein, no. (%)			0.221
IgG	54 (58.7)	23 (47.9)	
IgA	18 (19.6)	15 (31.3)	
IgD	2 (2.2)	3 (6.2)	
BJP	18 (19.6)	7 (14.6)	
ISS, no. (%)			0.579
I	28 (30.4)	12 (25.0)	
II	43 (46.7)	18 (37.5)	
III	20 (21.7)	12 (25.0)	
NA	1 (1.1)	6 (12.5)	
Response, no. (%)			0.115
≥ VGPR	30 (32.6)	10 (20.8)	
≤ PR	49 (53.3)	32 (66.7)	
NA	13 (14.1)	6 (12.5)	
Median time from initiation of anti-myeloma therapy			
Months (range)	14.3 (1.3–105.5)	40.2 (1.7–129.5)	<0.001

As shown in Fig. 3, the history of prior thalidomide treatment had no impact on OS with Rd, while PFS was significantly shorter in patients who had previously undergone treatment with thalidomide (median 19.0 vs. 16.0 months; $P = 0.045$). By contrast, previous history of treatment with bortezomib and high-dose therapy with autologous stem cell transplantation did not affect either OS or PFS following Rd therapy in our cohort. OS was superior in patients who achieved a better response to Rd therapy (median OS 41.2 months in the CR/VGPR group, 27.3 months in the PR, 14.3 months in the SD, and 8.4 months in the PD, respectively), and PFS was also superior in patients with better response to Rd therapy (median PFS 29.0, 16.0, 9.0 and 1.4 months in the CR/VGPR, PR, SD and PD groups, respectively) (Fig. 4). None of the other analyzed variables, including gender and type of M-protein, exhibited any influence on either OS or PFS (data not shown).

We further performed a multivariate analysis to determine the prognostic factors of patients' baseline characteristics, including the number of prior therapies, time from initiation of anti-myeloma therapy to initiation of Rd, age, type of M-protein, and the ISS stage. As shown in Tables 3 and 4, only the number of prior therapies was a significant predictor of both OS and PFS.

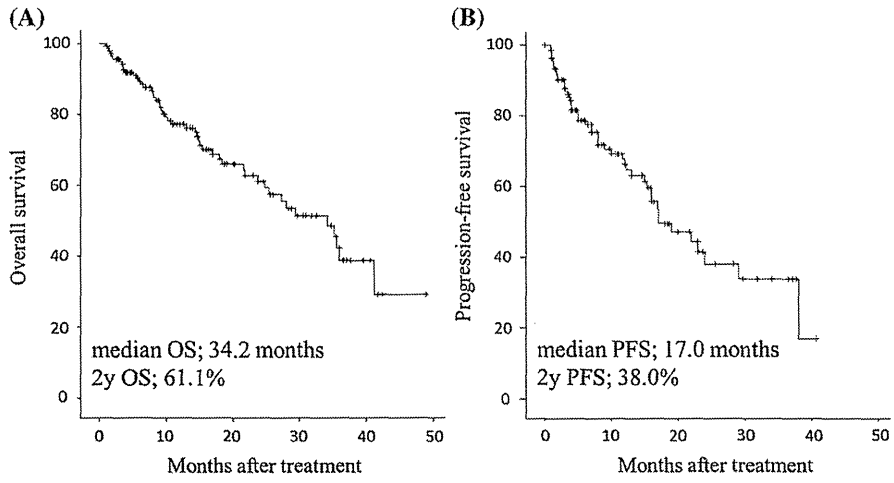

Fig. 1 Overall survival (OS) (*A*) and progression-free survival (PFS) (*B*) for 140 relapsed or refractory multiple myeloma (RRMM) patients treated with lenalidomide plus low-dose dexamethasone (Rd) therapy analyzed with the Kaplan–Meier method

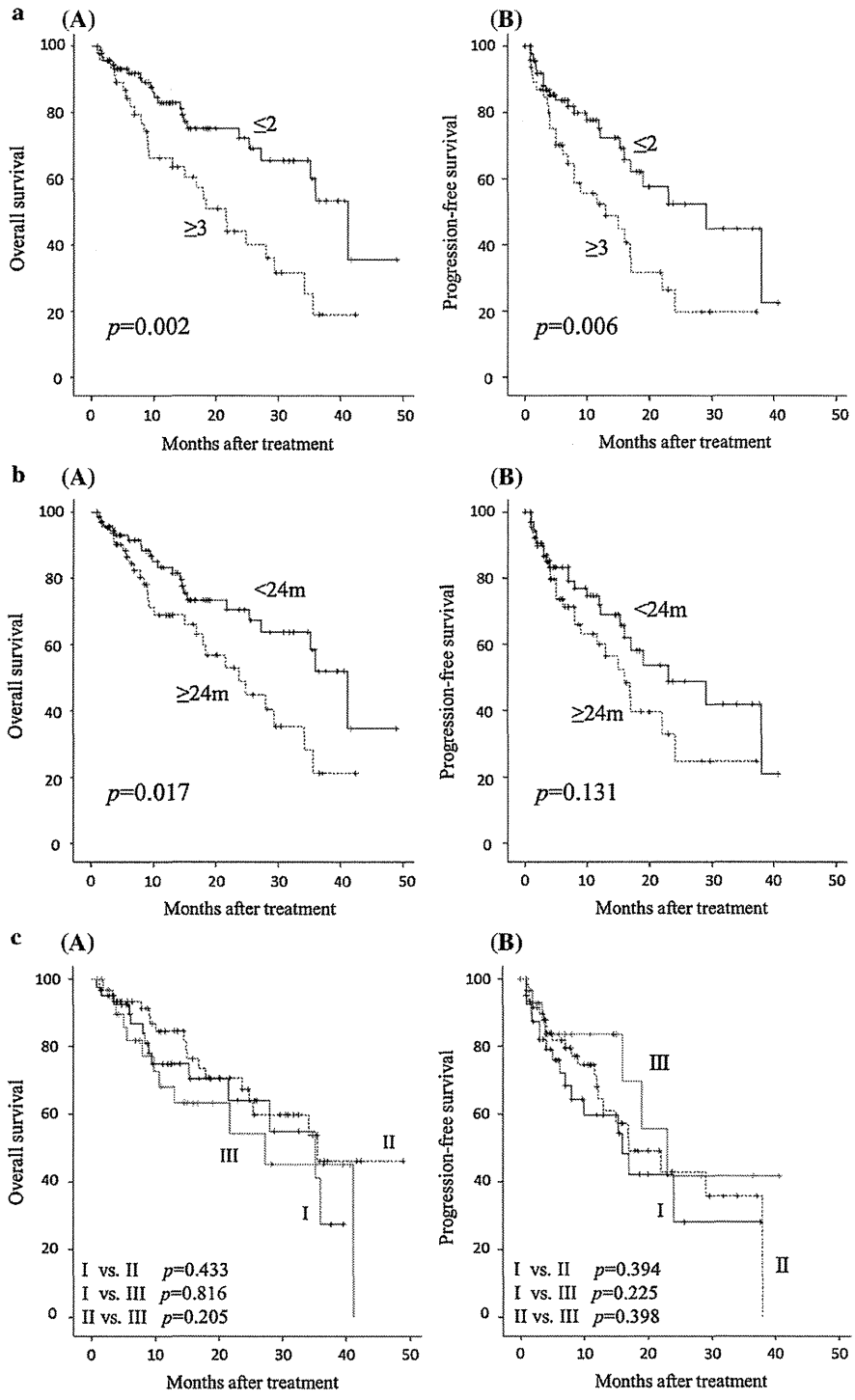

Fig. 2 **a** Impact of the number of prior regimens on OS and PFS following Rd therapy. *A* OS for patients who had received less than two prior therapies (*solid line*) and at least three prior therapies (*dotted line*) before Rd therapy. *B* PFS for patients who had received less than two prior therapies (*solid line*) and at least three prior therapies (*dotted line*). **b** Impact of the time to Rd therapy from the initiation of anti-myeloma therapy on OS and PFS following Rd therapy. *A* OS for patients who had received Rd therapy less than 24 months after the start of anti-myeloma therapy (*black solid line*), and 24 months or later (*dotted line*). *B* PFS for patients who had received Rd therapy less than 24 months after the start of anti-myeloma therapy (*black line*) and 24 months or later (*dotted line*). **c** OS (*A*) and PFS (*B*) for 133 patients according to the International Staging System (stage I *black solid line*; stage II *black dotted line*; stage III *gray solid line*)

Adverse events

Table 5 lists all grade 3–5 adverse events among 128 evaluable patients. At least one grade 3 or 4 adverse event was observed in 49.2 % of patients treated with Rd therapy. Among grade 3–5 adverse events, hematologic events of neutropenia, anemia, and thrombocytopenia were more frequent than various non-hematologic adverse events. No grade 3–5 thrombotic event, including deep vein thrombosis and pulmonary embolism, was observed in our cohort, probably due to a routinely prophylactic use of an anticoagulant. Four patients died due to infection.

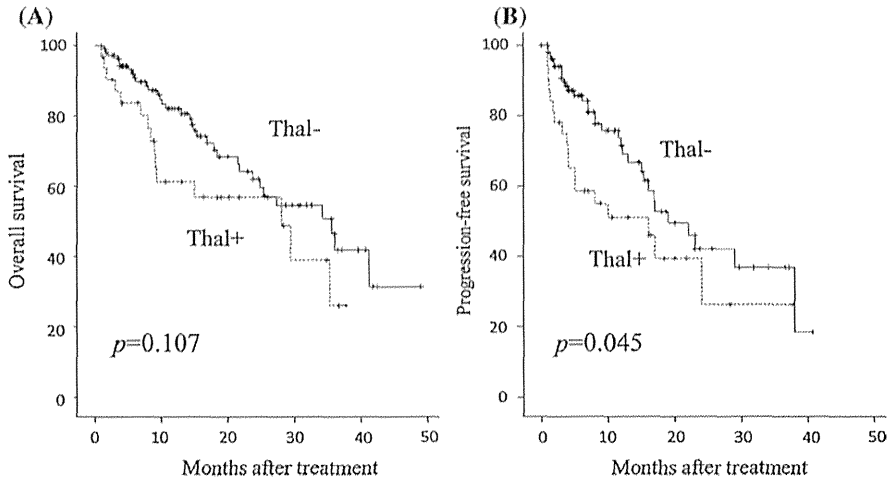

Fig. 3 Impact of previous exposure to thalidomide on OS and PFS following Rd therapy. OS (*A*) and PFS (*B*) for patients with (*dotted line*) or without (*solid line*) previous thalidomide exposure

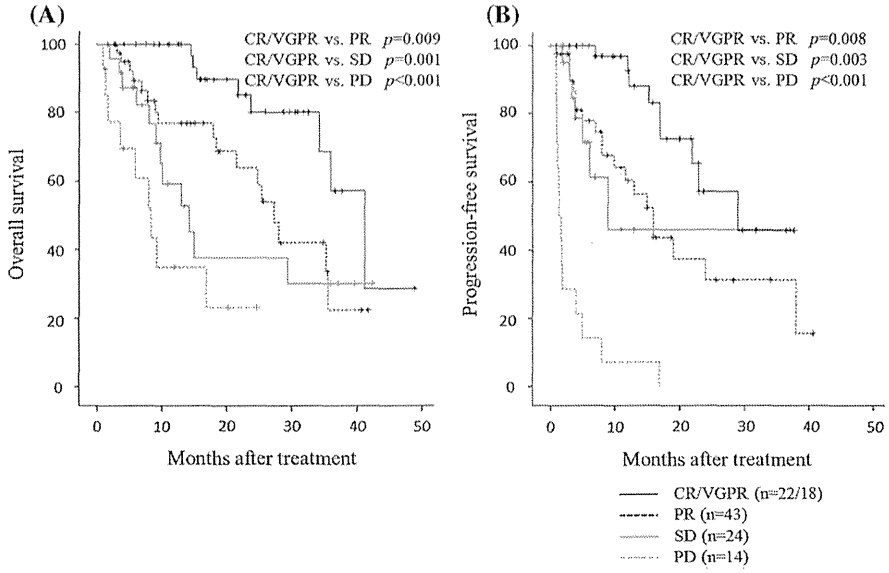

Fig. 4 OS (*A*) and PFS (*B*) for 121 patients according to the best response to Rd therapy (CR/VGPR *black solid line*; PR *black dotted line*; SD *gray solid line*; PD *gray dotted line*)

Discussion

Our results demonstrate that patients with fewer prior treatments may benefit more from salvage therapy with Rd, which is consistent with a previous study [16]. In general, the fewer prior regimens may be associated with a shorter duration until the initiation of Rd therapy, and, indeed, patients who received Rd within 24 months after the initiation of anti-myeloma therapy also had significantly longer OS and tended to have longer PFS compared with patients treated after more than 24 months in our cohort. One possible explanation for the unfavorable outcome of patients with more prior regimens (or a longer duration from the initiation of anti-myeloma therapy) is the acquisition and/or the selection of clones that can rapidly acquire resistance to Rd therapy during prior treatments. Presumably, while lenalidomide can modulate immunologic tumor surveillance and tumor microenvironment [17], there may be more chances for the emergence/expansion of aggressive subclones (clonal evolution) that become less dependent on bone marrow tumor microenvironment and less sensitive to immunologic attack by T and/or NK cells through the greater treatment regimens and during the longer treatment duration in MM [18].

Lenalidomide plus dexamethasone has been reported to be effective, even in patients with a history of thalidomide treatment. However, the shorter time to progression in patients with prior thalidomide treatment has suggested the potential for partial cross-resistance between lenalidomide and thalidomide. For instance, both agents share cereblon (CRBN)-mediated molecular effects in their anti-MM effects [19]. Meanwhile, the previous report by

Table 3 Statistical analyses of prognostic variables for OS

Baseline variable	#Event/*N*	HR	95 % CI	*P* value
Univariate Cox regression analyses for OS				
Number of prior therapy ≥ 3	49/138	2.298	1.307–4.038	0.004
Time to Rd ≥ 24 months	49/138	1.907	1.079–3.371	0.026
Age > 65	49/138	1.910	1.065–3.424	0.030
Type of M-protein	49/138			
IgG		1.000		0.438
IgA		1.725	0.889–3.344	0.107
IgD		1.139	0.265–4.894	0.861
BJP		1.397	0.639–3.057	0.402
ISS	44/132			
I		1.000		0.458
II		0.723	0.356–1.470	0.371
III		1.118	0.508–2.463	0.782
Multivariate Cox regression analyses of variables for OS selected by backward stepwise regression				
Number of prior therapy ≥ 3	44/132	3.119	1.645–5.913	0.001
Age > 65	44/132	2.775	1.420–5.424	0.003

HR hazard ratio, *C.I.* confidence interval, *Rd* lenalidomide plus low-dose dexamethasone, *CR* complete response, *VGPR* very good partial response, *ISS* International Staging System

Table 4 Statistical analyses of prognostic variables for PFS

Baseline variable	#event/*N*	HR	95 % CI	*P* value
Univariate Cox regression analyses for PFS				
Number of prior therapy ≥ 3	51/139	2.250	1.285–3.941	0.005
Time to Rd ≥ 24 months	51/139	1.575	0.897–2.766	0.114
Age > 65	51/139	1.475	0.837–2.597	0.179
Type of M-protein	51/139			
IgG		1.000		0.444
IgA		1.325	0.691–2.542	0.397
IgD		1.757	0.523–5.906	0.362
BJP		0.649	0.249–1.690	0.376
ISS	47/132			
I		1.000		0.424
II		0.786	0.416–1.486	0.459
III		0.555	0.227–1.356	0.196
Multivariate Cox regression analyses of variables for PFS selected by backward stepwise regression				
Number of prior therapy ≥ 3	47/132	2.359	1.291–4.308	0.005

Avet-Loiseau et al. [20] demonstrated that patients who were resistant to thalidomide had a higher incidence of the chromosomal abnormality of t(4;14), which may account for poorer outcomes observed in these patients.

Table 5 Grade 3 or higher adverse events

	Grade 3	Grade 4	Grade 5
Hematologic adverse events, *n* (%)			
Neutropenia	18 (14.1)	13 (10.2)	0 (0.0)
Anemia	30 (23.4)	1 (0.8)	0 (0.0)
Thrombocytopenia	14 (10.9)	13 (10.2)	0 (0.0)
Febrile neutropenia	3 (2.3)	2 (1.6)	0 (0.0)
Non-hematologic adverse events, *n* (%)			
Lung infection	7 (8.6)	2 (1.6)	2 (1.6)
Sepsis	0 (0.0)	7 (5.5)	2 (1.6)
Liver function tests abnormality	7 (5.5)	1 (0.8)	0 (0.0)
Constipation	2 (1.6)	2 (1.6)	0 (0.0)
Dizziness	4 (3.1)	0 (0.0)	0 (0.0)
Peripheral neuropathy	3 (2.3)	0 (0.0)	0 (0.0)
Nausea	2 (1.6)	0 (0.0)	0 (0.0)
Appetite loss	2 (1.6)	0 (0.0)	0 (0.0)
Skin disorders	2 (1.6)	0 (0.0)	0 (0.0)
Diarrhea	1 (0.8)	0 (0.0)	0 (0.0)
Fatigue	1 (0.8)	0 (0.0)	0 (0.0)
Hypothyroidism	1 (0.8)	0 (0.0)	0 (0.0)
All thromboembolic events	0 (0.0)	0 (0.0)	0 (0.0)

Similarly, our results also demonstrated that patients with previous exposure to thalidomide exhibited significantly shorter PFS than those without a history of thalidomide treatment. However, in our cohort, the proportion of patients with previous exposure to thalidomide was significantly higher in the group of patients with three or more prior therapies. Thus, it remains unclear whether the history of prior thalidomide treatment directly affected the long-term outcome with Rd in our cohort. In contrast, prior treatment with bortezomib or HDT/ASCT had no impact on long-term outcomes after the treatment with Rd, suggesting that there was no apparent cross-resistance between lenalidomide and bortezomib or high-dose melphalan.

The present analysis also demonstrated that better quality of response had a survival benefit, as patients who achieved a CR/VGPR had significantly longer OS and PFS compared with patients whose best response was PR or worse. This finding was similar to the previous study by Harousseau et al. [21], which showed that the quality of response with Rd had a positive prognostic impact, as patients who achieved better than VGPR had significantly longer time to progression, duration of response, and OS compared with patients whose best response was PR. As shown in Table 2, the number of prior therapies had no significant impact on the CR/VGPR rate, suggesting that the survival benefit by fewer pretreatment exposures was independent of the treatment response to Rd. Again, one of the conceivable reasons for this discrepancy may be that more

tumor subclones, including those less addicted to CRBN [19], less sensitive to immune surveillance, or less dependent to tumor microenvironment, emerge or expand along with the longer treatment history and the greater treatment regimens [18]. In addition, approximately half of the patients achieved the best response after cycle 5, supporting the evidence that continuous treatment of Rd provides greater clinical benefit over time. This finding seems to be in full accord with the results in previous studies [21]. Furthermore, the ORR of 68.6 % and the CR rate of 18.2 % in this study were also similar with those observed in previous studies [8, 9].

Our study also showed that the ISS stage did not affect OS or PFS in our cohort. Bataille et al. [22] demonstrated that the current ISS was a staging system for age-related comorbidity burden rather than a specific MM staging system and should not be used alone. Recently, Avet-Loiseau et al. [23] demonstrated that the combination of cytogenetic findings, i.e., t(4;14) and/or deletion (17p), with ISS staging was highly predictive of PFS and OS. Unfortunately, in this study, there were insufficient data regarding cytogenetic abnormalities to allow such an analysis. In the era of new drugs, the ISS may not be always useful for predicting outcomes in MM patients [24].

In conclusion, our results from the KMF study demonstrated that the combination of lenalidomide and low-dose dexamethasone is equally efficacious and feasible in Japanese patients with RRMM compared with previously reported data [8–10]. Patients with one or two therapies prior to Rd showed significantly longer OS and PFS compared with patients treated with three or more therapies.

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ORIGINAL ARTICLE

Phase III, single-arm study investigating the efficacy, safety, and tolerability of anagrelide as a second-line treatment in high-risk Japanese patients with essential thrombocythemia

Yuzuru Kanakura · Yoshitaka Miyakawa · Paul Wilde · Jonathan Smith · Heinrich Achenbach · Shinichiro Okamoto

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Abstract Essential thrombocythemia (ET) is usually managed by anti-platelet therapy. European guidelines recommend that patients with ET at high risk of developing thrombohemorrhagic events should be placed on cytoreductive therapy (CRT). In Japan, hydroxycarbamide (HC) is the most widely used CRT; however, treatment options for patients who become intolerant or refractory to initial treatment are limited. This study sought to determine the efficacy, safety, and tolerability of anagrelide in high-risk Japanese adults with ET who were intolerant or refractory to their first-line CRT. Fifty-three patients were enrolled in the study. Of those, 67.9 % had a platelet response ($<60 \times 10^4/\mu L$) and 45.3 % achieved normalization of platelet counts ($\leq 40 \times 10^4/\mu L$) on anagrelide therapy. The median time to platelet count response was 98.5 days and the median time to platelet count normalization was 274.0 days. The median daily dose administered was 1.9 mg/day. The most common adverse events observed during anagrelide treatment were anemia, headache, palpitations, and diarrhea. The majority of these were either mild or moderate in severity. Overall, the safety profile of anagrelide in high-risk Japanese patients with ET was consistent with the European Summary of Product Characteristics.

Keywords Essential thrombocythemia · Japan · Anagrelide · Second-line treatment

J. Smith Former contractor of Shire Pharmaceuticals.

Y. Kanakura (✉)
Graduate School of Medicine, Osaka University,
Osaka University Hospital, C9, 2-2, Yamada-oka, Suita,
Osaka 565-0871, Japan
e-mail: kanakura@bldon.med.osaka-u.ac.jp

Y. Miyakawa · S. Okamoto
Keio University, School of Medicine, Tokyo, Japan

Present Address:
Y. Miyakawa
Saitama Medical University, Saitama, Japan

P. Wilde · J. Smith
Shire Pharmaceutical Development Ltd, Basingstoke, UK

H. Achenbach
Shire AG, Eysins, Switzerland

Introduction

Essential thrombocythemia (ET) is predominantly characterized by thrombocytosis and abnormal megakaryocyte proliferation [1], and its clinical course is often complicated with thromboembolic events. According to European guidelines, it is strongly recommended that cytoreductive therapy (CRT) is initiated in patients who are at high risk of developing thrombotic or hemorrhagic events. High-risk patients can be categorized based upon three criteria: >60 years of age, history of thrombosis, or a high platelet count. Currently, at least one platelet count reading of $>150 \times 10^4/\mu L$ is required by the European LeukemiaNet guidelines to be categorized as a high-risk patient [2]; however, at the time of this study a platelet count of $>100 \times 10^4/\mu L$ was regarded as the cut-off for being a high-risk patient [3].

Hydroxycarbamide (HC) is the most widely used CRT for ET in Japan [4]. It has been suggested that long-term HC use is associated with a higher incidence of secondary leukemia [5]. Thus non-leukemogenic drugs such as anagrelide or interferon-α are treatments of choice for younger patients [2]. However, no compounds are currently licensed

as a second-line treatment for patients who become intolerant or refractory to their initial CRT in Japan. In Europe, anagrelide is approved as a second-line therapy for patients with ET who are intolerant or refractory to their prior CRT [6]. It is also licensed in the US as a first-line therapy for thrombocythemia in patients with myeloproliferative neoplasms (MPN) [7]. It is important to identify patients who become intolerant or refractory to HC treatment in order to avoid continuation of the drug that may produce intolerable side effects and to stop the use of an ineffective drug in a high-risk disease, but also to manage side effects appropriately to avoid the premature discontinuation of the drug that could otherwise prove efficacious [8].

The aims of this study were to evaluate the efficacy, safety, and tolerability of anagrelide as a second-line therapy in high-risk Japanese patients with ET who were intolerant or refractory to their first-line CRT.

Materials and methods

Study design

Study SPD422-308 (clinicaltrials.gov ID: NCT01214915) was a Phase III, open-label, single-arm study investigating the efficacy, safety, and tolerability of anagrelide in high-risk Japanese adults with ET who were intolerant or refractory to their first-line CRT. The study consisted of three periods: a 28-day screening period, a 12-month treatment period, and a 7-day follow-up period.

Patients

Patients aged 20 years or older were eligible to enroll in the study if they were previously diagnosed with ET according to the World Health Organization (WHO) criteria [1] and were considered at 'high risk' of thrombohemorrhagic events defined according to the anagrelide European Summary of Product Characteristics (SPC) (a platelet count of $>100 \times 10^4/\mu L$, >60 years of age, or history of previous thrombohemorrhagic events), and were refractory or intolerant to their first-line CRT. Refractory patients were defined as having a platelet count $>60 \times 10^4/\mu L$ after 3 months of at least 2 g/day of HC, and intolerant patients were defined as either having a platelet count $>40 \times 10^4/\mu L$ and white blood cell count $<2500/\mu L$ at any dose of HC, or platelet count $>40 \times 10^4/\mu L$ and hemoglobin <10 g/dL at any dose of HC, or the presence of leg ulcers or other mucocutaneous manifestations at any dose of HC, or HC-related fever [8]. All patients provided written, signed, and dated informed consent in order to participate in the study. Patients who were treated within 3 months prior to study entry with anagrelide, or were being treated with anticoagulant therapies, were excluded from the study. In addition, patients with the following were excluded: drug hypersensitivity or intolerance to anagrelide, receiving medication that had phosphodiesterase (PDE) III inhibitory properties, receiving medication that could affect their ET or the action of anagrelide, abnormal laboratory values, cardiac disease, hepatitis B, hepatitis C, human immunodeficiency virus, renal impairment, clinically significant malignancies or neoplasia, current or recurrent disease that might influence the action of anagrelide, current or relevant physical or psychiatric illness that might be affected by anagrelide treatment, a history of alcohol or other substance abuse in the 2 years prior to enrollment, or had been enrolled in a clinical study within the last 30 days. The study was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice.

Treatment

The starting dose of anagrelide was 0.5 mg/day twice daily (total dose 1.0 mg/day) as recommended in the anagrelide European SPC and as previously determined in a Phase I/II study in Japanese patients with ET to be clinically effective at reducing platelet counts [9]. This dose had to be maintained for at least 1 week prior to titration. Anagrelide titration was designed to achieve a response at the lowest effective dose and was assessed on an individual basis. Dosage increments could not exceed 0.5 mg/day in any one week and total daily doses could not exceed 10 mg. Patients could receive three to four doses of anagrelide per day following the first week of dosing if they were required to receive more than 5 mg/day, i.e. single doses could not exceed 2.5 mg/day. Following a protocol amendment, patients were allowed to continue HC treatment for the first month of the study after baseline measurements, if the treating physician determined that it was required to control platelet counts, while anagrelide was titrated to an effective dose.

Study objectives

The primary objective of the study was to evaluate the proportion of patients who had a response in platelet count ($<60 \times 10^4/\mu L$). The secondary objectives were to evaluate the proportion of patients who: (a) achieved a 50 % reduction in platelet count vs. their baseline values and (b) reached normalization in platelet count ($\leq 40 \times 10^4/\mu L$). To meet the definition of response or normalization, platelet counts had to be consistent across consecutive visits for at least 4 weeks following at least 3 months of anagrelide treatment (the same criteria were used to identify those patients who achieved a 50 % reduction in their platelet counts). In addition, patients were categorized according to their baseline platelet count (i.e. $\geq 60 \times 10^4/$

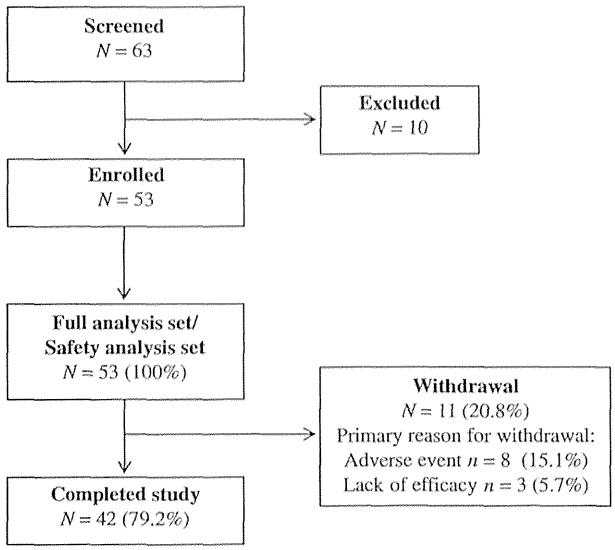

Fig. 1 Patient disposition

μL, >40 to <60 × 10^4/μL, <60 × 10^4/μL, ≤40 × 10^4/μL) and the proportion of each subgroup who achieved a response or normalization in their platelet counts was analyzed. The safety, tolerability, and utilization of anagrelide were also evaluated.

Post hoc subanalyses

Further analyses were carried out on the baseline characteristics to determine whether there were any trends in the efficacy and safety data.

Statistical methods

The study was not formally powered, but 60 patients were required to be enrolled to ensure that at least 50 would receive anagrelide treatment. It was planned that at least 10 patients would be required for each of the ≥60 × 10^4/μL and <60 × 10^4/μL platelet count baseline groups. These sample sizes were deemed large enough to give reasonably robust estimates on which to be able to draw conclusions. The efficacy variables were summarized using descriptive statistics, including the number and proportion of patients, together with a two-sided 95 % confidence interval.

Results

Study population

Of 63 patients screened, 53 met the inclusion criteria and were enrolled (Fig. 1). These patients met the WHO criteria for the diagnosis of ET (biopsy data were not collected as these were not a requirement of the protocol). Eleven patients (20.8 %) did not complete the study; the primary reasons for withdrawal were either due to an AE (n = 8; 15.1 %) or lack of efficacy (n = 3; 5.7 %). All 53 patients were included in the full analysis and safety analysis sets, which consisted of 30 females (56.6 %) and 23 males (43.4 %) with a median age of 66.0 years (range 36–86 years) (Table 1). The majority of patients were intolerant (n = 34; 64.2 %) to their previous or current CRT, rather than refractory (n = 19; 35.8 %) (Table 1).

Table 1 Baseline patient characteristics (safety set)

Characteristic	N = 53
Age (years)	
Median (range)	66.0 (36–86)
Age category, n (%)	
<50 years	12 (22.6)
50–59 years	5 (9.4)
60–69 years	18 (34.0)
70–79 years	17 (32.1)
≥80 years	1 (1.9)
Sex, n (%)	
Male	23 (43.4)
Female	30 (56.6)
Reason for stopping previous or current CRT (before entering the study), n (%)	
Refractory to CRT	19 (35.8)
Intolerant to CRT	34 (64.2)
Prior CRT, n (%)	
Anagrelide hydrochloride	2 (3.8)
Bulsulfan	2 (3.8)
Hydroxycarbamide	53 (100.0)
Interferon-α	2 (3.8)
Mercaptopurine	1 (1.9)
Ranimustine	6 (11.3)
Vincristine sulfate	1 (1.9)
Patients taking concomitant hydroxycarbamide up to month 1, n (%)	27 (50.9)
Time since ET diagnosis, years	
Median (range)	6.88 (0.12–29.06)
Baseline hemoglobin (g/dL)	
Mean (SD)	12.1 (1.91)

CRT cytoreductive therapy; *ET* essential thrombocythemia; *SD* standard deviation

Efficacy

The median length of anagrelide treatment was 358.0 days and the median daily dose was 1.904 mg/day (range 0.58–5.48 mg/day) (Table 2). The maximum final dose

Table 2 Anagrelide exposure (safety set)

Exposure	$N = 53$
Length of exposure, days	
Mean (SD)	305.2 (117.03)
Median (range)	358.0 (13–367)
Total dose (g)	
Mean (SD)	0.657 (0.4368)
Median (range)	0.535 (0.02–2.01)
Average daily dose (mg/day)	
Mean (SD)	2.126 (1.0482)
Median (range)	1.904 (0.58–5.48)
Length of exposure category, *n* (%)	
<3 months	7 (13.2)
3 to <6 months	2 (3.8)
6 to <9 months	1 (1.9)
9 to <12 months	1 (1.9)
12 months (complete)	42 (79.2)
Compliance, *n* (%)	
<80 %	0
80–90 %	1 (1.9)
90–100 %	45 (84.9)
100–110 %	7 (13.2)
110–120 %	0
>120 %	0

SD standard deviation

administered on the study was 7 mg/day, and was administered to one patient. Thirty-six patients (67.9 %) responded (platelet count of $<60 \times 10^4/\mu L$ for consecutive visits ≥4 weeks following ≥3 months of anagrelide treatment) while on anagrelide treatment (Fig. 2). The median time to response was 98.5 days. Twenty-four patients (45.3 %) achieved normalization in platelet count [platelet count of $\leq 40 \times 10^4/\mu L$ for consecutive visits ≥4 weeks following ≥3 months of anagrelide treatment (Fig. 2)], with a median time to normalization of 274.0 days. Half of the patients achieved a 50 % reduction in their platelet counts (Fig. 2). Mean platelet counts and mean study drug dose over time are presented in Fig. 3. Of the 47 patients who had a baseline platelet count of $\geq 60 \times 10^4/\mu L$, 32 (68.1 %) achieved a response and 21 (44.7 %) achieved normalization in their platelet counts. Of the six patients who had a baseline platelet count of $<60 \times 10^4/\mu L$, four (66.7 %) responded and three (50.0 %) achieved normalization. One patient had a baseline platelet count $\leq 40 \times 10^4/\mu L$ and was considered as not achieving a response or normalization as they did not complete at least 3 months of treatment (withdrew after 63 days). Five patients had baseline platelet counts of >40 to $<60 \times 10^4/\mu L$; four (80 %) of these responded and three (60.0 %) achieved platelet normalization.

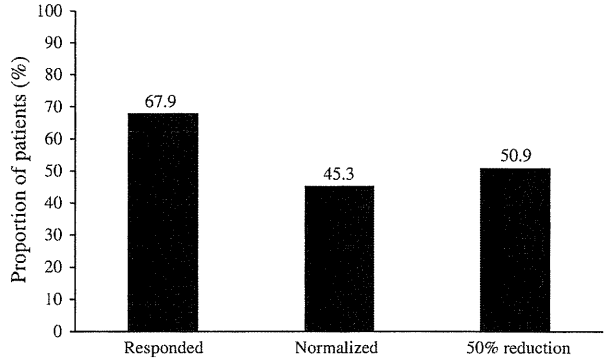

Fig. 2 Proportion of patients with a platelet count response ($<60 \times 10^4/\mu L$), platelet count normalization ($\leq 40 \times 10^4/\mu L$), and 50 % reduction in platelet count compared with their baseline values

The post hoc subanalyses explored any trends in the efficacy of anagrelide in terms of the baseline characteristics of the patients. Notable differences were observed in the mean baseline platelet counts in the following subgroups: refractory patients ($121.6 \times 10^4/\mu L$) compared with the intolerant patients [$91.3 \times 10^4/\mu L$ (Fig. 3b)]; patients who continued to receive concomitant HC for the first month ($91.0 \times 10^4/\mu L$) compared with those who switched directly to anagrelide treatment [$113.8 \times 10^4/\mu L$ (data not shown)]; patients with a baseline platelet count of $>100 \times 10^4/\mu L$ ($141.4 \times 10^4/\mu L$) compared with those with a baseline platelet count $\leq 100 \times 10^4/\mu L$ [$74.3 \times 10^4/\mu L$ (data not shown)]. Despite these differences at baseline, each of the subgroups analyzed achieved mean platelet counts of $<60 \times 10^4/\mu L$ at the 12-month visit. Also, variations were observed in the median time taken to achieve response in some subgroups: refractory patients (92.0 days) compared with the intolerant patients [124.0 days (Fig. 3b)]; patients with a baseline platelet count of $>100 \times 10^4/\mu L$ (144.5 days) compared with those with a baseline platelet count $\leq 100 \times 10^4/\mu L$ (92.0 days (data not shown)]; patients with a previous history of thrombohemorrhagic events (152.5 days) compared with patients without a previous history of thrombohemorrhagic events (92.0 days). In addition to this, it was also observed that the response rate varied in some subgroups: refractory patients (78.9 %) compared with intolerant patients (61.8 %).

Safety

All patients reported treatment-emergent adverse events (TEAEs) (Table 3), the majority of which were either mild or moderate in severity ($n = 46$; 86.8 %). The most common were anemia [$n = 25$; 47.2 % (mild 21; moderate 4)], headache [$n = 24$; 45.3 % (mild 19; moderate 3; severe 2)], palpitations [$n = 20$; 37.7 % (mild 19; severe 1)], and

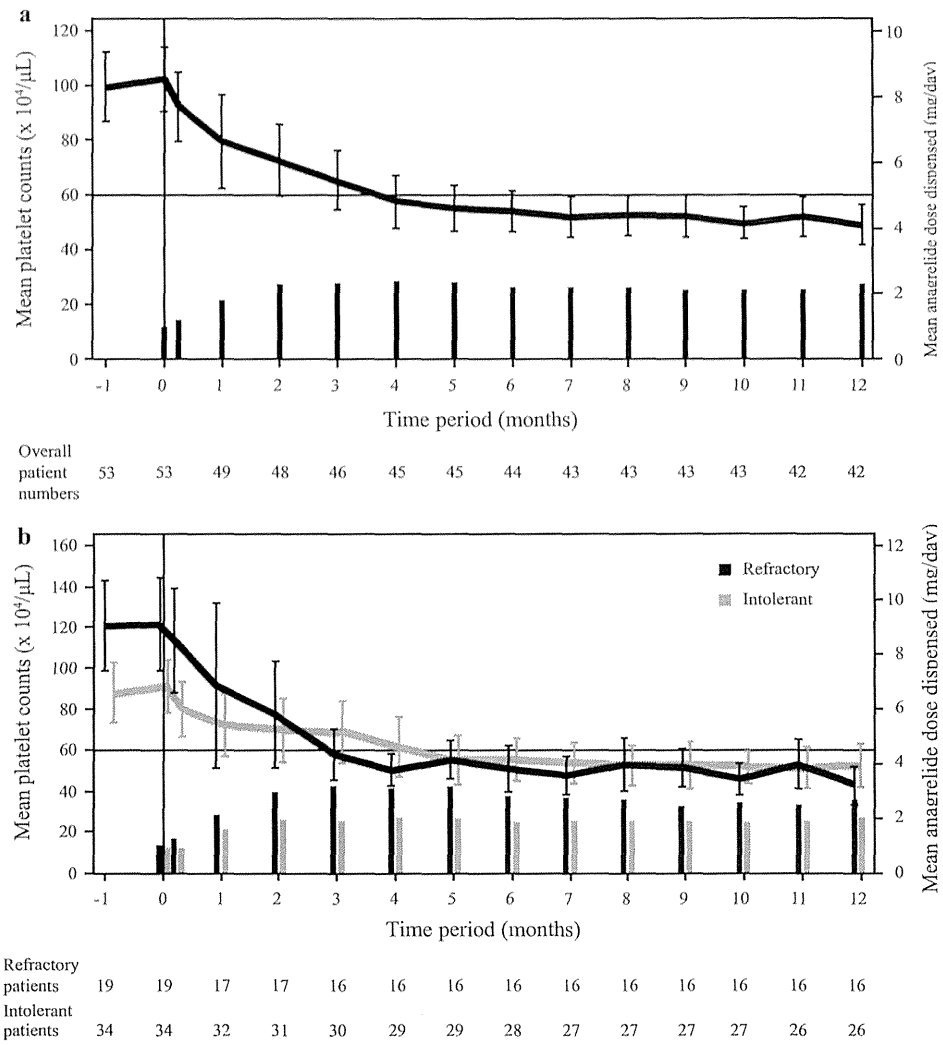

Fig. 3 **a** Mean platelet counts (and 95 % confidence intervals) and mean anagrelide dose over time (full analysis set) and **b** mean platelet counts and mean anagrelide dose over time in patients who were refractory (black line and bars) or intolerant (gray line and bars) to previous or current cytoreductive therapy. *Note* Baseline data are presented at 0 months. Overall patient numbers represent the number of patients that were still in the study at that time point. Patient numbers at Week 1 are not shown as no patients had discontinued the study by this time point

diarrhea [$n = 17$; 32.1 % (all mild)]. Mean hemoglobin levels were 12.1 g/dL [standard deviation (SD) 1.91] upon study entry (Table 1) and they declined to 10.7 g/dL (SD 1.58) by the end of the study. Two patients experienced Common Terminology Criteria for Adverse Events (CTCAE) grade 3 headache, and one patient experienced CTCAE grade 3 palpitations. No patients experienced CTCAE grade 4 or 5 adverse events. A total of 25 serious TEAEs were reported in 15 patients (28.3 %), including two patients with cerebral infarction and one patient with lacunar infarction (Table 3). Of the 25 serious TEAEs, cytogenetic abnormality, pneumonia ($n = 2$ each; 3.8 %), palpitations, visual impairment, melena, edema, altered state of consciousness, headache, interstitial lung disease, and cerebral infarction ($n = 1$ each; 1.9 %) were considered treatment-related. In two patients, transformation to leukemia was assumed and the patients were tested for other cytogenetic abnormalities in addition to the *BCR-ABL* fusion signals. Trisomy 8 was detected in one patient; however, *BCR-ABL* fusion signals were not detected in peripheral cells by fluorescence in situ hybridization. The other patient had a cytogenetic abnormality on chromosome 46. Myeloblasts were detected in peripheral blood and bone marrow, but no progression to leukemia was observed. A total of 16 TEAEs leading to dose discontinuation were reported in nine patients (17.0 %); all occurred in one patient each, except palpitations ($n = 2$; 3.8 %) and headache ($n = 3$; 5.7 %). Treatment was discontinued within 14 days of TEAE onset for nearly all patients ($n = 8/9$). One patient discontinued treatment 23 days after the first TEAE onset, but all four TEAEs experienced by this patient were reported as mild. The primary reason given for withdrawal in one of these nine patients (who reported an event of anemia that led to dose discontinuation) was given as lack of efficacy. Clinically significant abnormalities in electrocardiograms (ECG) were reported

Table 3 Treatment-emergent adverse events reported by ≥ 10 % of patients and treatment-emergent serious adverse events (safety set)

Preferred term, *n* (%)	*N* = 53
Treatment-emergent adverse events reported by ≥ 10 % of patients	
Anemia	25 (47.2)
Headache	24 (45.3)[a]
Palpitations	20 (37.7)[a]
Diarrhea	17 (32.1)
Edema peripheral	14 (26.4)
Nasopharyngitis	12 (22.6)
Pyrexia	10 (18.9)
Fatigue	9 (17.0)
Gamma-glutamyltransferase increased	7 (13.2)
Gingival bleeding	7 (13.2)
Back pain	6 (11.3)
Blood alkaline phosphatase increased	6 (11.3)
Contusion	6 (11.3)
Dyspnea	6 (11.3)
Epistaxis	6 (11.3)
Hypoesthesia	6 (11.3)
Treatment-emergent serious adverse events	
Cytogenetic abnormality	2 (3.8)
Pneumonia	2 (3.8)
Cerebral infarction	2 (3.8)
Leukocytosis	1 (1.9)
Splenomegaly	1 (1.9)
Palpitations	1 (1.9)
Visual impairment	1 (1.9)
Colonic polyp	1 (1.9)
Gastric ulcer	1 (1.9)
Melena	1 (1.9)
Edema	1 (1.9)
Pyrexia	1 (1.9)
Pyelonephritis	1 (1.9)
Laceration	1 (1.9)
Angioimmunoblastic T cell lymphoma	1 (1.9)
Prostate cancer	1 (1.9)
Altered state of consciousness	1 (1.9)
Headache	1 (1.9)
Hematuria	1 (1.9)
Interstitial lung disease	1 (1.9)

[a] Two patients experienced Common Terminology Criteria for Adverse Events (CTCAE) grade 3 headache, and one patient experienced CTCAE grade 3 palpitations. No patients experienced CTCAE grade 4 or 5 adverse events

in four patients: one patient had abnormalities in their ECG on four occasions, while the other three patients had one occurrence of an ECG abnormality. Two patients experienced QT prolongation but these were not considered clinically significant on an accompanying ECG. There were no deaths reported during the study.

The post hoc subanalyses explored any differences there may have been in the safety data in the different baseline characteristic groups. The only notable difference observed was a higher incidence of anemia in refractory patients [12/19 (63.2 %); median dose 2.622 mg/day] compared with intolerant patients [13/34 (38.2 %); median dose 1.695 mg/day]. Refractory patients entered the study with a mean baseline hemoglobin level of 12.7 g/dL, which decreased to 10.9 g/dL (change from baseline −1.8 g/dL) by the end of the study. Intolerant patients entered the study with a mean baseline hemoglobin level of 11.8 g/dL, and these values decreased to 10.6 g/dL (change from baseline −1.2 g/dL) by the end of the study. Thus it should be noted that hemoglobin levels, particularly in the intolerant patients, were low upon study entry and that some patients may have been considered anemic at study entry.

Discussion

In Japan, HC is licensed as a first-line treatment for patients with ET; however, currently there is no product specifically licensed for second-line treatment of the disease. Anagrelide is licensed in Europe as a second-line treatment for patients with ET who are intolerant or refractory to their current CRT [6]. In this Phase III, open-label, single-arm study, high-risk Japanese patients with ET who were intolerant or refractory to their first-line CRT were initiated on anagrelide therapy. Over the 12-month study period, anagrelide treatment reduced platelet counts, and demonstrated a safety profile consistent with the European SPC [6] and US prescribing information [10].

In this study, 67.9 % of patients achieved a platelet response ($<60 \times 10^4/\mu L$) with a median time to response of 98.5 days (approximately 3.2 months), 45.3 % achieved normalization ($\leq 40 \times 10^4/\mu L$) with a median time to normalization of 274.0 days, and half of the patients achieved a 50 % reduction in their platelet counts following second-line treatment with anagrelide. Studies using anagrelide as a first-line treatment in non-Japanese patients, including those in Europe, Australia, and Singapore, have revealed similar response rates [11, 12]. In the PT-1 study, patients who received anagrelide plus aspirin as a first-line therapy reached a platelet response 3–8 months after trial entry [12]. In the Anagrelide vs. Hydroxyurea in Patients with Essential Thrombocythaemia (ANAHYDRET) study, high-risk patients with newly diagnosed or treatment-naïve ET who received anagrelide first-line monotherapy reached a platelet response by 3 months of treatment [11]. In the present study, it should be noted that more refractory patients (78.9 %) reached a platelet response than the