year of increased survival.[2] In many countries, an additional year lived is judged to be "worth" ~$50 000 to $100 000.[6,7] In England, the National Institute for Health and Clinical Excellence values a year lived at about 30 000 British pounds, or ~$50 000.

The situation in CML is different. When imatinib was approved in 2001, its potential benefit in prolonging life was unknown. Considering a median survival of ~5 to 6 years in the pre-imatinib era, a 50% improvement in survival would have extended life by 3 years, which was then a very optimistic outlook. Therefore, the original imatinib price of $30 000 in 2001 may have reflected the cost of development and a projection of anticipated survival, using the price of interferon, the approved commercial drug for CML, as a starting point. In his book, Daniel Vasella, then Chairman and Chief Executive Officer of Novartis, discussed the development of imatinib, the moral imperatives and pressures exerted by oncologists and patients, the need for healthy profit margins, and the decision to price imatinib at a world average of $2200 per month, or $26 000 per year ($30 000 per year in the United States).[5] This, he explained, was considered at the time a high but worthwhile and profitable price. With a prevalence of 30 000 patients in the United States (the effect of imatinib on the prevalence of CML was then difficult to estimate) and full market penetration (ie, most patients with CML receiving imatinib), the annual revenue from imatinib sales in the United States would be ~$900 million, which would have more than recouped the cost of development within 2 years. The revenues over the subsequent years of the patent would represent generous profits to the company.

Imatinib and the new Bcr-Abl tyrosine kinase inhibitors (TKIs) became the most successful class of targeted therapies ever developed in cancer, exceeding all projected survival expectations. With TKI therapy, the annual all-cause mortality in CML declined to 2%, vs a historical rate of 10% to 20%, and the estimated 10-year survival increased from <20% to >80%.[8] Patients with CML now live close to normal lifespans,[9] as long as they receive the appropriate TKIs and adhere to treatment. Their CML condition has become very different from solid cancers, and more similar to indolent disorders like diabetes, hypertension, and cardiovascular disorders, where daily therapy is required indefinitely to produce the anticipated benefit of long-term survival. Grateful patients may have become the "financial victims" of the treatment success, having to pay the high price annually to stay alive.

In Europe and many developed countries, universal health coverage shields patients from the direct economic anxieties of illness. Not so in the United States where patients may pay an average of 20% of drug prices out of pocket (~$20 000-$30 000 per year, a quarter to a third of an average household budget), and where medical illnesses and drug prices are the single most frequent cause of personal bankruptcies.[10] High drug prices may be the single most common reason for poor compliance and drug discontinuation, and the reason behind different treatment recommendations in different countries.

Cancer drug prices vary widely in different geographic regions (Table 1[11,12]). This supports the notion that drug prices reflect geopolitical and socioeconomics dynamics unrelated to the cost of drug development. In the United States, prices represent the extreme end of high prices, a reflection of a "free market economy" and the notion that "one cannot put a price on a human life," as well as a failure of government and insurers to more actively negotiate pricing for anticancer and other pharmaceuticals, in contrast to practices in other parts of the world. This contributes to the very high cost of health care in the United States, estimated at $2.7 trillion in 2011, or 18% of the US gross domestic product, compared with 6% to 9% in Europe.[13] This increased expenditure does not add demonstrable benefit to US patients.[14] At the other extreme are more modest prices in the Middle East, Africa, Latin America, and other emerging nations, where only a minority of patients can afford, as individuals or through government subsidies, to access the CML drugs. In many emerging nations where governments cannot afford to budget for such drugs, CML experts are advocating frontline allogeneic stem cell transplantation because it costs an average of $30 000 to $80 000 as a one-time procedure.[15] This may harm patients because only a fraction may be eligible for transplantation (and may suffer from early mortality and lifelong complications); a smaller fraction are rich enough to pay individually for the price of the drugs, and most are treated intermittently or not at all. The effects of these financial pressures on the long-term survival of patients with CML in national follow-up studies are as yet unknown.

Table 1. Annual price estimates, by region, of drugs approved for the treatment of CML

	Price in thousands of US dollars (rounded to nearest $0.5 thousand)		
Country	Imatinib	Nilotinib	Dasatinib
United States	92	115.5	123.5
Germany*	54	60	90
United Kingdom	33.5	33.5	48.5
Canada	46.5	48	62.5
Norway	50.5	61	82.5
France	40	51.5	71
Italy	31	43	54
South Korea	28.5	26	22
Mexico	29	39	49.5
Argentina	52	73.5	80
Australia	46.5	53.5	60
Japan	43	55	72
China	46.5	75	61.5
Russia	24	48.5	56.5
South Africa	43	28	54.5

Prices in the United States from the Red Book online.[1] Other prices provided by CML experts from their countries.

*In Germany, a new rule, the "Pharmaceutical Market Restructuring Act" or AMNOG (arzneimittelneuordnungsgesetz), took effect in January 2011, by which the prices of new drugs are negotiated according to their benefit in comparison with other drugs on the market for the same indication. Similar rules or laws are also in effect in other European countries.[11] Prices of drugs in Germany may directly or indirectly influence drug prices in 31 countries.[12]

Imatinib was developed as a "goodwill gesture" by Novartis and became a blockbuster, with annual revenues of ~$4.7 billion in 2012. Being one of the most successful cancer targeted therapies, imatinib may have set the pace for the rising cost of cancer drugs. Initially priced at nearly $30 000 per year when it was released in 2001, its price has now increased to $92 000 in 2012,[1] despite the fact that (1) all research costs were accounted for in the original proposed price,[5] (2) new indications were developed and FDA approved, and (3) the prevalence of the CML population continuing to take imatinib was dramatically increasing.[16] This resulted in numerous appeals by patients and advocates to lower the price of imatinib, to no avail so far.[17,18]

What determines a morally justifiable "just price" for a cancer drug? A reasonable drug price should maintain healthy pharmaceutical company profits without being viewed as "profiteering" (making profit by unethical methods, like raising commodity prices after natural disasters). Hillner and Smith suggested this term may apply to the trend of high drug prices, where a life-threatening medical condition is the disaster.[19] Hopes that the fundamentals of a free market economy and market competition will settle cancer

drug prices at lower levels have not been fulfilled. All 5 TKIs approved for CML have annual price ranges of $92 000 to $138 000 in the United States, twice the prices in Europe where governments bargain for bulk prices (Table 1). A new branch of economics, called game theory, details how collusive behavior can tacitly maintain high prices over extended periods of time, despite competitive markets, thus representing a form of "collective monopoly."[20] Interestingly, in South Korea, where annual prices for TKIs range from $21 000 to $28 000, market competition may have worked well, perhaps because of the approval by the Korean health authorities of radotinib (annual prices $21 500), a locally discovered and developed TKI.

The patent expiration date of imatinib, originally set in the United States for May 28, 2013, was later extended by the US Patent Office to January 2015. Patent expiration dates may be different in different countries/regions. Two years is still a long time for patients with CML, the prevalence of which is estimated today worldwide at ~1.2 million to 1.5 million patients. Based on sales, it is estimated that about 235 000 to 250 000 patients (<20%-25%) are receiving imatinib. Support programs like the Glivec International Patient Assistance Program, a joint effort of Novartis and The Max Foundation, provide access to about 60 000 patients, perhaps ~30 000 to 40 000 of whom have CML (Glivec International Patient Assistance Program providing TKIs to 1%-3% of the world's CML population).[21] Thus, treatment penetration of TKIs in CML may be ~25% to 30% globally. When treatment penetration and compliance rates are high (such as in single institutional studies, in cooperative group trials, and in Sweden), the estimated 10-year survival rates are >80%.[8,9,22] When treatment penetration may be lower, outcome may be worse. In the United States, ~10% of patients fail to take prescribed drugs, largely because of cost.[23] Trends of CML survival in the United States show an improvement since 2001, but the estimated 5-year survival rate is still ~60%, suggesting lower treatment penetration rates in the United States compared with Sweden.[22,24] Unaffordable CML drug prices may be preventing many patients from accessing these lifesaving drugs. Lowering the prices of TKIs will improve treatment penetration, increase compliance and adherence to treatment, expand the population of patients with CML who live longer and continue on TKI therapy, and (paradoxically) increase revenues to pharmaceutical companies from sales of TKIs.

Early introduction of generics has been estimated to have saved the US health care budget about $1.1 trillion over 10 years.[25] In leveraging drug prices, companies may engage in "pay-for-delay" strategies that delay generic drugs from being available. Arrangements by pharmaceutical companies that pay generic companies to delay entering the market with a generic version profit both companies, but financially hurt the national health care system and patients. The Hatch-Waxman Act provides a 6-month market exclusivity for the first FDA-approved generic version of a branded drug. The intent of the act is to encourage the rapid launch of low-cost generics and reduce health care costs. Other generics can be marketed afterward. By launching their own generics (called "authorized generics") at low prices, branded drug companies have diminished generic company profits, resulting in delays of access of generics and reduced competition.[26] Delays of generic TKIs through "pay-for-delay" or "authorized generic" approaches may harm patients with CML and should be avoided at all cost.

As physicians, we follow the Hippocratic Oath of "*Primum non nocere*," first (or above all) do no harm. We believe the unsustainable drug prices in CML and cancer may be causing harm to patients. Advocating for lower drug prices is a necessity to save the lives of patients who cannot afford them. Pricing of cancer and other drugs involves complex societal and political issues which (1) demand immediate attention and (2) will need to consider many factors and involve many constituencies including FDA and governmental regulators; legislation changes; patent laws; multitudes of US and international regulatory agencies; offices of human research protection; impediments by lawyers and contract research organizations, which increase the cost of clinical research; patient advocacy groups; excessive regulation and bureaucracy; profits of physicians and hospitals/pharmacies; insurance companies; pharmaceutical companies; etc.

We propose to begin the dialogue by organizing regular meetings, involving all parties concerned, to address the reasons behind high cancer drug prices and offer solutions to reduce them. For CML, and for other cancers, we believe drug prices should reflect objective measures of benefit, but also should not exceed values that harm our patients and societies.

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Authorship

Contribution: All authors contributed equally to the creation of this manuscript.

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A complete list of the Experts in Chronic Myeloid Leukemia appears in "Appendix."

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Appendix

The Experts in Chronic Myeloid Leukemia are listed by region below.

North America

Camille Abboud; Ellin Berman; Adam Cohen; Jorge Cortes; Daniel DeAngelo; Michael Deininger; Steven Devine; Brian Druker; Amir Fathi; Elias Jabbour; Madan Jagasia; Hagop Kantarjian; Jean Khoury; Pierre Laneuville; Richard Larson; Jeffrey Lipton; Joseph O. Moore; Tariq Mughal; Susan O'Brien; Javier Pinilla-Ibarz; Alfonso Quintas-Cardama; Jerald Radich; Vishnu Reddy; Charles Schiffer; Neil Shah; Paul Shami; Richard T. Silver; David Snyder; Richard Stone; Moshe Talpaz; Ayalew Tefferi; Richard A. Van Etten; Meir Wetzler.

Europe and Russia

Elisabetta Abruzzese; Jane Apperley; Massimo Breccia; Jenny Byrne; Francisco Cervantes; Ekaterina Chelysheva; R. E. Clark; Hugues de Lavallade; Iryna Dyagil; Carlo Gambacorti-Passerini;

John Goldman; Ibrahim Haznedaroglu; Henrik Hjorth-Hansen; Tessa Holyoake; Brian Huntly; Philipp le Coutre; Elza Lomaia; Francois-Xavier Mahon; David Marin-Costa; Giovanni Martinelli; Jiri Mayer; Dragana Milojkovic; Eduardo Olavarria; Kimmo Porkka; Johan Richter; Philippe Rousselot; Giuseppe Saglio; Guray Saydam; Jesper Stentoft; Anna Turkina; Paolo Vigneri; Andrey Zaritskey.

Latin America

Alvaro Aguayo; Manuel Ayala; Israel Bendit; Raquel Maria Bengio; Carlos Best; Eduardo Bullorsky; Eduardo Cervera; Carmino DeSouza; Ernesto Fanilla; David Gomez-Almaguer; Nelson Hamerschlak; Jose Lopez; Alicia Magarinos; Luis Meillon; Jorge Milone; Beatriz Moiraghi; Ricardo Pasquini; Carolina Pavlovsky; Guillermo J. Ruiz-Arguelles; Nelson Spector.

Australia and Asia

Christopher Arthur; Peter Browett; Andrew Grigg; Jianda Hu; Xiao-jun Huang; Tim Hughes; Qian Jiang; Saengsuree Jootar; Dong-Wook Kim; Hemant Malhotra; Pankaj Malhotra; Itaru Matsumura; Junia Melo; Kazunori Ohnishi; Ryuzo Ohno; Tapan Saikia; Anthony P. Schwarer; Naoto Takahashi; Constantine Tam; Tetsuzo Tauchi; Kensuke Usuki; Jianxiang Wang.

Middle East and Africa

Fawzi Abdel-Rahman; Mahmoud Deeb Saeed Aljurf; Ali Bazarbachi; Dina Ben Yehuda; Naeem Chaudhri; Muheez Durosinmi; Hossam Kamel; Vernon Louw; Bassam Francis Matti; Arnon Nagler; Pia Raanani; Ziad Salem.

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ORIGINAL ARTICLE

Efficacy and safety of dasatinib versus imatinib in Japanese patients with newly diagnosed chronic-phase chronic myeloid leukemia (CML-CP): Subset analysis of the DASISION trial with 2-year follow-up

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Abstract Dasatinib is a highly potent BCR-ABL kinase inhibitor with established efficacy and safety in imatinib-resistant or -intolerant patients with chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia. In the global phase III DASISION trial in patients with newly diagnosed chronic phase CML (CML-CP), dasatinib was found to have an acceptable safety profile and demonstrated significantly faster and higher rates of complete cytogenetic response (CCyR) and major molecular response (MMR) compared with imatinib. Here, we report the results of a subset analysis of Japanese patients enrolled in the DASISION trial, showing safety and efficacy profiles generally consistent with patients enrolled worldwide, including higher response rates (CCyR, MMR) with dasatinib compared with imatinib and similar high rates of progression-free and overall survival with both therapies. However, the small sample size of the present study limits the strength of these conclusions, and further exploration is needed to confirm any differences observed in Japanese patients compared with the total

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treated population. These findings support the use of dasatinib 100 mg QD as a first-line treatment in Japanese patients with newly diagnosed CML-CP.

Keywords Dasatinib · Japanese · CML-CP · First-line · Newly diagnosed

Introduction

Chronic myeloid leukemia (CML) is caused by a translocation between chromosome 9 and 22, creating the Philadelphia chromosome and *BCR-ABL* gene, encoding a chimeric tyrosine kinase with constitutive activity. Imatinib, a first-generation BCR-ABL inhibitor, was for years the standard first-line treatment for patients with newly diagnosed CML in chronic phase (CML-CP). However, approximately one-third of patients receiving imatinib for newly diagnosed CML-CP experience treatment failure due to inadequate response, loss of response, disease progression, or toxicity [1]. More recently, additional first-line treatment options have become available due to the approval of more potent second-generation BCR-ABL inhibitors, including dasatinib and nilotinib for patients with newly diagnosed CML-CP.

Various mechanisms of resistance have been proposed, including *BCR-ABL* kinase mutations, genomic amplification or overexpression, pathologic activation of SRC family kinases, altered expression of drug influx and efflux proteins, and polymorphisms in genes essential for tyrosine kinase-mediated apoptosis [2–6]. Dasatinib is 325-fold more potent than imatinib in vitro, and has inhibitory activity against the majority of *BCR-ABL* mutants associated with clinical resistance to imatinib [7]. In addition to being less susceptible to *BCR-ABL*-mediated mechanisms of resistance than imatinib, data suggest that dasatinib may also overcome other mechanisms of resistance through differential binding to numerous other proteins involved in imatinib resistance [3, 8]. Dasatinib has been shown to be associated with a high response rate for CML-CP patients resistant or intolerant to imatinib treatment [9–11]. Based on significant efficacy in the second-line setting and the failure rate of first-line imatinib, the global randomized phase III DASISION (**DAS**atinib versus **I**matinib **S**tudy **I**n treatment-**N**aive CML patients) trial was designed to evaluate whether treatment of newly diagnosed CML-CP patients with dasatinib improves response rates and outcomes compared with imatinib treatment [12]. In the DASISION trial, 519 patients with newly diagnosed CML-CP were randomized to receive first-line treatment with either dasatinib 100 mg once daily (QD; $n = 259$) or imatinib 400 mg QD ($n = 260$). Patients treated with dasatinib had significantly faster and higher rates of complete cytogenetic response (CCyR) and major molecular response (MMR) compared with those who received imatinib. After a minimum follow-up of 12 months, patients in the dasatinib arm experienced superior efficacy compared with those treated with imatinib, including higher rates of CCyR (83 vs. 72 %; $P = 0.001$) and MMR (46 vs. 28 %; $P < 0.0001$). Transformation to accelerated-phase or blast-phase (AP/BP) CML by 12 months occurred in 1.9 % of dasatinib-treated patients compared with 3.5 % of imatinib-treated patients. Dasatinib in the first-line setting was also found to have an acceptable safety and tolerability profile. Based on the findings of this trial, dasatinib was approved as a first-line therapy for patients with newly diagnosed CML-CP by various regulatory authorities worldwide.

Following a minimum follow-up of 24 months in the DASISION trial, efficacy and safety results are consistent with the 12-month findings and support the continued use of dasatinib as a first-line therapy for CML-CP. In addition to significantly higher rates of CCyR and MMR, patients in the dasatinib arm experienced significantly higher rates of $MR^{4.5}$ after 24 months of follow-up (17 vs. 8 %, $P = 0.002$) [13]. A recent retrospective exploratory analysis of DASISION data showed that dasatinib also provided faster and deeper cytogenetic and molecular responses compared with imatinib at 3 months and 6 months. *BCR-ABL* transcript level reduction of <10 % at both time points were predictive of progression-free survival (PFS) and overall survival (OS) at 36 months and a reduced risk of transformation to AP/BP [14].

Due to genetic and environmental factors, the efficacy and safety profiles of BCR-ABL inhibitors may differ globally. Indeed, a recent report suggested that a proportion of East Asian patients with CML (including Japanese patients) harbor a genetic polymorphism not identified in non-East Asian patients that may confer intrinsic resistance to imatinib [6]. Japanese patients may also have lower response rates to first-line imatinib due to dose-limiting toxicities [15]. In contrast, clinical studies suggest that second-line dasatinib safety and efficacy are similar in Asian and non-Asian patients (including Japanese patients) with CML-CP resistant or intolerant to imatinib [16, 17].

To date, the DASISION trial is the only study that evaluated dasatinib 100 mg QD in the treatment of Japanese patients with newly diagnosed CML-CP, although a phase II trial to investigate the efficacy of first-line dasatinib is currently being conducted in Japan [18]. Therefore, to compare the efficacy and safety of dasatinib 100 mg QD with imatinib 400 mg QD, data from Japanese patients enrolled in the DASISION trial were assessed after a 2-year minimum follow-up. The efficacy and safety profiles of dasatinib and imatinib in Japanese patients were also compared with data from all patients (enrolled in 26 countries worldwide including Japan).

Methods

Study design and patients

DASISION (NCT00481247) is an ongoing open-label, multinational, randomized, phase III trial. Details of trial design, eligibility criteria, and evaluations have been reported previously [12]. Adults with Philadelphia chromosome-positive (Ph+) CML-CP diagnosed within 3 months who had received no previous treatment for CML (excluding anagrelide or hydroxyurea) were eligible. Patients were stratified according to Hasford risk score and randomly assigned (1:1) to receive oral dasatinib 100 mg QD (with or without food) or imatinib 400 mg QD (with food). Treatment was discontinued due to protocol-defined disease progression, unacceptable toxicity, patient/investigator decision, or pregnancy. In both arms, interruptions to treatment or dose reductions were permitted for managing adverse events (AEs), and dose escalations were permitted for patients with a suboptimal response according to the ELN 2006 definition [19]. The study protocol, amendments, and patient informed consent were approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) before study initiation at each site. Written informed consent was obtained from each patient before randomization in accordance with the Declaration of Helsinki. All exposure, safety, and efficacy results described herein are based on exploratory analyses on the 49 Japanese patients (26 treated with dasatinib, 23 with imatinib) and analysis of the total patient population treated (including Japanese patients), hereafter referred to as "all patients". Efficacy analyses are based on all randomized patients (259 dasatinib, 260 imatinib), whereas all other analyses are based on all treated patients (258 in each arm).

Efficacy and safety assessments

Efficacy and safety were assessed using data obtained during the initial 2-year period of the DASISION trial. CCyR was defined as the absence of Ph+ metaphases as determined by G-banding in $\geq$20 cells in metaphase per bone marrow sample. Molecular responses were assessed by quantitative reverse-transcriptase polymerase chain reaction (RT-qPCR) assay and converted to the International Scale (IS). MMR was defined as a *BCR-ABL* transcript level in peripheral blood of IS $\leq$0.1 %, (i.e., $\geq$3-log reduction in *BCR-ABL* transcript level from the standardized baseline); MR^4, reduction to IS $\leq$0.01 % ($\geq$4-log reduction in *BCR-ABL* transcript level); and $MR^{4.5}$, reduction to IS $\leq$0.0032 % (i.e., $\geq$4.5-log reduction in *BCR-ABL* transcript level—sometimes termed complete molecular response). Progression was defined in the DASISION trial as doubling of white blood cell count to more than 20×10^9 per liter in the absence of complete hematologic response (CHR), loss of CHR, loss of major cytogenetic response (MCyR), transformation to AP/BP CML, or death from any cause. The definition of PFS in the DASISION trial is similar to that of event-free survival (EFS) in the International Randomized Study of Interferon and STI571 (IRIS) trial [20].

As previously described, *BCR-ABL* mutational analysis by direct sequencing was required following discontinuation of study therapy for any reason (samples obtained within 45 days before or after discontinuation were tested). Molecular and mutational assessments were performed at a centralized laboratory (MolecularMD, Portland, OR) [13]. AEs were assessed continuously during the DASISION trial and were graded according to the Common Terminology Criteria for AEs version 3.0 of the National Cancer Institute. Whereas previous DASISION publications have reported AE rates based on the number of patients who experienced an AE by the time of the 1-year or 2-year database locks [12, 13], in the present analysis, 1-year and 2-year rates include AEs occurring during the first 12 and 24 months of treatment on a per-patient basis. The percentage of patients experiencing an AE was calculated by counting only the first incidence of a particular AE in a particular patient. To assess patients for pleural effusion, a chest radiograph was obtained in all patients at baseline and at 6 months after start of treatment or more frequently if indicated clinically.

Statistical analyses

Efficacy was analyzed in all randomized patients based on the intention-to-treat principle. For response rates, 95 % confidence intervals (CIs) were calculated using the Clopper and Pearson method. Safety was analyzed in all patients who received $\geq$1 dose of study drug. No comparisons of geographic or other patient subsets were specified in the trial protocol, and the study was not powered to show a statistically significant difference between subgroups of the dasatinib and imatinib arms; hence, any p values provided are descriptive and not adjusted for multiple comparisons. Statistical data were analyzed using SAS version 8.2 (SAS Institute, Cary, NC) or R version 2.15 (Free Software Foundation, Boston, MA), and the RT-qPCR results were analyzed using SDS software (Applied Biosystems, Foster City, CA).

Results

Patients and treatment

As previously reported [12, 13], 519 patients with newly diagnosed CML-CP from 108 centers in 26 countries were

randomized to receive dasatinib ($n = 259$) or imatinib ($n = 260$). Of these, 41 % were from the Asia Pacific region (18 % India, 9 % Japan, 7 % China, 2 % Korea, 2 % Singapore, and 2 % Australia), with Japan having the second largest enrollment in the world. Among the 49 Japanese patients, all assigned to receive dasatinib ($n = 26$) and imatinib ($n = 23$) were treated.

Baseline characteristics and demographics of Japanese patients were relatively well balanced between the two treatment groups (Table 1) and were similar to the study population overall [12] with the possible exception of: median age for Japanese patients compared with all patients (dasatinib: 56 vs. 46 years; imatinib: 52 vs. 49 years), low or intermediate baseline Hasford risk scores (96 vs. 81 %; 91 vs. 81 %), ECOG performance status 0 (96 % vs. 82 %; 87 % vs. 79 %), and prior treatment with hydroxyurea (dasatinib: 19 vs. 73 %; imatinib: 44 vs. 73 %).

At the time of this analysis, all patients who remained on study (dasatinib: 85 vs. 77 %; imatinib: 83 vs. 75 %; Japanese vs all patients) had a minimum follow-up of 2 years (Table 2). Reasons for discontinuation were similar among Japanese patients and all treated patients, including drug-related AEs, treatment failure, poor adherence to treatment, and request to discontinue.

The extent of drug exposure was evaluated in terms of average daily dose, duration of therapy, and number and length of dose modifications (Table 3). Compared with all treated patients, Japanese patients had similar average daily dose and duration of treatment, although more Japanese patients appeared to have had at least one dose interruption (dasatinib: 77 vs. 59 %; imatinib: 61 vs. 43 %) or dose reduction (50 vs. 28 %; 44 vs. 15 %) and fewer to have had dose escalations (0 vs. 7 %; 17 vs. 20 %). Most first dose reductions and first dose interruptions were due to hematologic or nonhematologic toxicities, regardless of treatment and patient population.

Dose escalations were reported for Japanese patients receiving imatinib and for all global patients who received either treatment (Table 3). No Japanese patients receiving dasatinib required a dose escalation. The most common reasons for first dose escalation in Japanese patients treated with imatinib were consistent with those provided for all patients, and were failure to achieve CCyR ($n = 1$), partial cytogenic response (PCyR; $n = 1$), or MMR ($n = 2$) (data not shown).

Table 1 Demographic and baseline disease characteristics

	Japanese patients ($n = 49$)		All patients [12] ($N = 519$)	
	Dasatinib ($n = 26$)	Imatinib ($n = 23$)	Dasatinib ($n = 259$)	Imatinib ($n = 260$)
Age, years				
Median (range)	56 (21–70)	52 (22–77)	46 (18–84)	49 (18–78)
Gender, *n* (%)				
Male	15 (58)	17 (74)	144 (56)	163 (63)
Female	11 (42)	6 (26)	115 (44)	97 (37)
Hasford risk score, *n* (%)				
Low	12 (46)	10 (44)	86 (33)	87 (33)
Intermediate	13 (50)	11 (48)	124 (48)	123 (47)
High	1 (4)	2 (9)	49 (19)	50 (19)
Performance status (ECOG), *n* (%)				
0	25 (96)	20 (87)	213 (82)	205 (79)
1	1 (4)	3 (13)	46 (18)	53 (20)
2	0	0	0	2 (1)
Time from diagnosis to randomization, months				
Median (range)	0.9	1	1	1
Previous therapy for CML, *n* (%)				
Hydroxyurea	5 (19)	10 (44)	189 (73)	190 (73)
Anagrelide	0	0	8 (3)	3 (1)

All patient data adapted with permission of the Massachusetts Medical Society, from Kantarjian et al. [12]; permission conveyed through Copyright Clearance Center, Inc.

CML chronic myeloid leukemia

Table 2 Treatment status of study participants

	Randomized patients, *n* (%)			
	Japanese patients ($n = 49$)		All patients ($N = 519$)	
	Dasatinib ($n = 26$)	Imatinib ($n = 23$)	Dasatinib ($n = 259$)	Imatinib ($n = 260$)
Received treatment, *n* (% of randomized)	26 (100)	23 (100)	258 (100)	258 (99)
Still on treatment at last follow-up	22 (85)	19 (83)	199 (77)	194 (75)
Discontinued treatment	4 (15)	4 (17)	59 (23)	64 (25)
Reason for discontinuation				
Drug-related AE	3 (12)[b]	2 (9)[c]	18 (7)	12 (5)
Progression[a]	0	0	14 (5)	17 (7)
Treatment failure	0	1 (4)	8 (3)	11 (4)
Nonadherent to therapy	0	1 (4)	0	2 (1)
Lost to follow-up	0	0	0	3 (1)
Requested to discontinue	1 (4)	0	2 (1)	3 (1)
Death	0	0	4 (2)	1 (<1)
Other	0	0	13 (5)	15 (6)

[a] Progression was defined as doubling of white-cell count to more than 20×10^9 per liter in the absence of CHR, loss of CHR, increase in Ph+ bone marrow metaphases to >35 %, transformation to AP/BP, or death from any cause

[b] Elevated creatine phosphokinase, ECG QT prolongation, thrombocytopenia

[c] Hypophosphatemia, thrombocytopenia

Although the length of dose interruptions was similar, dose interruptions or reductions due to toxicity may have occurred earlier in Japanese patients than among all patients, with a median time to first interruption/reduction of 47 versus 52 days with dasatinib and 34 versus 57 days with imatinib for Japanese versus all patients, respectively (Table 3).

Efficacy

As shown in Table 4, rates of cumulative CCyR were higher with dasatinib compared with imatinib in Japanese patients (96 vs. 87 %) and in all patients (86 vs. 82 %). Cumulative CCyR rates were numerically higher in Japanese patients compared with all patients for either treatment (dasatinib: 96 vs. 86 %; imatinib: 87 vs. 82 %). The rate of achieving the primary endpoint of confirmed CCyR at 12 months was also numerically higher in Japanese patients (dasatinib: 96 vs. 77 %; imatinib: 70 vs. 66 %; Japanese vs. all patients, respectively).

As in previously published analyses of all patients [13], the cumulative incidence of MMR among Japanese patients in the dasatinib arm was significantly higher versus imatinib across the period analyzed (Japanese: $P = 0.0255$; all patients: $P < 0.0001$; Fig. 1a). For either treatment, cumulative MMR rates for Japanese patients were numerically higher than for all patients (Table 4). By 12 months, 69 % of Japanese versus 46 % of all patients in the dasatinib arm achieved MMR compared with 44 % of Japanese and 28 % of all patients randomized to receive imatinib. By 24 months, 85 % of Japanese versus 64 % of all patients in the dasatinib arm achieved MMR compared with 61 % of Japanese and 46 % of all patients in the imatinib arm. Among Japanese patients treated with dasatinib, MMR rates were 92 % (11/12), 85 % (11/13), and 0 % (0/1) for patients with low, intermediate, and high baseline Hasford risk scores, respectively. The corresponding MMR rates with imatinib were 50 % (5/10), 82 % (9/11), and 50 % (1/2). Similar to MMR rates in Japanese patients receiving dasatinib, rates based on all patients tended to decrease with increasing Hasford risk scores as previously shown [13]. For patients with low or intermediate Hasford scores, rates of MMR with dasatinib were numerically higher in Japanese compared with all patients (Table 4; 92 vs. 73 % for patients with low scores, 85 vs. 61 % for patients with intermediate scores). However, the small number of Japanese patients within each Hasford score group makes it difficult to compare response rates in these patients.

Cumulative MR^4 rates across the period analyzed were higher with dasatinib compared with imatinib for both Japanese and all patients (Fig. 1b), and in the analysis of all patients, this trend was statistically significant ($P = 0.003$). Cumulative rates of MR^4 by 12 months were higher with dasatinib versus imatinib for both Japanese patients (27 vs. 13 %) and all patients (12 vs. 5 %) and over the period analyzed (Table 4). Cumulative rates of MR^4 were numerically higher among Japanese patients compared with all patients, both with dasatinib (42 vs. 30 %) and imatinib (26 vs. 19 %).

Cumulative $MR^{4.5}$ rates across the period analyzed were higher with dasatinib versus imatinib in Japanese patients (Fig. 1c), consistent with the trend previously reported for all patients [13]. As in the analysis of all patients, cumulative rates of $MR^{4.5}$ in Japanese patients during the period analyzed were higher with dasatinib

Table 3 Extent of exposure and dose modification

	Japanese patients ($n = 49$)		All treated patients ($N = 516$)	
	Dasatinib ($n = 26$)	Imatinib ($n = 23$)	Dasatinib ($n = 258$)	Imatinib ($n = 258$)
Average daily dose (mg/day)				
Median [range]	95 [57–100]	397 [279–429]	100 [21–137]	400 [125–704]
Duration of therapy (months)				
Median [range]	27 [<1–37]	26 [6–36]	26 [<1–37]	25 [<1–44]
Duration of therapy excluding interruptions (months)				
Median [range]	26 [<1–35]	25 [6–35]	25 [<1–35]	25 [<1–44]
Patients with ≥1 dose interruption, *n* (%)	20 (77)	14 (61)	152 (59)	111 (43)
Reason for first dose interruption, *n* (%)				
Dosing error	2 (8)	0	20 (8)	13 (5)
Hematologic toxicity	8 (31)	6 (26)	71 (28)	51 (20)
Nonhematologic toxicity	9 (35)	8 (35)	55 (21)	39 (15)
Surgical/medical procedure	1 (4)	0	3 (1)	3 (1)
Other	0	0	3 (1)	5 (2)
Patients with dose reductions, *n* (%)	13 (50)	10 (44)	71 (28)	39 (15)
Reason for first dose reduction				
Dosing error	0	0	6 (2)	3 (1)
Hematologic toxicity	5 (19)	2 (9)	32 (12)	21 (8)
Nonhematologic toxicity	8 (31)	8 (35)	33 (13)	15 (6)
Patients with dose escalations, *n* (%)	0	4 (17)	19 (7)	52 (20)
Patients with first dose interruption/reduction due to toxicity, *n* (%)	18 (69)	14 (61)	132 (51)	92 (36)
Time to first dose interruption/reduction due to toxicity (days)				
Median [range]	47 [8–731]	34 [12–407]	52 [2–823]	57 [3–854]
Length of first dose interruption due to toxicity (days)				
Median [range]	18 [2–58]	11 [2–27]	14 [2–81]	13 [2–91]

compared with imatinib (35 vs. 17 %; Table 4). Cumulative rates of $MR^{4.5}$ were numerically higher in Japanese patients compared with all patients, both with dasatinib (35 vs. 18 %) and with imatinib (17 vs. 9 %; Table 4). Rates of cumulative incidence of $MR^{4.5}$ by 12 months for Japanese patients were 4 and 9 % with dasatinib versus imatinib, respectively, and 5 versus 3 % for all patients.

At both 12 and 24 months, PFS and OS rates for patients in either arm were similar in Japanese patients and all patients. At 12 months, PFS rates for Japanese patients were 96 and 100 % with dasatinib and imatinib, respectively, compared with 96 % for all patients for both treatment groups. The 12-month OS rates were 100 % for Japanese patients in either treatment arm, and 97 and 98 % for all patients in the dasatinib and imatinib arms, respectively. At 24 months, PFS rates among Japanese patients were 94 and 90 % with dasatinib and imatinib, respectively, in line with the respective PFS rates of 94 and 92 % previously reported for all patients [13]. The 24-month OS rates for both treatment groups were 96 % for Japanese patients, similar to the 95 % reported in the analysis of all patients [13].

Consistent with data based on all patients, a higher percentage of Japanese patients achieved 3-month *BCR-ABL* levels ≤10 % with dasatinib compared with imatinib (Table 4). Of the 24 Japanese patients in the dasatinib arm, 100 % achieved 3-month *BCR-ABL* levels ≤10 %, compared with only 74 % of the 23 patients in the imatinib arm. This is comparable with the 84 % of dasatinib-arm and 64 % of imatinib-arm patients who achieved the same level in the analysis of all patients.

Mutations

All Japanese patients who discontinued treatment (4 in the dasatinib group and 4 in the imatinib group) were tested for *BCR-ABL* mutations as per protocol. No mutations were found in 3 out of 4 dasatinib-treated patients and in all 4 patients treated in the imatinib arm. For one of the

Table 4 Cytogenetic and molecular response

	Response rate, *n* (%) [95 % CI]			
	Japanese patients ($n = 49$)		All patients [12, 13] ($N = 519$)	
	Dasatinib ($n = 26$)	Imatinib ($n = 23$)	Dasatinib ($n = 259$)	Imatinib ($n = 260$)
CCyR at any time	25 (96)	20 (87)	223 (86)	213 (82)
MMR				
By 3 months	5 (19)	1 (4)	22 (9)	1 (< 1)
By 6 months	11 (42)	2 (9)	70 (27)	21 (8)
By 12 months	18 (69)	10 (44)	120 (46)	73 (28)
By 18 months	20 (77)	13 (57)	147 (57)	97 (37)
By 24 months	22 (85)	14 (61)	165 (64)	120 (46)
At any time	22 (85)	15 (65)	167 (65)	130 (50)
	[65–96]	[43–84]	[58–70]	[44–56]
Confirmed MMR at any time	16 (62)	13 (57)	144 (56)	103 (40)
	[41–80]	[35–77]	[49–62]	[34–46]
MMR at any time according to Hasford risk score				
Low	11/12 (92)	5/10 (50)	63/86 (73)	49/87 (56)
Intermediate	11/13 (85)	9/11 (82)	76/124 (61)	62/123 (50)
High	0/1 (0)	1/2 (50)	28/49 (57)	19/50 (38)
MR^4 at any time	11 (42)	6 (26)	77 (30)	50 (19)
	[23–63]	[10–48]	[24–36]	[15–25]
$MR^{4.5}$ at any time	9 (35)	4 (17)	47 (18)	23 (9)
	[17–56]	[5–39]	[14–23]	[6–13]
BCR-ABL levels ≤10 % at 3 months, n/N_{tested} (%)	24/24 (100)	17/23 (74)	198/235 (84)	154/239 (64)

N_{tested} number of evaluable patients

dasatinib-treated patients who discontinued, the mutation assay did not yield results.

Safety

The profile of drug-related nonhematologic AEs experienced by Japanese patients was similar to that among all patients (Table 5; Fig. 2). Drug-related nonhematologic AEs were primarily grade 1/2 (Table 5) and most occurred initially during the first 12 months of treatment (Fig. 2). Of the nonhematologic AEs experienced in ≥10 % of Japanese patients, overall fluid retention, superficial edema, face edema, peripheral edema, generalized edema, rash, nausea, vomiting, diarrhea, fatigue, and musculoskeletal pain tended to be more frequent in patients treated with imatinib, whereas pleural effusion, mucosal inflammation, constipation, infections, hemorrhage, and headache were more frequent in patients treated with dasatinib. Similar trends were observed in analyses of all patients.

In both the dasatinib and imatinib treatment groups, the percentages of patients experiencing the most common drug-related nonhematologic AEs were numerically higher in Japanese compared with all patients (Fig. 2). In the dasatinib arm, common drug-related nonhematologic AEs that appeared to occur more frequently in Japanese than in all patients were fluid retention, superficial edema, pleural effusion, face edema, peripheral edema, rash, nausea, mucosal inflammation, constipation, fatigue, infections, and hemorrhage. Compared with all imatinib-treated patients, these AEs also appeared to be more prevalent in Japanese patients, with the exception of hemorrhage, which occurred in a similar proportion of Japanese and all patients, and pleural effusion, which did not occur in imatinib-treated patients. Among patients treated with imatinib, a numerically higher percent of Japanese compared with all patients experienced generalized edema, diarrhea, and musculoskeletal pain, whereas a numerically lower percent of patients experienced headache.

Drug-related pleural effusion only occurred in patients treated with dasatinib, and was numerically higher in Japanese compared with all patients (27 vs. 13 %; Table 5; Fig. 2). Pleural effusion events in Japanese patients were grade 1 in 2 patients (7.7 %) and grade 2 in 5 patients (19.2 %). No grade 3–5 pleural effusion events occurred. Among Japanese patients, 7/7 who experienced pleural effusion achieved CCyR, compared with 18 of the 19

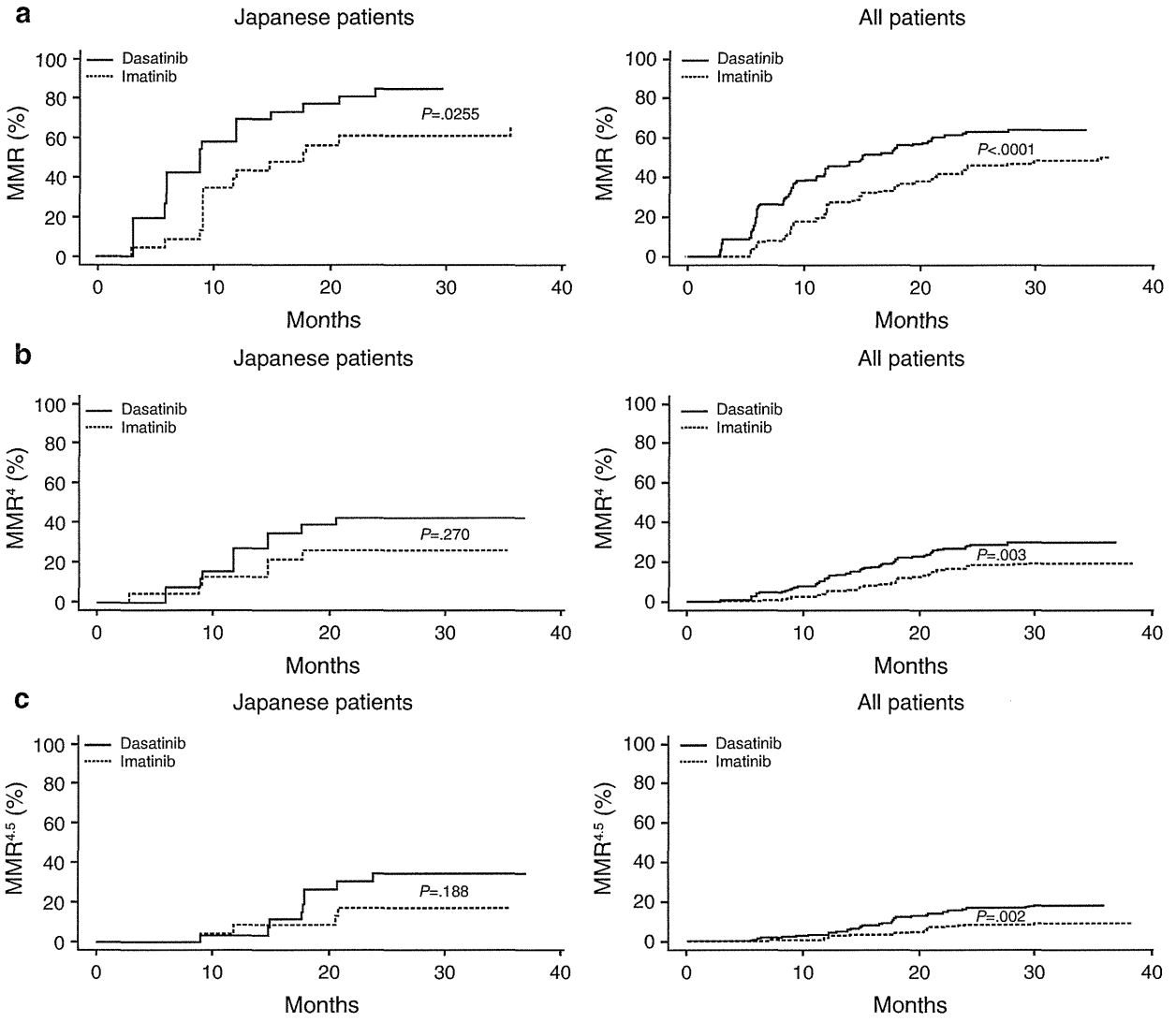

Fig. 1 Molecular response over time. Cumulative incidence of MMR, MR^4, and $MR^{4.5}$ during the first 24 months of treatment are shown in **a**, **b**, and **c**, respectively, for Japanese patients (*left*) and for all patients (*right*). *P* values indicate statistical significance of differences in molecular response across the entire period analyzed for patients in the dasatinib (*solid lines*) versus imatinib (*dashed lines*) arms. Graphs of MMR and $MR^{4.5}$ for all patients are reproduced with permission of the American Society of Hematology, from Kantarjian et al. [13]; permission conveyed through Copyright Clearance Center, Inc.

patients who did not experience pleural effusion; 5 of the 7 Japanese patients who experienced pleural effusion achieved MMR, compared with 17 of the 19 patients who did not experience pleural effusion. Pleural effusion in Japanese patients was first observed between 4 and 8 weeks after the initiation of treatment in 2 patients (28.6 %), and >8 weeks after the initiation of treatment in the remaining 5 patients (71.4 %). Likewise, in the analysis of all patients, time to the first occurrence of pleural effusion was between 4 and 8 weeks and after >8 weeks following the initiation of treatment in 12.1 and 87.9 % of patients, respectively. Of the 7 Japanese patients who experienced pleural effusion, the incident was managed with dose interruptions ($n = 5$), diuretics ($n = 3$), dose reductions ($n = 3$), and corticosteroids ($n = 1$).

For both Japanese patients and all patients, neutropenia was the most common grade 3/4 hematologic AE, and generally occurred during the first year of treatment (Fig. 3). In Japanese patients, a similar percentage treated with dasatinib and imatinib experienced grade 3/4 hematologic AEs (Table 6). A slightly lower percentage of Japanese patients treated with dasatinib experienced grade 3/4 neutropenia versus imatinib (31 vs. 39 %, respectively), and conversely, a slightly higher percentage

Table 5 Nonhematologic drug-related AEs occurring in ≥10 % of patients: percentage of patients experiencing AEs during the first 24 months of treatment

	Japanese patients, *n* (%) (*n* = 49)				All treated patients, *n* (%) (*N* = 516)			
	Dasatinib (*n* = 26)		Imatinib (*n* = 23)		Dasatinib (*n* = 258)		Imatinib (*n* = 258)	
Grade	All	3/4	All	3/4	All	3/4	All	3/4
Fluid retention	10 (39)	0	18 (78)	0	59 (23)	2 (1)	110 (43)	2 (1)
Superficial edema	6 (23)	0	13 (57)	0	27 (11)	0	91 (35)	1 (< 1)
Pleural effusion	7 (27)	0	0	0	33 (13)	0	0	0
Generalized edema	0	0	6 (26)	0	7 (3)	0	19 (7)	0
Face edema	6 (23)	0	9 (39)	0	20 (8)	0	75 (29)	0
Peripheral edema	3 (12)	0	5 (22)	0	13 (5)	0	25 (10)	1 (<1)
Rash	7 (27)	0	11 (48)	0	28 (11)	0	42 (16)	3 (1)
Diarrhea	4 (15)	0	8 (35)	2 (9)	49 (19)	1 (<1)	50 (19)	2 (1)
Nausea	4 (15)	0	10 (44)	0	26 (10)	0	57 (22)	0
Vomiting	1 (4)	0	3 (13)	0	12 (5)	0	26 (10)	0
Mucosal inflammation (GI)[a]	3 (12)	0	1 (4)	0	10 (4)	0	3 (1)	0
Constipation	3 (12)	0	1 (4)	0	10 (4)	0	2 (1)	0
Headache	4 (15)	0	0	0	33 (13)	0	28 (11)	0
Fatigue	4 (15)	0	6 (26)	0	21 (8)	1 (< 1)	27 (11)	0
Musculoskeletal Pain	3 (12)	0	7 (30)	0	30 (12)	0	40 (16)	1 (<1)
Infections	5 (19)	0	3 (13)	0	24 (9)	2 (1)	17 (7)	1 (<1)
Hemorrhage	3 (12)	0	1 (4)	0	15 (6)	0	11 (4)	2 (1)

[a] Includes mucositis/stomatitis

experienced grade 3/4 anemia (12 vs. 9 %). In contrast, in the analysis of all patients, all 3 hematologic AEs (grade 3/4) occurred in more patients treated with dasatinib versus imatinib (Table 6). For both treatments, grade 3/4 neutropenia appeared to be more frequent and thrombocytopenia appeared to be less frequent in Japanese patients than among all patients, and the percent of Japanese patients experiencing anemia was similar to the percent of all patients (Fig. 3).

Most grade 3/4 laboratory abnormalities occurred in <2 % of patients, and trends in Japanese patients were similar to those seen across all patients with the potential exception of (Table 6): grade 3/4 decreased phosphate with dasatinib (19 vs. 6 %, Japanese vs. all patients) or imatinib (48 vs. 24 %); grade 3/4 decreased calcium with dasatinib versus imatinib (23 vs. 4 %, Japanese patients).

Among Japanese patients, 3/26 (12 %) treated with dasatinib and 2/23 (9 %) treated with imatinib discontinued treatment due to drug-related AEs, compared with 18/259 (7 %) and 12/260 (5 %), respectively, for all patients (Table 2). In Japanese patients, drug-related AEs leading to discontinuation of dasatinib included elevated creatine phosphokinase ($n = 1$), prolonged QT ($n = 1$), and platelet count ($n = 1$), and in patients treated with imatinib included thrombocytopenia ($n = 1$) and hypophosphatemia ($n = 1$). No Japanese patients died on study or within 30 days of last treatment.

Discussion

This is the first published analysis of first-line dasatinib 100 mg QD in Japanese patients with newly diagnosed CML-CP. The results reported here suggest that the efficacy and safety profiles of dasatinib in Japanese patients are similar to those seen in the analysis of all patients worldwide. This may reflect a high level of pathological conservation of CML-CP among ethnic groups. Comparisons of efficacy in Japanese patients in the dasatinib versus imatinib arms yielded similar trends as observed in all patients, with patients in the dasatinib arm having numerically higher rates of cumulative long-term response (CCyR, MMR, MR^4, $MR^{4.5}$) and numerically faster responses (time to MMR, 3-month *BCR-ABL* levels ≤10 %). Patients randomized to either treatment also experienced high rates of PFS and OS after a minimum 2-year follow-up. Since small sample size limits the strength of conclusions, further exploration is needed to confirm any potential differences observed in Japanese patients compared with the total treated population.

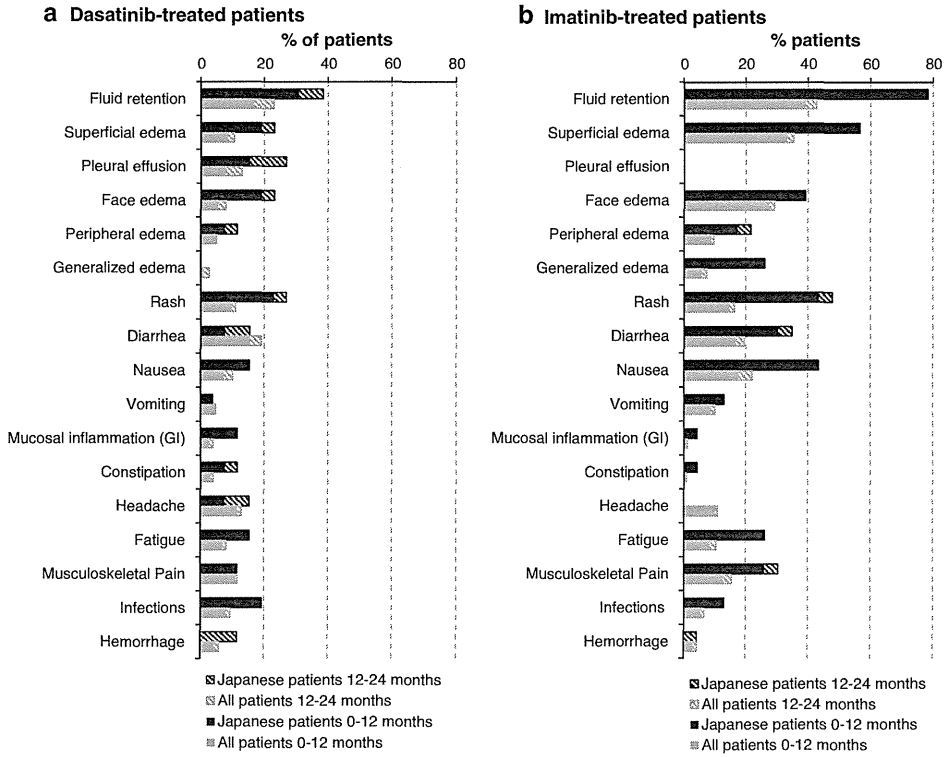

Fig. 2 Rates of drug-related nonhematologic adverse events of special interest. The percent of patients experiencing new drug-related nonhematologic AEs between 0–12 and 12–24 months of treatment are shown for the Japanese patients (*black*) and for all patients (*grey*) treated with dasatinib (**a**) or imatinib (**b**)

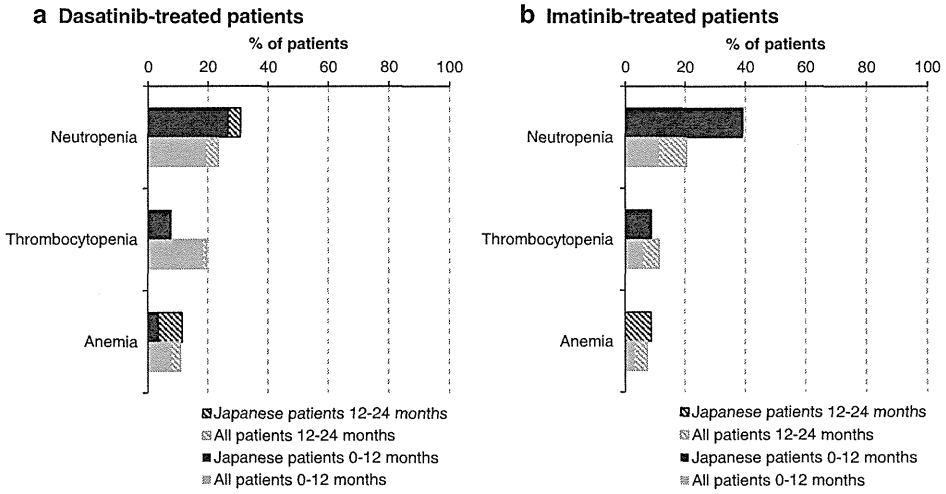

Fig. 3 Rates of grade 3/4 hematologic adverse events. The percent of patients experiencing new drug-related grade 3/4 hematologic AEs between 0–12 and 12–24 months of treatment are shown for Japanese patients (*black*) and for all patients (*grey*) treated with dasatinib (**a**) or imatinib (**b**)

Whereas for all patients, molecular response rates (MMR, MR^4, $MR^{4.5}$) were significantly higher in the dasatinib versus imatinib arm, a larger sample size is needed to accurately assess the statistical significance of similar comparisons for Japanese patients. Notably, response rates (CCyR, MMR, MR^4, $MR^{4.5}$, 3-month *BCR-ABL* levels $\leq$10 %) were numerically higher in Japanese compared with all patients, and MMR rates in Japanese

Table 6 Grade 3/4 hematologic AEs and biochemical abnormalities: percent of patients experiencing AEs during the first 24 months of treatment

	Japanese patients, *n* (%) (*n* = 49)		All patients, *n* (%)[a] (*N* = 519)	
	Dasatinib (*n* = 26)	Imatinib (*n* = 23)	Dasatinib (*n* = 256)	Imatinib (*n* = 257)
Hematologic AEs				
Neutropenia	8 (31)	9 (39)	60 (23)	53 (21)
Thrombocytopenia	2 (8)	2 (9)	50 (20)	29 (11)
Anemia	3 (12)	2 (9)	28 (11)	19 (7)
Biochemical abnormalities				
Elevated total bilirubin	0 (0)	0 (0)	3 (1)	0 (0)
Elevated alanine aminotransferase	0 (0)	0 (0)	1 (<1)	3 (1)
Elevated aspartate aminotransferase	0 (0)	0 (0)	1 (<1)	2 (1)
Elevated creatinine	0 (0)	0 (0)	1 (<1)	2 (1)
Elevated uric acid	0 (0)	0 (0)	4 (2)	2 (1)
Elevated alkaline phosphatase	0 (0)	0 (0)	1 (<1)	0 (0)
Decreased phosphate	5 (19)	11 (48)	15 (6)	62 (24)
Decreased potassium	0 (0)	1 (4)	0 (0)	6 (2)
Decreased calcium	6 (23)	1 (4)	8 (3)	5 (2)
Decreased sodium	0 (0)	0 (0)	2 (1)	2 (1)
Decreased magnesium	0 (0)	0 (0)	1 (<1)	2 (1)

[a] In evaluable patients

patients appeared to remain numerically higher than those for all patients even after stratification by baseline Hasford score. However, the small number of Japanese patients within each Hasford group makes it difficult to compare response rates across Hasford groups.

As in the analysis of all patients, PFS and OS rates in Japanese patients were high and showed little difference between dasatinib and imatinib after 2-year minimum follow-up. Several exploratory analyses have identified correlations between achievement of 3-month *BCR-ABL* levels $\leq$10 % and improved long-term outcomes, including two studies of patients treated with first-line imatinib (8-year follow-up of patients treated at the Hammersmith Hospital [21]; 5-year follow-up CML Study IV [22]) and two studies on patients treated with first-line dasatinib (2-year follow-up SPIRIT II [23], and 3-year follow-up DASISION [13]). As in the analysis of all patients, the numerically higher rate of achieving 3-month *BCR-ABL* levels $\leq$10 % for Japanese patients in the dasatinib (100 %) versus imatinib (74 %) arms suggests that longer follow-up may reveal superior outcomes with dasatinib. The rates of 3-month *BCR-ABL* levels $\leq$10 % may also suggest that dasatinib treatment in Japanese patients may have particularly good long-term outcomes.

Safety analysis of dasatinib and imatinib in Japanese patients demonstrated similar trends in nonhematologic AEs as seen in all patients. Most AEs were grade 1/2 and initially occurred during the first year of treatment. For a number of nonhematologic AEs, the percentage of Japanese patients affected was numerically higher than among all patients, both with dasatinib or imatinib, most notably fluid retention and related AEs (superficial edema, face edema, peripheral edema, generalized edema) and rash. Although a numerically higher percentage of Japanese patients experienced pleural effusion compared with all patients, both those experiencing and not experiencing pleural effusion had similar response rates (CCyR, MMR). After 2 years of treatment, the percentage of Japanese patients experiencing pleural effusion (all grades) in the present analysis was 27 %, similar to the 26 % reported in a surveillance study of 893 patients with newly diagnosed CML (41.7 % in chronic phase) [24]. Consistent with results from all patients, most events of pleural effusion in Japanese patients were grade 1/2, first occurred after >8 weeks of treatment, and were managed by dose interruption, diuretics, steroids, and dose reduction.

Whereas for both treatments a numerically higher percentage of Japanese patients experienced drug-related grade 3/4 neutropenia than in all patients, the difference appeared to be more pronounced with imatinib versus dasatinib. The prevalence of drug-related grade 3/4 anemia for either treatment group was similar for Japanese and all patients. A numerically lower percentage of Japanese patients experienced thrombocytopenia than in all patients (dasatinib: 8 vs. 20 %; imatinib: 9 vs. 11 %). Most grade 3/4 laboratory abnormalities did not occur in Japanese patients, the exceptions being decreased phosphate (dasatinib: 19 %; imatinib: 48 %), decreased calcium (23 %; 4.3 %), and decreased potassium with imatinib

(4.3 %). In contrast, grade 3/4 laboratory abnormalities occurred in <6 % of all patients, with the exception of decreased phosphate with imatinib treatment (24 %). Japanese patients treated with BCR-ABL inhibitors may therefore be more susceptible to decreased phosphate, decreased calcium, and decreased potassium.

Higher levels of exposure to dasatinib during the study are not supported as an explanation for potential efficacy and safety differences since Japanese patients had similar average daily dose and duration of treatment, no dose escalations, and a trend for more frequent dose reductions/interruptions than seen in the analysis of all patients. There was a trend for fewer Japanese patients to have had prior hydroxyurea or baseline ECOG 1 or 2, but their average age was numerically higher than in all patients.

In conclusion, the efficacy and safety profiles of dasatinib in Japanese patients with newly diagnosed CML-CP were consistent with those observed across all patients. Similar to results based on all patients, there was a trend among Japanese patients for deeper and faster response rates with dasatinib versus imatinib treatment. Dasatinib is therefore an important first-line option for the treatment of Japanese patients with newly diagnosed CML-CP, improving long-term outcomes.

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ORIGINAL ARTICLE

Effect of related donor availability on outcome of AML in the context of related and unrelated hematopoietic cell transplantation

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Although allogeneic hematopoietic cell transplantation (HCT) from a related donor is effective therapy for younger patients with AML, it remains unknown how the availability of a related donor affects the outcome when unrelated HCT is a treatment option for patients without a related donor. To address this issue, we retrospectively analyzed 605 cytogenetically non-favorable AML patients younger than 50 years for whom a related donor search was performed during first CR (CR1). The 4-year OS was 62% in 253 patients with a related donor and 59% in 352 patients without a related donor ($P = 0.534$). Allogeneic HCT was performed during CR1 in 62% and 41% of patients with and without a related donor, respectively. Among patients transplanted in CR1, the cumulative incidence of non-relapse mortality was significantly higher in patients without a related donor ($P = 0.022$), but there was no difference in post-transplant OS between the groups ($P = 0.262$). These findings show the usefulness of unrelated HCT in younger patients with cytogenetically non-favorable AML who do not have a related donor. The extensive use of unrelated HCT for such patients may minimize the potential disadvantage of lacking a related donor.

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Keywords: AML; allogeneic hematopoietic cell transplantation; donor; related transplantation; unrelated transplantation; first CR

INTRODUCTION

Owing to the strong anti-leukemic effect of pre-transplant conditioning therapy in combination with the post-transplant GVL effect, allogeneic hematopoietic cell transplantation (HCT) is currently the most powerful method for preventing relapse of AML.[1] However, the efficacy of allogeneic HCT is compromised by a high risk of treatment-related mortality, which raises the question of whether allogeneic HCT is truly beneficial for AML patients who are in their first CR (CR1). Historically, this question has been investigated in prospective studies that used biologic assignment according to donor availability, in which patients with an HLA-identical sibling donor were assigned to allogeneic HCT, whereas those without an HLA-identical sibling donor were assigned to chemotherapy and/or autologous HCT.[2–8] If we combine the results from those studies, we find that allogeneic HCT during CR1 confers a survival advantage in patients with cytogenetically intermediate and unfavorable risk.[8–10] However, such 'donor vs no-donor' studies do not provide an accurate picture of clinical practice, because an HLA-identical sibling is not the only donor source and a substantial proportion of patients without a related donor receive allogeneic HCT from an unrelated donor.

To examine how related donor availability affects the outcome of AML in a situation where unrelated HCT is a treatment option for patients without a related donor, we retrospectively analyzed cytogenetically non-favorable AML patients under the age of 50 years for whom a related donor search was conducted during CR1. The main objectives of this study were to assess the difference in survival according to related donor availability in terms of (1) overall outcome, (2) outcome after allogeneic HCT in CR1 (that is, comparison between related and unrelated HCT) and (3) outcome after first relapse following chemotherapy. We also looked at how unrelated HCT was incorporated into the treatment strategy in our patient cohort.

PATIENTS AND METHODS

Patients

Adults with AML who had achieved CR1 were retrospectively registered in a Japanese nationwide AML database, which formed the basis of this study. Seventy institutions contributed patients to the database. Patients were eligible if they were younger than 50 years, were diagnosed with AML from 1999 to 2006 according to the World Health Organization (WHO) classification,[11] had achieved CR with one or two courses of chemotherapy, and had a related donor search performed during CR1. We excluded patients with acute promyelocytic leukemia and core-binding factor AML, as well as those whose pre-treatment cytogenetic results were not available. Patients who underwent haploidentical HCT were also excluded. Overall, 605 patients fulfilled these criteria, and thus were subjected to

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subsequent analyses. Information was collected and compiled with regard to patient-related factors (that is, age and sex), disease-related factors (that is, cytogenetics, WBC count and dysplasia in morphology), number of induction courses, related donor availability, and clinical outcome. For patients who underwent allogeneic HCT, complementary information on HCT (that is, interval from CR1 to HCT, disease status at time of HCT, conditioning regimen and donor source) was also collected. Patients were considered to have a related donor if HLA typing identified a matched or one Ag-mismatched family donor. Unrelated donor selection was based on matching at the level of resolution available at the time of transplantation. This study was approved by the Institutional Review Board at the National Cancer Center Hospital.

Statistical analysis

Distributions of patient characteristics between groups were compared by using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The probabilities of OS and relapse-free survival (RFS) were estimated by the Kaplan–Meier method, with differences between groups qualified by the log-rank test. Relapse and non-relapse mortality (NRM) were considered as competing risk events for each other. The probabilities of relapse and NRM were estimated by the cumulative incidence functions, and differences between groups were qualified by the Gray test. The Cox proportional hazards regression model was used for univariate and multivariate analyses, and a hazard ratio (HR) was calculated in conjunction with a 95% confidence interval (CI). All statistical analyses were performed with SPSS software version 11.0.1 (SPSS, Chicago, IL, USA) and R software version 2.13.0 (The R Foundation for Statistical Computing).

RESULTS

Patient characteristics

Of the 605 patients eligible for analysis, a related donor was found for 253 patients (42%) during CR1. There were no significant differences between the groups in the distribution of baseline characteristics, with the exception of WBC count (Table 1). Figure 1 shows the patient flow with respect to related donor availability, allogeneic HCT in CR1 and relapse. Among the 253 patients with a related donor, 157 (62%) underwent allogeneic HCT in CR1 (156 from a related donor and 1 from an unrelated BM donor). Of the 352 patients without a related donor, allogeneic HCT was performed during CR1 in 146 patients (41%), of whom 109 and 37 received unrelated BMT and umbilical cord blood (UCB) transplantation, respectively. In all, 96 patients with a related donor and 206 patients without a related donor did not receive allogeneic HCT during CR1. Among them, 25 (26%) and 49 (24%) patients experienced early relapse within 6 months after achievement of CR1. Autologous HCT was performed during CR1 in 5 and 14 patients with and without a related donor, respectively.

Characteristics of patients who underwent allogeneic HCT in CR1

The characteristics of patients who underwent allogeneic HCT in CR1 are summarized according to related donor availability in Table 2. The two groups were well balanced in terms of baseline characteristics. However, patients without a related donor were more likely to receive two courses of induction therapy instead of one course ($P = 0.023$). The interval from CR1 to transplantation differed significantly between the groups (Figure 2), with a median interval of 3.7 months for patients with a related donor vs 5.9 months for patients without a related donor ($P < 0.001$). Myeloablative conditioning was used in 89% and 88% of patients with and without a related donor, respectively.

Outcome after CR1 according to related donor availability

The median follow-up of surviving patients was 4.4 years (range, 0.1–9.7), and the 4-year OS was 60% for the entire population. Figure 3 shows Kaplan–Meier survival estimates for patients with and without a related donor. The 4-year OS was 62% in patients with a related donor and 59% in patients without a related donor, with no significant difference detected ($P = 0.534$). Similar results were obtained when the analysis was restricted to patients with unfavorable cytogenetic risk (51% vs 44% at 4 years, $P = 0.213$) or those with intermediate cytogenetic risk (67% vs 67% at 4 years, $P = 0.744$). In the multivariate analysis, cytogenetics and number of induction courses were identified as factors that were significantly associated with OS, whereas related donor availability had no significant impact (Table 3).

Table 1. Patient characteristics

	Related donor+ N = *253*	*Related donor−* N = *352*	P-*value*
Age, years			0.547
Median	34	35	
Range	16–49	16–49	
Sex			0.232
Male	127 (50%)	194 (55%)	
Female	126 (50%)	158 (45%)	
Cytogenetic risk by SWOG			0.74
Intermediate	153 (60%)	211 (60%)	
Unfavorable	72 (28%)	94 (27%)	
Unknown	28 (11%)	47 (13%)	
WBC count, × 10^9/L			0.049
Median	13.8	18	
Range	0.6–794.0	0.5–410.7	
Dysplasia			0.9
No	204 (81%)	285 (81%)	
Yes	49 (19%)	67 (19%)	
No. of induction courses			0.186
1 Course	196 (77%)	256 (73%)	
2 Courses	57 (23%)	96 (27%)	
Allogeneic HCT			<0.001
CR1	157 (62%)	146 (41%)	
CR2	27 (11%)	44 (13%)	
Other disease phases	38 (15%)	63 (18%)	
Not performed	31 (12%)	99 (28%)	

Abbreviations: CR1 = first CR; CR2 = second CR; SWOG = Southwest Oncology Group.

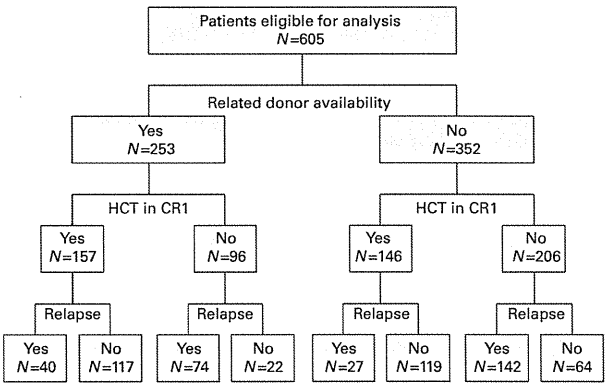

Figure 1. Flow diagram of patients.

Table 2. Characteristics of patients who underwent allogeneic HCT in CR1

	Related donor+ N = *157*	*Related donor−* N = *146*	P-*value*
Age, years			0.441
Median	34	35	
Range	16–49	16–49	
Sex			0.252
Male	80 (51%)	84 (58%)	
Female	77 (49%)	62 (42%)	
Cytogenetic risk by SWOG			0.178
Intermediate	97 (62%)	78 (53%)	
Unfavorable	40 (25%)	47 (32%)	
Unknown	20 (13%)	21 (14%)	
WBC count, × 10^9/L			0.644
Median	12.7	11.5	
Range	0.9–794.0	0.6–410.7	
Dysplasia			0.729
No	118 (75%)	112 (77%)	
Yes	39 (25%)	34 (23%)	
No. of induction courses			0.023
1 Course	115 (73%)	89 (61%)	
2 Courses	42 (27%)	57 (39%)	
Interval from CR1 to HCT, days			<0.001
Median	113	178	
Range	0–620	14–770	
Type of donor			<0.001
Related	156 (99%)	0 (0%)	
Unrelated, BM	1 (1%)	109 (75%)	
Unrelated, cord blood	0 (0%)	37 (25%)	
Type of conditioning			0.969
Myeloablative	140 (89%)	128 (88%)	
Reduced-intensity	14 (9%)	13 (9%)	
Not specified	3 (2%)	5 (3%)	

Abbreviations: CR1 = first CR; HCT = hematopoietic cell transplantation; SWOG = Southwest Oncology Group.

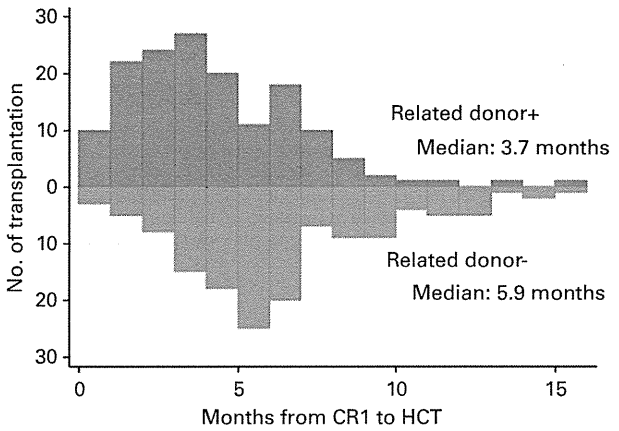

Figure 2. Interval from CR1 to HCT in patients who underwent allogeneic HCT during CR1. Patients with (Related donor +, $N = 157$) and without a related donor (Related donor −, $N = 146$) are shown separately. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

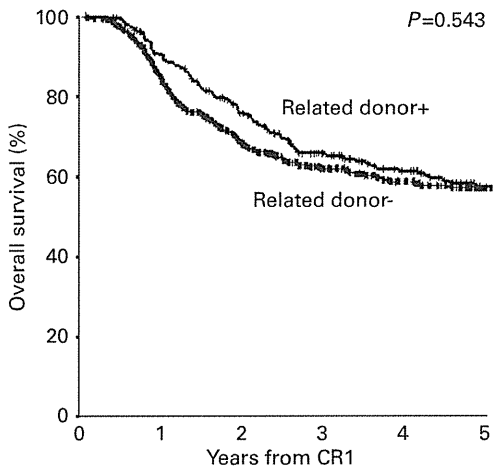

Figure 3. Kaplan–Meier curves for OS after CR1 according to related donor availability. All patients with (Related donor +, $N = 253$) and without a related donor (Related donor −, $N = 352$) are compared.

Outcome after allogeneic HCT in CR1 according to related donor availability

Figure 4 compares post-transplant OS between patients with and without a related donor who underwent allogeneic HCT during CR1. There was no difference in OS between the groups: the 4-year OS was 65% in patients with a related donor and 61% in patients without a related donor ($P = 0.262$). The cumulative incidence of NRM in patients with a related donor was significantly lower than that in patients without a related donor (13% vs 21% at 4 years, $P = 0.022$). In terms of relapse, patients with a related donor appeared to show a higher incidence, but the difference was not statistically significant (26% vs 21% at 4 years, $P = 0.292$). OS with unrelated BMT was superior to that with UCB transplantation (66% vs 48% at 4 years, $P = 0.044$): the former was equivalent to the result with related HCT ($P = 0.897$), whereas the latter was worse ($P = 0.003$). Related HCT from a matched ($N = 140$) and one Ag-mismatched donor ($N = 16$) showed no difference in OS (66% vs 56% at 4 years, $P = 0.304$).

Effect of allogeneic HCT during CR1 in patients with or without a related donor

To examine how allogeneic HCT in CR1 impacted RFS and OS, we performed separate multivariate analysis for patients with and without a related donor. In this analysis, HCT was considered as a time-dependent covariate, and adjustments were made for all of the variables listed in Table 3 except for related donor availability. In patients with a related donor, allogeneic HCT in CR1 was associated with superior RFS (HR, 0.28; 95% CI, 0.19–0.41) and OS (HR, 0.65; 95% CI, 0.43–0.98). In patients without a related donor, allogeneic HCT in CR1 had favorable effect on RFS (HR, 0.58; 95% CI, 0.41–0.82) and OS (HR, 0.82; 95% CI, 0.56–1.19), although the effect on OS did not reach statistical significance.

Outcome after first relapse following chemotherapy according to related donor availability

Among patients who did not undergo allogeneic HCT in CR1, 74 patients with a related donor and 142 patients without a related

Table 3. Factors associated with OS

	Univariate analysis			*Multivariate analysis*		
	HR	*(95% CI)*	P-*value*	*HR*	*(95% CI)*	P-*value*
Related donor availability						
Yes	1		—	1		—
No	1.09	(0.84–1.40)	0.534	1.08	(0.83–1.39)	0.576
Age						
As a numerical variable (per 1 year)	1	(0.99–1.01)	0.799	1	(0.99–1.01)	0.926
Sex						
Male	1		—	1		—
Female	0.98	(0.76–1.27)	0.899	1	(0.78–1.30)	0.979
Cytogenetic risk by SWOG						
Intermediate	1		—	1		—
Unfavorable	1.92	(1.45–2.54)	<0.001	2.00	(1.51–2.65)	<0.001
Unknown	1.72	(1.18–2.50)	0.005	1.52	(1.04–2.22)	0.031
WBC count						
As a numerical variable (per 10×10^9/L)	1.02	(1.00–1.03)	0.035	1.01	(1.00–1.03)	0.065
Dysplasia						
No	1		—	1		—
Yes	0.7	(0.49–1.00)	0.052	0.71	(0.50–1.02)	0.061
No. of induction courses						
1 Course	1		—	1		—
2 Courses	2.44	(1.88–3.17)	<0.001	2.46	(1.88–3.21)	<0.001

Abbreviations: CI = confidence interval; HR = hazard ratio; SWOG = Southwest Oncology Group.

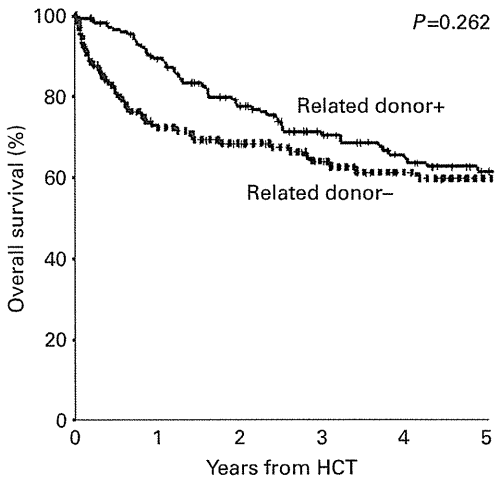

Figure 4. Kaplan–Meier curves for OS after allogeneic HCT in CR1 according to related donor availability. Patients with (Related donor+, $N = 157$) and without a related donor (Related donor−, $N = 146$) who underwent allogeneic HCT in CR1 are compared.

donor experienced relapse (Figure 1). After relapse, 65 (88%) patients with a related donor received allogeneic HCT (62 from a related donor, 2 from an unrelated BM donor and 1 from UCB), as did 107 (75%) patients without a related donor (63 from an unrelated BM donor, 42 from UCB and 1 from a related donor who had not been included in the initial related donor search; information was missing for 1 patient). In all, 27 patients with a related donor and 44 patients without a related donor received allogeneic HCT during CR2. For patients who experienced relapse without having received allogeneic HCT in CR1, the 4-year OS after relapse was 33% in patients with a related donor and 33% in patients without a related donor ($P = 0.245$).

DISCUSSION

The outcome of unrelated HCT has recently improved primarily due to the introduction of high-resolution HLA-typing technology and improvements in supportive care. In addition, the growth of unrelated donor registries as well as the increased use of UCB grafts has increased the chance of finding an unrelated donor.[1] These advances have made unrelated HCT a more feasible option for patients who lack a related donor. As our analyses were based on a nationwide multicenter survey, the finding that 41% of patients without a related donor received unrelated HCT during CR1 reflects the widespread use of unrelated HCT in Japan. On the other hand, in patients with a related donor, the proportion of patients who underwent allogeneic HCT during CR1 reached 62%. This value was comparable to or only slightly lower than the HCT compliance rates reported in previous donor vs no-donor studies, where allogeneic HCT was offered to all patients with a related donor as per the study protocol.[2–8] These findings show that allogeneic HCT, from both related and unrelated donors, was actively incorporated into the treatment strategy in our patient population.

When we take into account that patients with core-binding factor AML were excluded from our study, the 60% 4-year OS for the entire cohort appears quite favorable. Recently, the Japan Adult Leukemia Study Group reported results from a prospective study (designated AML201) for newly diagnosed AML patients, in which standard-dose and high-dose cytarabine (AraC)-based regimens were compared for post-remission therapy.[12] In that study, for patients younger than 50 years, the 5-year OS was 66%