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RESEARCH ARTICLE

Four-year follow-up of patients with imatinib-resistant or intolerant chronic myeloid leukemia receiving dasatinib: efficacy and safety

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Abstract **Dasatinib is a highly effective second-generation tyrosine kinase inhibitor used to treat chronic myeloid leukemia (CML). In 2007, a pivotal phase-2 study of dasatinib as second-line treatment was initiated in 140 Chinese CML patients. This report from the 4-year follow-up revealed that 73% of 59 patients in chronic phase (CML-CP) and 32% of 25 patients in accelerated phase (CML-AP) remained under treatment. The initial dosage of dasatinib for CML-CP and CML-AP patients were 100 mg once daily and 70 mg twice daily (total = 140 mg/day), respectively. The cumulative major cytogenetic response (MCyR) rate among patients with CML-CP was 66.1% (versus 50.8% at 18 months), and the median time to MCyR was 12.7 weeks. All CML-CP patients who achieved MCyR after a 4-year follow-up also achieved a complete cytogenetic response. The cumulative complete hematological response (CHR) rate among patients with CML-AP was 64% (16/25), with three CML-AP patients achieving CHR between 18 months and 4 years of follow-up; the median time to CHR was 16.4 weeks. The adverse event (AE) profile of dasatinib at 4 years was similar to that at 6 and 18 months. The most frequently reported AEs (any grade) included pleural effusion, headache, and myelosuppression. These long-term follow-up data continue to support dasatinib as a second-line treatment for Chinese patients with CML.**

Keywords chronic myeloid leukemia (CML); dasatinib; tyrosine kinase inhibitor; long-term follow-up

Introduction

For patients with Philadelphia chromosome-positive (Ph^+) chronic myeloid leukemia (CML), imatinib mesylate has been widely accepted as a first-line therapy, except for treatment of a small percentage of patients, who are intolerant to imatinib [1]. Although most CML patients treated with imatinib achieve a cytogenetic response, approximately one-third of patients will develop imatinib resistance [1]. With the emergence of generic imatinib, patients with newly-diagnosed Ph^+ CML may tend to select imatinib as first-line therapy; thus, imatinib resistance/intolerance becomes a more prominent issue.

Data from clinical studies and real-world settings have shown that the selected second-generation tyrosine kinase inhibitors (TKIs) are effective second-line treatment options [2]. However, long-term follow-up data from patients receiving a second-generation TKI in the second-line setting are relatively scarce, especially for CML patients from Asia.

In 2007, we initiated a registration study in China for dasatinib as second-line treatment for Asian CML patients, who were intolerant or resistant to imatinib. Dasatinib is a potent, second-generation, oral inhibitor of the BCR-ABL1 tyrosine kinase that is currently approved in more than 60 countries as first- and/or second-line treatment for Ph^+ CML or Ph^+ acute lymphoblastic leukemia (ALL).

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Ample evidence shows that dasatinib yields long-term, hematologic, cytogenetic, and molecular responses in CML patients from diverse races/ethnicities [1,3]. Nonetheless, to date, no long-term outcome data ($>$ 18 months) for Chinese CML patients, who initiated dasatinib as a second-line therapy after developing resistance or intolerance to imatinib, are available.

Patient outcomes at 18 months after dasatinib treatment initiation were previously reported [4]. In summary, 91.5% and 50.8% of patients with CML in chronic phase (CML-CP) achieved a complete hematological response (CHR) or major cytogenetic response (MCyR), respectively; none of the patients, who achieved MCyR, died or experienced disease progression. Hematological adverse events (AEs), including neutropenia and thrombocytopenia, were relatively common and were consistent with the results from global phase-3 studies of dasatinib [5–8].

Here, we report the 4-year safety and efficacy data for Chinese CML-CP and CML in accelerated phase (CML-AP) patients. In addition, we report the results of a post-hoc analysis conducted to assess the association between pre/on-treatment factors and dasatinib treatment efficacy after 4 years of follow-up.

Materials and methods

Study design, patients, and treatment

From March 2008 to October 2009, 140 Ph^+ CML or ALL patients were enrolled; 59 patients had CML-CP, 60 had advanced CML (25 in the CML-AP and 35 in blast phase [CML-BP]), and two had Ph^+ ALL. A total of 121 patients received at least one dose of dasatinib. The 4-year follow-up data were collected between 2008 and 2013. The median treatment duration of the CML-BP/Ph^+ ALL patients was 3.1 months, and the results for this patient population were previously reported [3] and are not repeated here.

The study methods were previously reported by Huang *et al*. (2012) [4]. In summary, this study was an open-label, single-arm, phase-2 study conducted at 10 centers in China. Eligible patients were aged $\geqslant$ 18 years with imatinib-resistant or-intolerant Ph^+ CML or Ph^+ ALL, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, and adequate hepatic and renal function. Exclusion criteria included pleural effusion at baseline, previous use of any small-molecule, targeted cancer therapy within 7 days of the study (including imatinib), any previous use of dasatinib, and uncontrolled significant cardiovascular disease. The study was registered at clinicaltrials.gov (NCT00529763).

Eligible CML-CP patients received oral dose of 100 mg once daily of dasatinib, and patients with advanced CML or Ph^+ ALL received a starting dose of 70 mg twice daily (total = 140 mg/day). Patients were disqualified from the study if they discontinued study treatment, died, failed to follow-up, or withdrew the informed consent.

Assessments

Complete blood counts were conducted every 6 months. Cytogenetic analyses were performed annually to assess treatment efficacy, and at least 20 bone marrow cell metaphases were evaluated to determine cytogenetic response. AEs were evaluated continuously and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3. Serum chemistry laboratory tests were conducted every 6 months, and a complete physical examination and a bone-marrow biopsy were performed annually to assess safety. Chest X-ray imaging was performed when a patient reported dyspnea on exertion and when clinically indicated. All assessments were repeated until the date of treatment discontinuation.

Endpoints

The primary endpoint for patients with CML-CP was the cumulative rate of MCyR, and secondary endpoints included time to MCyR, rate of progression-free survival (PFS), and safety. The primary endpoint for patients with CML-AP was the cumulative rate of CHR and overall hematological response (OHR), and the secondary endpoints included time to CHR, OHR, and the duration, rate of cytogenetic response (CyR), and PFS.

PFS refers to the time from the first dosing date until the time that the disease progression was documented. Patients, who died without a reported prior progression, were considered to have progressed on the date of their death. Disease progression in CML-CP occurs when: patients with MCyR and no longer satisfied the criteria for MCyR after starting their maximum dose of dasatinib, patients with CHR and no longer satisfied the criteria for CHR consistently over a consecutive 2-week period after starting their maximum dose of dasatinib, patients did not achieve CHR after receiving their maximum dose of dasatinib and showed an increase in their white blood cell count (a doubling of the count from the lowest value to $>$ 20 000/mm^3 or an increase of $>$ 50 000/mm^3 on two assessments performed at least 2 weeks apart or a $\geqslant$ 30% absolute increase in the number of Ph^+ metaphases), patients with CML-CP and satisfied the criteria of advanced CML at any time, and patients, who died during follow-up.

Statistical analysis

Patients, who discontinued treatment, were not routinely followed up. Therefore, disease progression and survival data were not available for patients, who dropped out of the

study. In the calculation of PFS, these patients were censored at the date of last cytogenetic assessment if progressive disease did not occur. PFS was estimated using the Kaplan–Meier product-limit methodology. For patients with CML-CP, the association between baseline factors such as age, sex, prior treatment history (complete cytogenetic response [CCyR], treatment duration, imatinib dose, imatinib resistance, interferon treatment, and pleural effusion), and CCyR was investigated by a *post-hoc* univariate regression analysis.

Safety analyses included treated patients, and AEs were summarized as cumulative incidence. Comparisons were for exploratory purposes; therefore, *P* values were not adjusted for multiple comparisons.

Ethics statement

The study was conducted in accordance with the principles of the *Declaration of Helsinki* and in-line with the guidelines for Good Clinical Practice set out in the International Conference on Harmonization Tripartite Guideline. All study subjects provided written informed consent.

Results

Patient demographics

A total of 59 patients with CML-CP and 25 with CML-AP received dasatinib treatment. Patient demographics and background disease characteristics have been previously published, and are summarized in Table 1 [4]. The median age (± SD) of CML-CP and CML-AP patients was 42.8 ± 11.3 and 39.5 ± 10.5 years, respectively. Overall, more than 90% of patients were resistant to previous imatinib therapy. Four patients with CML-CP commenced dasatinib treatment at 70 mg twice daily, but had their dose reduced to 100 mg once daily, in line with a protocol amendment. One additional patient commenced dasatinib at a starting dose of 70 mg twice daily because of an inaccurate diagnosis of advanced CML at the beginning of treatment. This patient's dosing regimen was then adjusted to 100 mg once daily after the diagnosis was confirmed as CML-CP.

At the 4-year follow-up, the median duration of dasatinib treatment (from first dose to the date of treatment discontinuation, or data cut-off date) was 50.1 months for patients with CML-CP and 34.1 months for patients with CML-AP. A total of 73% of 59 CML-CP patients and 32% of 25 CML-AP patients remained on treatment at 4 years. The most common reason for treatment discontinuation was disease progression; 8.5% of patients had CML-CP and 28.0% of patients had CML-AP (Table 2).

Table 1 Patient demographics and disease characteristics

Characteristic	CML-CP (*n* = 59)	CML-AP (*n* = 25)
Median age, year ±standard deviation	42.8±11.3	39.5±10.5
Male, *n* (%)	36 (61.0)	15 (60.0)
ECOG performance status, *n* (%)		
0	25 (42.4)	8 (32.0)
1	34 (57.6)	16 (64.0)
2	0 (0)	1 (4.0)
Median time between diagnosis and first dose of dasatinib, month (range)	46.3 (5.4–214.6)	72.0 (18.0–140.7)
Years of prior imatinib therapy, *n* (%)		
<1	13 (22.0)	4 (16.0)
1–3	34 (57.6)	13 (52.0)
>3	12 (20.3)	8 (32.0)
Highest dose (mg/d) of prior imatinib, *n* (%)		
400–600	46 (78.0)	15 (60.0)
>600	13 (22.0)	10 (40.0)
Best cytogenetic response to imatinib, *n* (%)		
Complete	4 (6.8)	1 (4.0)
Minimal	9 (15.3)	2 (8.0)
Minor	11 (18.6)	6 (24.0)
Partial	16 (27.1)	11 (44.0)
None	17 (28.8)	1 (4.0)
Unable to determine	2 (3.4)	4 (16.0)
Patients resistant to prior imatinib, *n* (%)	55 (93.2)	23 (92.0)
Patients intolerant to prior imatinib, *n* (%)	7 (11.9)	4 (16.0)
Prior therapy other than imatinib[a], *n* (%)		
Any[b]	51 (86.4)	25 (100.0)
Interferon	31 (52.5)	19 (76.0)
Hydroxyurea or anagrelide	48 (81.4)	22 (88.0)
Cytarabine	9 (15.3)	10 (40.0)

[a] Patients may have received more than one prior therapy other than imatinib, with or prior to imatinib.
[b] Therapy with one or more agents including interferon, cytarabine, hydroxyurea, or anagrelide.
CML-AP, chronic myeloid leukemia in accelerated phase; CML-CP, chronic myeloid leukemia in chronic phase; ECOG, Eastern Cooperative Oncology Group.

Treatment efficacy

At the 4-year follow-up, the cumulative MCyR rate among patients with CML-CP was 66.1%, which represented an increase of 30% compared with the MCyR rate at 18 months of follow-up (50.8%) [4]. The median time to MCyR for these patients was 12.7 weeks (Table 3). In addition, all of the CML-CP patients, who achieved MCyR after 4 years of follow-up (*n* = 39), achieved CCyR,

Table 2 Patient disposition after 4 years of follow-up

	CML-CP (n = 59)	CML-AP (n = 25)
On study treatment, n (%)	43 (72.9)	8 (32.0)
Discontinued treatment, n (%)	16 (27.1)	17 (68.0)
Reason for treatment discontinuation, n (%)		
Adverse event unrelated to study drug	1 (1.7)	1 (4.0)
Death	1 (1.7)	0 (0)
Disease progression	5 (8.5)	7 (28.0)
Lost to follow-up	1 (1.7)	0 (0)
Study drug toxicity	1 (1.7)	2 (8.0)
Withdrawn consent	3 (5.1)	2 (8.0)
Stem cell transplant	0 (0)	0 (0)
Patient request	0 (0)	1 (4.0)
Unknown	4 (6.8)	4 (16)
Median duration of dasatinib treatment, months (range)	50.1 (1.6–60.7)	34.1 (3.4–61.6)

CML-AP, chronic myeloid leukemia in accelerated phase; CML-CP, chronic myeloid leukemia in chronic phase.

whereas at the 18-month follow-up, 44.1% of patients with MCyR achieved CCyR, and 6.8% achieved PCyR.

After 4-year follow-up, the cumulative CHR rate among patients with CML-AP was 64% (16/25), and three additional patients achieved CHR between the 18-month and 4-year follow-up. Among these patients, the median time to CHR was 16.4 weeks (Table 3). At 4 years, no new cases of MCyR were observed among the CML-AP patients; the MCyR rate among CML-AP patients at 18 months was 40%, which remained the same at the 4-year follow-up.

After 4 years of follow-up, five patients with CML-CP and five with advanced CML-AP died. The investigators considered none of these deaths related to treatment. A total of three deaths (one patient with CML-CP and two with CML-AP) occurred after disease progression. One patient with CML-AP died of cardiovascular disease. Other deaths were due to other/unknown causes. Overall survival data are not available.

A total of 57/59 patients with CML-CP were included in the calculation of PFS; for two patients, cytogenetic assessment data were not available at the 4-year follow-up, and these patients were, therefore, excluded from the analysis. After 4 years of follow-up, the PFS rate was 85.7% (Fig. 1, Table 4). At 12, 24, and 36 months, the PFS rate was 94.7%, 91.2%, and 85.7%, respectively. None of the patients, who remained on treatment for 4 years, experienced disease progression between 3 and 4 years.

Predictors of treatment response

Univariate logistic regression analysis revealed that for CML-CP patients, an early response to treatment (MCyR within 90 days of treatment initiation) was associated with achieving CCyR after 4 years of follow-up (odds ratio: 42.1, 95% CI: 2.37–746.84; P = 0.01) (Fig. 2). Furthermore, none of the 20 patients, who achieved MCyR within 90 days of treatment initiation, experienced disease progression after 4 years of follow-up (Fig. 3). In addition, 12/14 CML-CP patients, who experienced at least one event of pleural effusion, had achieved CCyR through the 4-year follow-up.

Table 3 Summary of treatment response after 18 months and 4 years of follow-up in patients with CML-CP or CML-AP

	Follow-up period	
	18-month	4-year
CML-CP (n = 59)		
Cumulative MCyR, n (%) [95% CI]	30 (50.8) [37.5–64.1]	39 (66.1) [52.6–77.9]
Median time to MCyR, week (range)	12.7 (4.3–48.0)	12.7 (4.3–206.1)
Cytogenetic response[a], n (%)		
CCyR	26 (44.1)	39 (66.1)
PCyR	4 (6.8)	0 (0)
Minor	10 (16.9)	5 (8.5)
Minimal	8 (13.6)	7 (11.9)
No response	9 (15.3)	6 (10.2)
Unable to determine[b]	2 (3.4)	2 (3.4)
CML-AP (n = 25)		
CHR, n (%) [95% CI]	13 (52.0) [31.3–72.2]	16 (64.0)[42.5–82.0]
Median time to CHR, weeks (range)	16.0 (11.7–52.1)	16.4 (11.7–88.6)
Best hematologic response, n (%)		
No Response	2 (8.0)	2 (8.0)
Minor	2 (8.0)	2 (8.0)
No evidence of leukemia	8 (32.0)	5 (20.0)
Complete	13 (52.0)	16 (64.0)
Cumulative MCyR, n (%) [95% CI]	10 (40.0) [21.1–61.3]	10 (40.0) [21.1–61.3]
Median time to MCyR, weeks (range)	12.1[11.7-48.9]	Not available
Cytogenetic response[a], n (%)		
CCyR	9 (36.0)	9 (36.0)
PCyR	1 (4.0)	1 (4.0)
Minor	2 (8.0)	2 (8.0)
Minimal	4 (16.0)	5 (20.0)
No response	7 (28.0)	6 (24.0)
Unable to determine[c]	2 (8.0)	2 (8.0)

[a]Cytogenetic responses defined by the percentage of Philadelphia chromosome-positive cells in metaphase: CCyR = 0%, PCyR ⩾ 0%–35%; minor response ⩾ 35%–65%; minimal response ⩾ 65%–95%; no response ⩾ 95%.
[b]No valid cytogenetic assessment available; one patient was lost to follow-up, and one withdrew consent before an assessment can be made.
[c]No valid cytogenetic assessment available.
CI, confidence interval; CML-AP, chronic myeloid leukemia in accelerated phase; CML-CP, chronic myeloid leukemia in chronic phase; CCyR, complete cytogenetic response; MCyR, major cytogenetic response; PCyR, partial cytogenetic response.

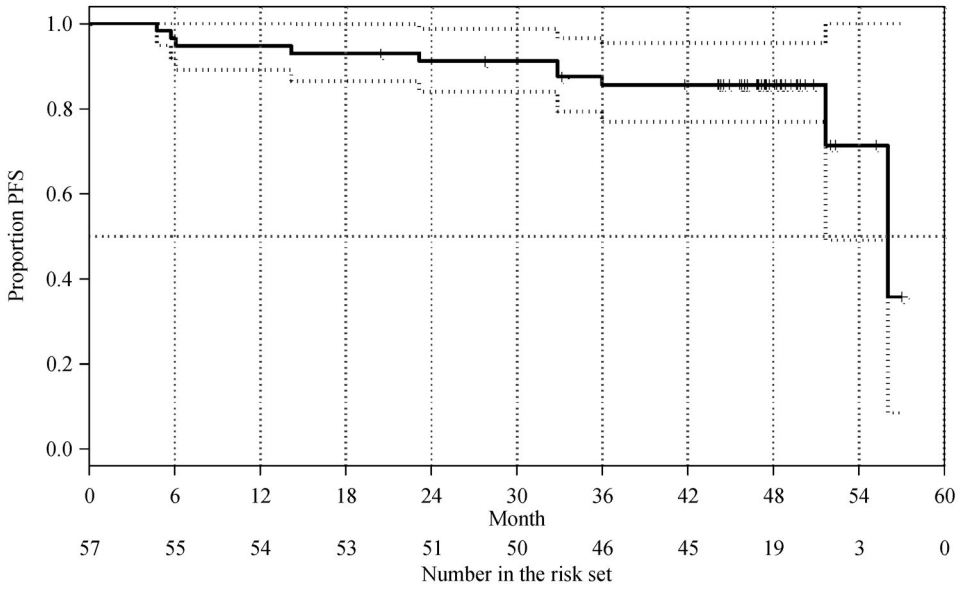

Fig. 1 Kaplan–Meier curve for progression-free survival in dasatinib-treated CML-CP patients. Two patients did not have cytogenetic assessment data and were excluded from the PFS analysis. PFS, progression-free survival.

Table 4 Summary of safety data and the most common adverse events after 4 years of follow-up

AEs, *n* (%)	CML-CP (*n* = 59)		CML-AP (*n* = 25)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
⩾1 drug-related AE	41 (69.5)	11 (18.6)	21 (84.0)	16 (64.0)
Treatment discontinuation due to AEs	7 (11.9)	3 (5.1)	2 (8.0)	1 (4.0)
Most common drug-related AEs (⩾10% of patients)				
Pleural effusion	14 (23.7)	2 (3.4)	10 (40.0)	0
Headache	13 (22.0)	0 (0)	3 (12.0)	0
Thrombocytopenia	7 (11.9)	7 (11.9)	6 (24.0)	6 (24.0)
Diarrhea	4 (6.8)	1 (1.7)	5 (20.0)	2 (8.0)
Neutropenia	4 (6.8)	4 (6.8)	6 (24.0)	6 (24.0)
Pulmonary hypertension	4 (6.8)	1 (1.7)	2 (8.0)	0
Pneumonia	0	0	5 (20.0)	1 (4.0)
Lung infection	0	0	4 (16.0)	2 (4.0)
Pericardial effusion	2 (3.4)	0	3 (12.0)	1 (4.0)

AE, adverse event; CML-AP, chronic myeloid leukemia in accelerated phase; CML-CP, chronic myeloid leukemia in chronic phase.

Safety

Dasatinib was generally well-tolerated. Treatment discontinuation due to AEs occurred in 11.9% of patients with CML-CP and 8.0% of patients with CML-AP. Overall, drug-related AEs of any grade were experienced by 69.5% of patients with CML-CP and 84.0% of patients with CML-AP. A total of 18.6% and 64% of patients with CML-CP and CML-AP, respectively, experienced grade 3–4 AEs.

The most frequently reported AEs (any grade) were pleural effusion, headache, thrombocytopenia, and neutropenia, and most common grade 3–4 AEs were thrombocytopenia and neutropenia (Table 4). Pleural effusion was reported in 23.7% (14/59) and in 40% (10/25) of patients with CML-CP and CML-AP, respectively. Two of the CML-CP patients and none of the CML-AP patients developed grade 3–4 pleural effusion. Cumulative rates of pleural effusion increased gradually over time (Table 5). The median time to onset of pleural effusion was 14.7 months (range, 0.7–27.2 months) in CML-CP patients and 21.2 months (0.3–50.1 months) in CML-AP patients. In one CML-CP patient, pleural effusion led to study discontinuation. Among the 12 CML-AP patients, eight experienced at least one event of pleural effusion and were still under treatment at the 4-year follow-up.

Pulmonary hypertension was reported in 6.8% (4/59)

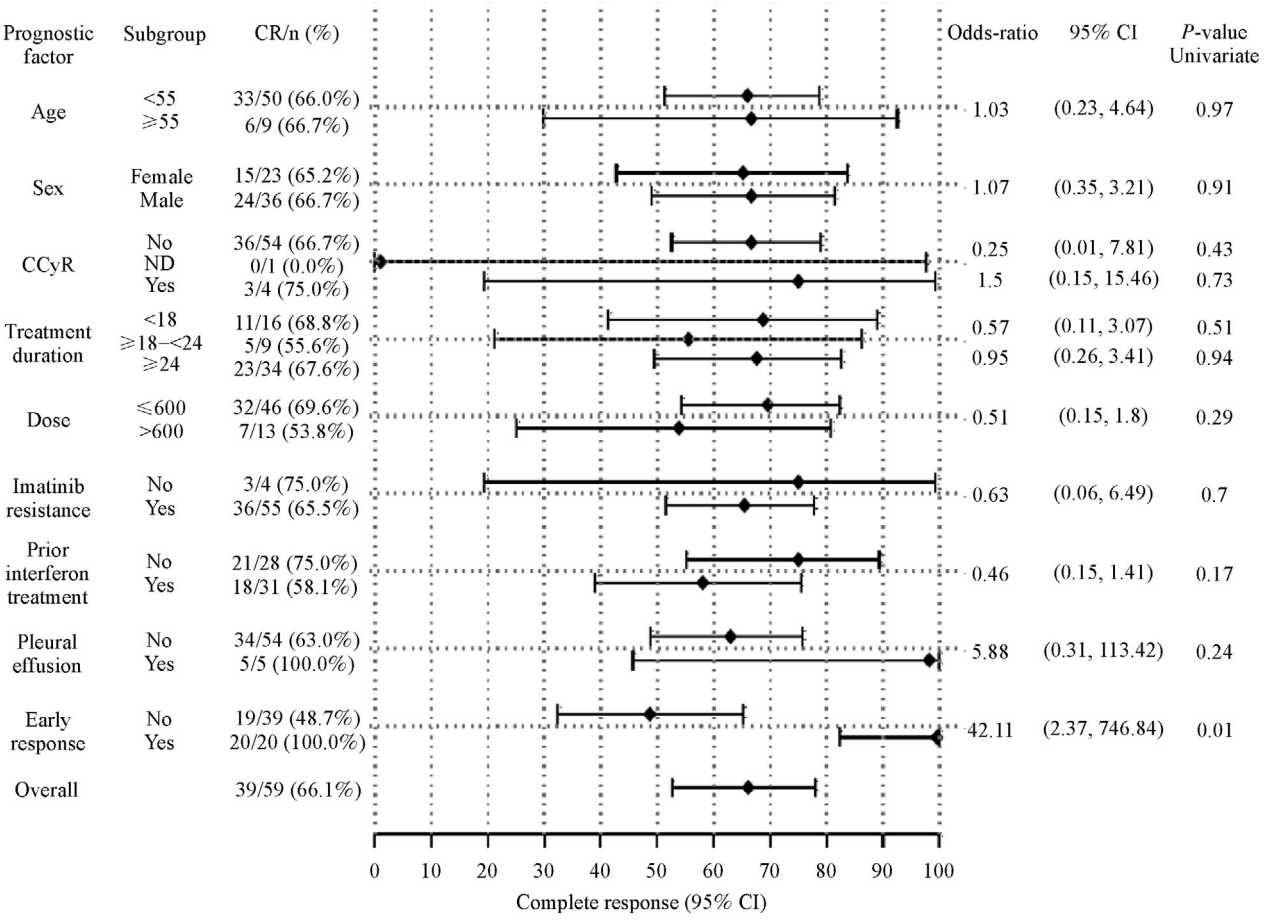

Fig. 2 Univariate logistic regression subgroup analysis of the relationship between baseline factors and complete cytogenetic response after 4 years of follow-up. Odds ratios were calculated using the lower subgroup odds of complete response in the denominator. CI, confidence interval.

and 8.0% (2/25) of patients with CML-CP and CML-AP, respectively. For one patient, pulmonary hypertension was resolved once but recurred and led to the patient's disqualification from the study. For the other five patients, pulmonary hypertension was resolved in three patients with symptomatic treatment (one patient experienced dasatinib interruption and symptomatic treatment), but the other two patients discontinued participation in the study. Pulmonary hypertension in the present study is diagnosed by echocardiography, and none of the patients underwent right heart catheterization to confirm the diagnosis.

The most common cardiovascular AE reported in all patients was pericardial effusion, which occurred in 3.4% and 12.0% of the patients with CML-CP and CML-AP, respectively. No ischemic cardiovascular events were reported for the CML-CP patients after a median of 50.1 months of follow-up.

Discussion

Several large clinical studies as well as real-world data, mostly from Western countries, have shown dasatinib to be an effective and tolerable first- or second-line treatment option for CML. The long-term follow-up data from the present study reflect the findings from global studies of dasatinib [5–11] and continue to support dasatinib as second-line treatment for Chinese patients with CML. The 4-year follow-up data presented in this report show that dasatinib induced a durable MCyR in 66.1% of the CML-CP, and CHR in 64% of the CML-AP patients resistant or intolerant to imatinib.

Imatinib was the first TKI that became available for the treatment of CML and, currently, imatinib is widely prescribed as first-line therapy for patients with CML-CP [1]. A large body of evidence shows that imatinib can induce a lasting response in CML-CP [1]. However,

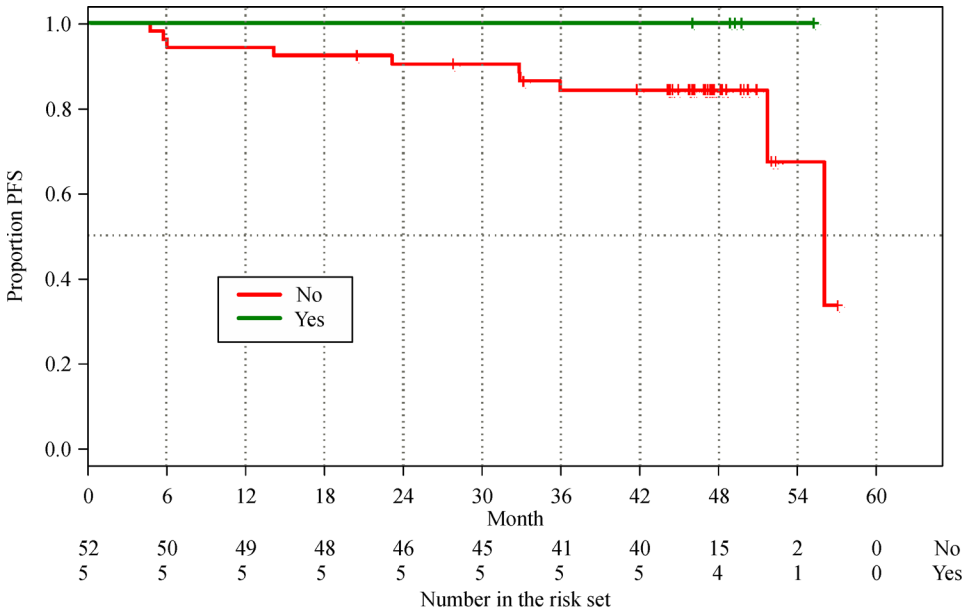

Fig. 3 Kaplan–Meier progression-free survival curve by early response (MCyR within 90 days of treatment initiation; green line) or no early response (red line). MCyR, major cytogenetic response.

Table 5 Cumulative incidence of pleural effusion at 6 months, 18 months and 48 months follow-up

% (*n*/*n*)	6 months follow-up	18 months follow-up	48 months follow-up
CML-CP	13.6 (8/59)	15.3 (9/59)	23.7 (14/59)
CML-AP	20.0 (5/25)	20.0 (5/25)	40.0 (10/25)

CML-AP, chronic myeloid leukemia in accelerated phase; CML-CP, chronic myeloid leukemia in chronic phase.

approximately one-third of patients develops resistance to, or do not tolerate imatinib therapy [1]. Dasatinib is an oral dual TKI active against the ABL1 and SRC family of kinases with the capability to bind to the active and inactive conformations of ABL1 kinase domain (different from imatinib, which binds only to the inactive conformation of ABL). After evaluation in several phase-2 and-3 studies, dasatinib was shown to be an effective second-line therapy in imatinib-resistant or-intolerant patients. However, long-term follow-up data of dasatinib as a second-line treatment in Asian patients with CML are limited.

In the present study, the majority of the patients are imatinib-resistant rather than imatinib-intolerant at the time of enrollment. At 4-year follow-up, 72.9% of the CML-CP patients remained under treatment, and all patients, who achieved MCyR (39/59 patients; 66.1%) in 4 years, also achieved CCyR. Our data in Chinese patients are similar to those reported in a phase-3 study in Western patients with CML, which obtained an MCyR rate of 63.0% (106/167) in CML-CP patients treated with 100 mg dasatinib once daily [8]. Importantly, the high PFS rates reported in the Chinese patients in this study in the earlier follow-up period were sustained; at 2, 3, and 4 years, the PFS rate was 91.2%, 85.7%, and 85.7%, respectively.

Among the CML-AP patients treated with dasatinib, the cumulative CHR rate increased from 52% to 64% between the 18-month and 4-year follow-up. This result supports studies on dasatinib in Western CML patients; these studies reported similar CHR rates after 1 year of treatment; 52% [10] and 45% [9] after 15 and 14 months of treatment, respectively. At 18 months, 40% of the CML-AP patients achieved MCyR, and at 4 years, the MCyR rate remained unchanged. Similar rates of MCyR were reported by previous studies [9,11].

Methods to identify patients that are likely to benefit from a switch to second-generation TKIs after failing imatinib are not well established. A scoring system based on the cytogenetic response to imatinib, a patient's Sokal score, and recurrent neutropenia during imatinib treatment was developed to predict the probability of CML patients in achieving CCyR when treated with a second-generation TKI [12]. Prior to treatment initiation, the response to treatment can be predicted relatively accurately by certain factors, which were included in the scoring system. However, we were not able to validate the scoring system in the present study because of insufficient baseline information. Furthermore, in a logistic regression analysis we cannot identify any baseline characteristics that predicted treatment response. However, this may be because of the limited number of patients in our study.

Nonetheless, the achievement of an early response to treatment is predictive of better PFS and OS, irrespective

of the selected TKI or the treatment line (first or second) [6,8,12,13]. Furthermore, the BCR-ABL1 of $\leqslant$ 10% and/or Ph^+ of $<$ 65% were also identified as 3-month optimal response criteria by the European Leukemia Net guideline [12]. Our *post-hoc* univariate logistic regression analysis showed that achieving MCyR by the CML-CP patients within 90 days after treatment initiation is a positive predictor of long-term treatment outcome; none of the 20 patients, who achieved MCyR within 90 days, experienced disease progression at 4 years of follow-up. These findings strongly suggest close and early follow-up strategies for patients receiving second-line treatment. Moreover, patients, who do not achieve an optimal early treatment response, should undergo benefit/risk evaluation between TKIs and allogeneic hematopoietic stem cell transplantation.

Overall, dasatinib was effectively tolerated, with a low rate of discontinuation and a safety profile that supports previous data from large phase-3 clinical trials [5,9,11]. No new safety signals were observed. The risk of pleural effusion is associated with several TKIs currently indicated for CML (imatinib, dasatinib, and nilotinib), but is most commonly observed with dasatinib. The reported rate of pleural effusion is approximately 20%–28%, and grade 3–4 pleural effusion varied between 3% and 7% [6,11–16]. In a Korean study (48% CML-CP, 35% CML-AP, 17% CML-BP), 54% (35/65) patients developed pleural effusion with only 1% (1/72) episode considered as grade 3 [17]. The annual incidence of first pleural effusions, following initiation of dasatinib therapy is highest in the first 2 years of treatment; however, a small number of new first events have been reported as late as 7 years after treatment initiation [16]. In Korean patients, 38% pleural effusion episodes occurred in the first year and 18% in the second year [17]. Data from global studies also showed that pleural effusion may be more common in patients with advanced disease; these observations were confirmed in the present study [2,17,18]. In our study, grade 3–4 pleural effusion was relatively rare and only one patient discontinued dasatinib because of an SAE of pleural effusion. Previous data indicated that patients older than 60 years were more likely to experience fluid retention events, and these patients should also be monitored closely [18]. Our patients were relatively young (42.8 $\pm$ 11.3 years for the CML-CP group and 39.5 $\pm$ 10.5 years for the CML-AP group), probably contributing to the low incidence of grade 3–4 pleural effusion.

Dasatinib-treated CML and Ph^+ ALL patients, who develop pleural effusions, were reported to have elevated T/NK (natural killer) lymphocytes in their pleural fluid [19], and an oscillating large granule lymphocytosis was observed; this finding has not been noted with other TKIs [18–21]. Lymphocytosis (total or large granule lymphocytes) has been found to occur and persist in patients, who receive dasatinib treatment, with all phases of CML. Its presence was associated with the development of pleural effusion, a higher response rate, longer response duration, and improved survival, thereby suggesting that this condition may be attributable to an immunomodulatory effect [18–21].

Lymphocytosis or immunophenotyping was not assessed in this study; however, pleural effusion data in our CML-CP patients correlated well with a better response rate, which has been reported previously [18–21]. Twelve of the 14 CML-CP patients, who had at least one pleural effusion event, achieved CCyR as compared with 26 of the 45 CML-CP patients in the non-pleural effusion group ($P < 0.01$).

The present study has some limitations, including a relatively small number of patients and the lack of routine follow-up once patients had left the study. In addition, interpretation of our findings at a molecular level was limited, because the study was not designed to determine the occurrence and impact of *BCR-ABL1* mutations on dasatinib therapy or assess the *BCR-ABL1* transcript level at baseline and during the study. Moreover, molecular responses were not included in the end-point analysis. At the time the study was designed, no detailed molecular understanding was provided, thereby leading to the establishment of internationally recognized standard for *BCR-ABL1* testing. The quantitative real-time polymerase chain reaction (qRT-PCR) is the only tool that can monitor responses after CCyR has been achieved, and the use of the International Scale is preferred to standardize molecular monitoring with qRT-PCR [2]. An increase in *BCR-ABL1* transcripts may be associated with increased detection of *BCR-ABL1* mutations and cytogenetic relapse [2], and the NCCN guideline recommends evaluation of the *BCR-ABL1* domain mutation status in the selection of subsequent TKI therapy for patients with an inadequate initial response to first- or second-line TKI therapy [2].

In summary, during the 4-year follow-up, dasatinib treatment demonstrated durable efficacy and a tolerable long-term safety profile as second-line treatment in Chinese CML patients, who are imatinib-resistant or -intolerant.

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Compliance with ethics guidelines

Xiaojun Huang, Qian Jiang, Jianda Hu, Jianyong Li, Jie Jin, Fanyi Meng, Zhixiang Shen, Ting Liu, Depei Wu, Jianmin Wang, and

Jianxiang Wang declare that they have no conflict of interest. All study procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000. Informed consent was obtained from all patients before inclusion in the study.

References

1. de Lavallade H, Apperley JF, Khorashad JS, Milojkovic D, Reid AG, Bua M, Szydlo R, Olavarria E, Kaeda J, Goldman JM, Marin D. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. J Clin Oncol 2008; 26(20): 3358–3363
2. NCCN Clinical Practice Guidelines in Oncology(NCCN Guidelines®). Chronic Myeloid Leukemia. Version 1. 2018
3. Bristol-Myers Squibb company. Sprycel (dasatinib) prescribing information. Princeton, NJ: Bristol-Myers Squibb company, 2017
4. Huang XJ, Hu JD, Li JY, Jin J, Meng FY, Shen ZX, Liu T, Wu DP, Wang JM, Wang JX. Study on efficiency and safety of dasatinib in Chinese patients with chronic myelogenous leukemia who are resistant or intolerant to imatinib. Chin J Hematol (Zhonghua Xue Ye Xue Za Zhi) 2012; 33(11): 889–895 (in Chinese)
5. Jabbour E, Kantarjian HM, Saglio G, Steegmann JL, Shah NP, Boqué C, Chuah C, Pavlovsky C, Mayer J, Cortes J, Baccarani M, Kim DW, Bradley-Garelik MB, Mohamed H, Wildgust M, Hochhaus A. Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). Blood 2014; 123(4): 494–500
6. Shah NP, Guilhot F, Cortes JE, Schiffer CA, le Coutre P, Brümmendorf TH, Kantarjian HM, Hochhaus A, Rousselot P, Mohamed H, Healey D, Cunningham M, Saglio G. Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: follow-up of a phase 3 study. Blood 2014; 123(15): 2317–2324
7. Shah NP, Kantarjian HM, Kim DW, Réa D, Dorlhiac-Llacer PE, Milone JH, Vela-Ojeda J, Silver RT, Khoury HJ, Charbonnier A, Khoroshko N, Paquette RL, Deininger M, Collins RH, Otero I, Hughes T, Bleickardt E, Strauss L, Francis S, Hochhaus A. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and-intolerant chronic-phase chronic myeloid leukemia. J Clin Oncol 2008; 26(19): 3204–3212
8. Shah NP, Kim DW, Kantarjian H, Rousselot P, Llacer PE, Enrico A, Vela-Ojeda J, Silver RT, Khoury HJ, Müller MC, Lambert A, Matloub Y, Hochhaus A. Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. Haematologica 2010; 95(2): 232–240
9. Apperley JF, Cortes JE, Kim DW, Roy L, Roboz GJ, Rosti G, Bullorsky EO, Abruzzese E, Hochhaus A, Heim D, de Souza CA, Larson RA, Lipton JH, Khoury HJ, Kim HJ, Sillaber C, Hughes TP, Erben P, Van Tornout J, Stone RM. Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: the START a trial. J Clin Oncol 2009; 27(21): 3472–3479
10. Hanfstein B, Müller MC, Hehlmann R, Erben P, Lauseker M, Fabarius A, Schnittger S, Haferlach C, Göhring G, Proetel U, Kolb HJ, Krause SW, Hofmann WK, Schubert J, Einsele H, Dengler J, Hänel M, Falge C, Kanz L, Neubauer A, Kneba M, Stegelmann F, Pfreundschuh M, Waller CF, Branford S, Hughes TP, Spiekermann K, Baerlocher GM, Pfirrmann M, Hasford J, Saußele S, Hochhaus A; SAKK; German CML Study Group. Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). Leukemia 2012; 26(9): 2096–2102
11. Kantarjian H, Cortes J, Kim DW, Dorlhiac-Llacer P, Pasquini R, DiPersio J, Müller MC, Radich JP, Khoury HJ, Khoroshko N, Bradley-Garelik MB, Zhu C, Tallman MS. Phase 3 study of dasatinib 140 mg once daily versus 70 mg twice daily in patients with chronic myeloid leukemia in accelerated phase resistant or intolerant to imatinib: 15-month median follow-up. Blood 2009; 113 (25): 6322–6329
12. Milojkovic D, Nicholson E, Apperley JF, Holyoake TL, Shepherd P, Drummond MW, Szydlo R, Bua M, Foroni L, Reid A, Khorashad JS, de Lavallade H, Rezvani K, Paliompeis C, Goldman JM, Marin D. Early prediction of success or failure of treatment with second-generation tyrosine kinase inhibitors in patients with chronic myeloid leukemia. Haematologica 2010; 95(2): 224–231
13. Marin D, Hedgley C, Clark RE, Apperley J, Foroni L, Milojkovic D, Pocock C, Goldman JM, O'Brien S. Predictive value of early molecular response in patients with chronic myeloid leukemia treated with first-line dasatinib. Blood 2012; 120(2): 291–294
14. Cortes JE, Saglio G, Kantarjian HM, Baccarani M, Mayer J, Boqué C, Shah NP, Chuah C, Casanova L, Bradley-Garelik B, Manos G, Hochhaus A. Final 5-year study results of DASISION: the dasatinib versus imatinib study in treatment-naïve chronic myeloid leukemia patients trial. J Clin Oncol 2016; 34(20): 2333–2340
15. Saglio G, Hochhaus A, Goh YT, Masszi T, Pasquini R, Maloisel F, Erben P, Cortes J, Paquette R, Bradley-Garelik MB, Zhu C, Dombret H. Dasatinib in imatinib-resistant or imatinib-intolerant chronic myeloid leukemia in blast phase after 2 years of follow-up in a phase 3 study: efficacy and tolerability of 140 milligrams once daily and 70 milligrams twice daily. Cancer 2010; 116(16): 3852–3861
16. Shah NP, Rousselot P, Schiffer C, Rea D, Cortes JE, Milone J, Mohamed H, Healey D, Kantarjian H, Hochhaus A, Saglio G. Dasatinib in imatinib-resistant or-intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034. Am J Hematol 2016; 91(9): 869–874
17. Kim D, Goh HG, Kim SH, Cho BS, Kim DW. Long-term pattern of pleural effusion from chronic myeloid leukemia patients in second-line dasatinib therapy. Int J Hematol 2011; 94(4): 361–371
18. Steegmann JL, Baccarani M, Breccia M, Casado LF, García-Gutiérrez V, Hochhaus A, Kim DW, Kim TD, Khoury HJ, Le Coutre P, Mayer J, Milojkovic D, Porkka K, Rea D, Rosti G, Saussele S, Hehlmann R, Clark RE. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia 2016; 30(8): 1648–1671
19. Schiffer CA, Cortes JE, Hochhaus A, Saglio G, le Coutre P, Porkka

K, Mustjoki S, Mohamed H, Shah NP. Lymphocytosis after treatment with dasatinib in chronic myeloid leukemia: Effects on response and toxicity. Cancer 2016; 122(9): 1398–1407

20. Paydas S. Dasatinib, large granular lymphocytosis, and pleural effusion: useful or adverse effect? Crit Rev Oncol Hematol 2014; 89 (2): 242–247

21. Eskazan AE, Eyice D, Kurt EA, Elverdi T, Yalniz FF, Salihoglu A, Ar MC, Ongoren Aydin S, Baslar Z, Ferhanoglu B, Aydin Y, Tuzuner N, Ozbek U, Soysal T. Chronic myeloid leukemia patients who develop grade I/II pleural effusion under second-line dasatinib have better responses and outcomes than patients without pleural effusion. Leuk Res 2014; 38(7): 781–787