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Phase III Clinical Trial (RERISE study) Results of Efficacy and Safety of Radotinib Compared with Imatinib in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia

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Abstract

Purpose: Radotinib is a second-generation BCR-ABL1 tyrosine kinase inhibitor (TKI) approved in Korea for chronic phase chronic myeloid leukemia (CML-CP) in patients newly diagnosed or with insufficient response to other TKIs. This study was conducted to evaluate the efficacy and safety of radotinib as first-line therapy for CML-CP.

Experimental Design: This multinational, open-label study assigned patients (1:1:1) to one of two twice-daily radotinib doses, or imatinib daily. The primary endpoint was major molecular response (MMR) by 12 months.

Results: Two hundred forty-one patients were randomized to receive radotinib 300 mg ($n = 79$) or 400 mg twice-daily ($n = 81$), or imatinib 400 mg daily ($n = 81$). MMR rates by 12 months were higher in patients receiving radotinib 300 mg (52%) or radotinib 400 mg twice-daily (46%) versus imatinib (30%; $P = 0.0044$ and $P = 0.0342$, respectively). Complete cytogenetic response (CCyR) rates by 12 months were higher for radotinib 300 mg (91%) versus imatinib (77%; $P = 0.0120$). Early molecular response at 3 months occurred in 86% and 87% of patients receiving radotinib 300 mg and radotinib 400 mg, respectively, and 71% of those receiving imatinib. By 12 months, no patients had progression to accelerated phase or blast crisis. Most adverse events were manageable with dose reduction.

Conclusions: Radotinib demonstrated superiority over imatinib in CCyR and MMR in patients newly diagnosed with Philadelphia chromosome–positive CML-CP. This trial was registered at www.clinicaltrials.gov as NCT01511289. *Clin Cancer Res; 23(23); 7180–8. ©2017 AACR.*

Introduction

Chronic myeloid leukemia (CML) is usually characterized by the presence of the Philadelphia chromosome (Ph+), which forms as the result of a reciprocal translocation between chromosomes 9 and 22, leading to production of the BCR–ABL1 fusion protein (1–3). Imatinib, nilotinib, and dasatinib [BCR–ABL1 tyrosine kinase inhibitors (TKI)], have greatly improved outcomes for patients with Ph+ chronic phase CML (CML-CP) and are currently recommended for first-line use (4, 5). Early molecular response (EMR; defined as a *BCR–ABL1* transcript level $\leq$ 10% at

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Translational Relevance

TKI therapy targeting the BCR–ABL1 fusion protein has greatly improved outcomes for patients with chronic myelogenous leukemia, but therapy is indefinite and the costs of first- and second-generation TKIs are high. Radotinib is a second-generation BCR–ABL-targeted TKI, currently marketed in Korea. In this study, we demonstrate statistically superior rates of complete cytogenetic response (CCyR) and major molecular response (MMR) with radotinib 300 mg twice-daily compared with imatinib 400 mg daily. Adverse reactions to radotinib were manageable with dose reductions; however, poorer efficacy and tolerability with the higher dose of radotinib (400 mg twice-daily) highlight the need to consider body size and the potential for weight-based dosing of TKIs, particularly in Asian populations. Cost-effective solutions and alternative pricing models are required for equitable access to innovative therapies, particularly in resource-limited practice settings.

3 months; ref. 4) has been linked to deeper molecular responses and long-term survival outcomes with prognostic significance (6, 7). The quantification of molecular and cytogenetic responses at 3 months allows for prognostic stratification of patients' risk (8–10), and may affect treatment decisions. Because TKI therapy continues throughout patients' lives, it is important to ensure that the selected treatment is effective, and has minimal and manageable toxicities. Radotinib is a novel, selective oral BCR–ABL1 TKI with a mutant sensitivity profile similar to nilotinib (11, 12).

In a phase II trial, radotinib was effective and well tolerated in patients with CML-CP that did not respond to previous TKIs (11). A total of 77 patients received radotinib 400 mg twice daily. Major cytogenetic response was achieved in 65% of patients, including 47% with complete cytogenetic response (CCyR) by 12 months. Overall survival (OS) and progression-free survival (PFS) rates at 12 months were 96% and 86%, respectively. Grade 3 or 4 adverse events (AE) included thrombocytopenia (25%), hyperbilirubinemia (23%), anemia (5%), fatigue (4%), asthenia (4%), and nausea (3%); most were managed with dose modification. On the basis of those findings, radotinib was initially approved in Korea for patients with CML-CP that did not respond to previous TKI therapy; in 2015, it was approved for first-line use.

To explore the benefit of radotinib in newly diagnosed CML-CP, here, we report data from a phase III study that was the basis for first-line approval, which compared two radotinib doses (twice daily) and one imatinib daily dose (daily).

Patients and Methods

Participants

Key eligibility criteria included patients age of $\geq$18 years with an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, who were diagnosed with Ph+ CML-CP $\leq$ 3 months before enrollment, and had adequate organ function. Exclusion criteria included a diagnosis of Ph- CML, use of imatinib for $\geq$8 days before study entry, use of targeted anticancer therapy (except hydroxyurea and/or anagrelide), impaired cardiac function, and confirmed central nervous system involvement.

Study design

This study was an open-label, phase III clinical trial conducted at 24 sites in Korea, Thailand, Philippines, and Indonesia. The accrual period was between August 2011 and February 2014. The study protocol and its amendments were approved by an Institutional Review Board at each site, and the trial was conducted in accordance with the protocol and with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent.

Patients were randomized sequentially using a scheme generated by a Statistical Analysis System (SAS) v9.2 randomization program and an Interactive Web Response System. Investigational products were taken according to a generated randomization code. All eligible patients were stratified by Sokal risk score (low [L], relative risk < 0.8; intermediate [M], 0.8 to 1.2; high [H], relative risk > 1.2), and balance between the groups was maintained using an independent stratified block randomization at a ratio of 1:1:1. Patients were assigned to one of three treatment groups: radotinib 300 mg twice daily, radotinib 400 mg twice daily, or imatinib 400 mg daily. The two radotinib dose regimens of 300 mg twice daily and 400 mg twice daily were selected to decrease the risk of adverse events while maintaining sufficient efficacy based on the phase II study (11).

The treatment was administered for 12 months; patients who benefited from radotinib or imatinib could receive an extension for long-term efficacy and safety of up to 3 years of additional radotinib or imatinib treatment. One or two dose reductions were allowed in the radotinib group if required because of toxicity. The minimal doses allowed were 200 mg twice daily for radotinib and 300 mg daily for imatinib. Dose escalation was not allowed in any group.

Study assessments

Efficacy assessments. The primary endpoint was the rate of major molecular response (MMR) by 12 months as defined by *BCR-ABL1/ABL1* ratio $\leq$ 0.1% by the international scale. Secondary endpoints included CCyR, deep molecular response (DMR), disease progression, OS, PFS, and the rate of point mutation by 12 months. CCyR was defined as zero Ph+ in $\geq$ 20 metaphases (no fluorescence in situ hybridization allowed). DMR was defined as $\geq$4.5 log ($MR^{4.5}$) reduction in *BCR–ABL1* transcript levels from standardized baseline or *BCR–ABL1/ABL1* ratio $\leq$ 0.0032% by the international scale. *BCR–ABL1/ABL1* levels were measured at screening and every 3 months during treatment by internationally standardized real-time quantitative polymerase chain reaction assay in a central laboratory. *BCR–ABL1* mutation was assessed by Sanger sequencing performed at 12 months and at study discontinuation. Disease progression was defined as progression to accelerated or blast phases. OS and PFS included data from the extension study.

Cytogenetic and molecular assessments and mutation analysis used peripheral blood samples (hematologic and molecular response), bone marrow aspiration, and/or biopsy (hematologic response, cytogenetic response).

Safety assessments

All observed AEs were recorded, including information on their severity and presumed relationship to study treatment. Vital signs, physical examination, laboratory tests, and electrocardiograms were performed according to a predetermined schedule. Toxicities

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were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Statistical analysis

Primary and secondary analysis populations included the intention-to-treat (ITT) population, defined as all patients who received ≥1 dose of study medication. Efficacy variables (MMR by and at 12 months; CCyR and DMR rates by 12 months; and disease progression) were summarized using descriptive statistics, including response rates with 95% confidence intervals (CI) by normal approximation method and Kaplan–Meier curves. MMR rates by 12 months were compared using the Cochran–Mantel–Haenszel (CMH) test, with study participants stratified by Sokal risk group; statistical analysis results were interpreted according to the Hochberg's step-up method for multiple testing. Kaplan–Meier estimates of time to secondary variables were provided and analyzed by stratified log-rank test. Point mutation incidence by 12 months was calculated, and differences in incidence between each study group and control group were analyzed using a χ^2 test or Fisher exact test.

The safety analysis population was defined as all patients who received ≥1 dose of the study drug. The incidence of each AE was calculated in all groups with 95% CI. The differences in the incidence of AEs between the imatinib group and each radotinib group were analyzed by the Fisher exact test. Assessments of molecular response, cytogenetic efficacy, and overall safety of radotinib and imatinib were performed at 3, 6, 9, and 12 months.

Additional methodology is presented in the Supplementary Information Section.

Results

Patients

A total of 263 patients were screened and provided consent, and 241 patients were randomized to radotinib 300 mg ($n = 79$) or 400 mg twice daily ($n = 81$), or imatinib 400 mg daily ($n = 81$; Fig. 1). The remaining 22 patients were reported as screen failures (20 patients had inclusion/exclusion criteria violations, and two patients withdrew consent). The median age range was 43 to 45 years, and most patients were male and Asian with relatively

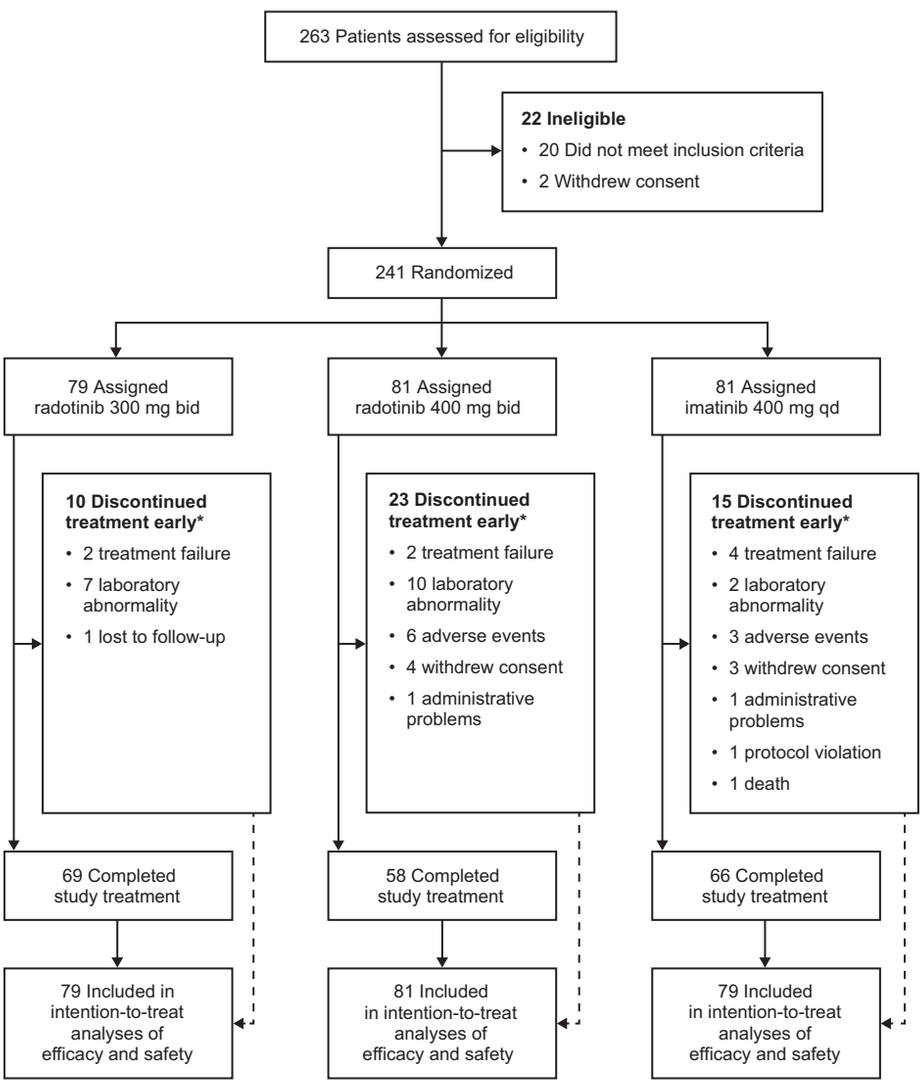

Figure 1.
CONSORT Diagram for Patient Disposition. Disposition of patients with Philadelphia chromosome–positive CML-CP in the RERISE study (NCT01511289). Patients were randomly assigned to radotinib 300 mg twice-daily (bid), radotinib 400 mg twice-daily, or imatinib 400 mg daily (qd). Reasons for patients discontinuing therapy are indicated.

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Table 1. Patient characteristics and disposition

	Radotinib 300 mg bid (*n* = 79) *N* (%)	Radotinib 400 mg bid (*n* = 81) *N* (%)	Imatinib 400 mg qd (*n* = 81) *N* (%)
Age, years			
Median	45	43	45
Range	20–75	18–84	18–83
Sex			
Male	52 (66)	47 (58)	50 (64)
Female	27 (34)	34 (42)	31 (36)
Weight, kg			
Median	61	60	62
Range	43–100	40–96	41–96
ECOG performance status			
0	53 (67)	55 (68)	51 (63)
1	26 (33)	25 (31)	29 (36)
2	0 (0)	1 (1)	1 (1)
Additional chromosomal abnormalities	6 (8)	7 (9)	6 (7)
Sokal risk			
Low	21 (27)	22 (27)	22 (27)
Intermediate	38 (48)	38 (47)	39 (48)
High	20 (25)	21 (26)	20 (25)
Duration of CML, days			
Median	22	23	22
Range	7–102	7–66	6–71
Prior treatment			
Hydroxyurea	70 (86)	69 (87)	72 (89)
Anagrelide[a]	5 (6)	5 (6)	8 (10)
Imatinib	0 (0)	2 (2)	2 (2)
On treatment at 12 months	69 (87)	58 (72)	66 (81)
Discontinuation of treatment before 12 months	10 (13)	23 (28)	15 (19)
Treatment failure or suboptimal response[b]	2 (3)	2 (2)	4 (5)
Laboratory abnormality	7 (9)	10 (12)	2 (2)
Hematologic	4 (5)	6 (7)	2 (2)
Biochemical	3 (4)	4 (5)	0 (0)
Adverse event(s)	0 (0)	6 (7)	3 (4)
Withdrew consent	0 (0)	4 (5)	3 (4)
Others[c]	1 (1)	1 (1)	2 (2)
Death	0 (0)	0 (0)	1 (1)
Dose reduction	43 (54)	53 (65)	19 (24)

Abbreviations: bid, twice daily; ELN, European Leukemia; qd, daily.

[a]All patients who were administered anagrelide also received hydroxyurea.

[b]Treatment failure or suboptimal response was assessed according to ELN 2009 recommendation.

[c]Others include administrative problems (radotinib 400 mg, *n* = 1; imatinib, *n* = 1), lost to follow-up (radotinib 300 mg, *n* = 1), and protocol violations (imatinib, *n* = 1).

small body size. Patients with high, intermediate, or low Sokal risk represented approximately 25%, 50%, and 25% of patients, respectively. The median duration of CML before treatment was 22 days. Baseline characteristics were balanced across treatment groups (Table 1).

Treatment and patient disposition

By 12 months, the proportion of patients remaining on treatment was similar in the radotinib 300 mg twice-daily and imatinib 400 mg daily groups [69 (87%) patients and 66 (81%) patients, respectively], in contrast with the radotinib 400 mg twice-daily group [58 (72%) patients]. The most common reason for treatment discontinuation in the radotinib groups was laboratory abnormality; treatment failure or suboptimal response was the most common reason for discontinuation in the imatinib group (Table 1).

The median dose intensity was 509 mg/day for radotinib 300 mg twice daily, 621 mg/day for radotinib 400 mg twice-daily, and 392 mg/day in the imatinib 400 mg daily group. Dose adjustment or study drug interruption, regardless of reason, occurred in 53 (67%), 59 (73%), and 42 (52%) of patients in the radotinib 300 mg twice-daily, radotinib 400 mg twice-daily, and imatinib groups, respectively.

Efficacy

By 12 months, MMR rates were significantly higher in patients receiving radotinib 300 mg twice daily (52%; 95% CI, 41%–63%; $P = 0.0044$ vs. imatinib) and radotinib 400 mg twice daily (46%; 95% CI, 35%–67%; $P = 0.0342$ vs. imatinib) compared with imatinib 400 mg daily (30%; 95% CI, 20%–40%; Fig. 2). The CCyR rate by 12 months was also significantly higher for radotinib 300 mg twice daily (91%) versus imatinib (77%; $P = 0.0120$). The difference between radotinib 400 mg twice daily (82%) and imatinib was not significant (Fig. 2). Optimal molecular responses at landmark time points 3, 6, and 12 months were significantly higher in both radotinib groups (Table 2). The median time (months) to MMR among responders was faster for radotinib 300 mg (5.7) and 400 mg twice daily (5.6) versus imatinib (8.2). $MR^{4.5}$ rates by 12 months were higher for both radotinib 300 mg (15%) and 400 mg twice daily (14%) compared

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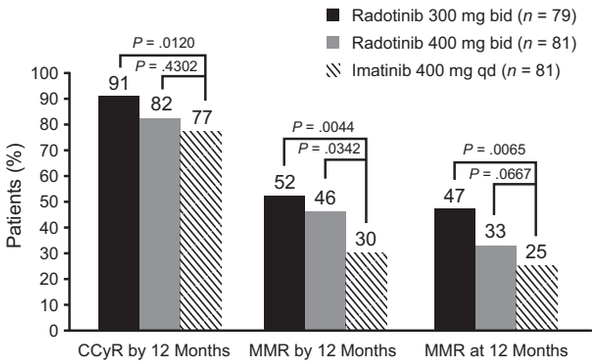

Figure 2.

Cytogenetic and molecular response at and by 12 months by treatment group. The results in the intention-to-treat population were calculated by means of the Cochran–Mantel–Haenszel test, stratified by Sokal risk score. Primary endpoint is MMR (defined as *BCR–ABL1/ABL1* ratio $\leq$0.1%; $MR^{3.0}$) by 12 months. Secondary endpoints are CCyR (defined as 0% Ph+ in $\geq$20 metaphases) by 12 months, and MMR at 12 months. Abbreviations: bid, twice daily; CCyR, complete cytogenetic response; MMR, major molecular response; Ph, Philadelphia (chromosome); qd, daily.

with imatinib (9%): differences did not reach statistical significance ($P = 0.2012$ and $P = 0.3274$ for radotinib 300 mg and 400 mg twice daily versus imatinib, respectively).

EMR rates at 3 months were assessed in 236 patients with available data. EMR was observed in 86% ($P = 0.0111$ vs. imatinib) of patients in the radotinib 300 mg and 87% ($P = 0.0206$ vs. imatinib) in the radotinib 400 mg twice-daily group, and 71% in the imatinib group. More patients treated with radotinib who had EMR at 3 months achieved CCyR and MMR by 12 months: 94% and 57% in the radotinib 300 mg twice-daily group, 89% and 51% in the radotinib 400 mg twice-daily group, and 86% and 38% in the imatinib group, respectively (Supplementary Fig. S1). MMR rates did not vary markedly by Sokal score within the radotinib 300 mg twice-daily group, and a lower MMR rate correlated with higher Sokal scores (intermediate and high risks) in imatinib patients (Supplementary Fig. S2).

There was no progression to accelerated or blast phase in any group by 12 months. At data cutoff (March 17, 2015; median, 362 days), OS and PFS rates were both 100% for radotinib 300 mg twice-daily, 80% and 81% for radotinib 400 mg twice-daily, and both 99% in the imatinib group, respectively (Supplementary Fig. S3). One patient treated with imatinib died at 8.4 months because of pneumonia during treatment. Three deaths occurred among patients receiving radotinib 400 mg twice daily. One patient discontinued treatment due to adverse events at 3 months and died at 5.5 months from an unknown cause. Two patients died due to disease progression after 12 months: one patient died 27.3 months after discontinuation due to adverse events at 7.2 months, and one patient died 1.1 months after discontinuation by disease progression at 17.4 months.

Two patients (3%) in the radotinib 400 mg twice-daily group had a response but had *BCR–ABL1* mutations (T315I, PCyR, and Y253H, CCyR). One patient receiving radotinib 300 mg twice-daily (1%) also achieved CCyR, but developed a T315I mutation by 12 months. Nevertheless, none of these patients progressed to accelerated or blast phase. No patients in the imatinib group had mutations.

Safety

All 241 patients were treated with $\geq$1 dose of the study drug, had $\geq$1 post-baseline safety assessment, and were included in the safety analysis population. AEs of any grade were reported in 78 (99%) patients receiving radotinib 300 mg twice daily, 78 (96%) patients receiving radotinib 400 mg twice daily, and 80 (99%) patients receiving imatinib 400 mg daily; treatment-related AEs were observed in 94%, 91%, and 93% of patients, respectively.

The most frequently reported hematologic abnormalities (all grades) were thrombocytopenia and neutropenia (67% and 41%, 53% and 36%, and 68% and 63% in the radotinib 300 mg twice daily, radotinib 400 mg twice daily, and imatinib groups, respectively). Grade 3 or 4 thrombocytopenia and neutropenia occurred in 16% and 19% of patients receiving radotinib 300 mg twice daily, 14% and 24% receiving radotinib 400 mg twice daily, and 20% and 30% receiving imatinib, respectively (Fig. 3 and Table 3). The most frequent biochemical abnormalities (all grades) in the radotinib groups were hyperbilirubinemia and alanine transaminase/aspartate transaminase (ALT/AST) elevation; hypophosphatemia and lipase elevation were most frequent in the imatinib group. Grade 3 or 4 hyperbilirubinemia occurred in 27% and 42%, respectively, of patients in the radotinib 300 and 400 mg twice-daily groups (Supplementary Table S1), primarily due to an increase in direct bilirubin. Most cases of hyperbilirubinemia occurred within 4 months (range, 0.2 to 11 months) and were reversible by dose reduction or transient interruption; 3 patients discontinued treatment because of hyperbilirubinemia in the radotinib 400 mg twice-daily group. Frequency of grade 3 or 4 elevations in ALT and AST, respectively, was 20% and 6% for radotinib 300 mg twice daily, 26% and 6% with radotinib 400 mg

Table 2. Molecular and cytogenetic response rate[a] at landmark time point

	Radotinib 300 mg bid ($n = 79$)				Radotinib 400 mg bid ($n = 81$)				Imatinib 400 mg qd ($n = 81$)			
	3 mo *N* (%)	6 mo *N* (%)	9 mo *N* (%)	12 mo *N* (%)	3 mo *N* (%)	6 mo *N* (%)	9 mo. *N* (%)	12 mo. *N* (%)	3 mo. *N* (%)	6 mo. *N* (%)	9 mo. *N* (%)	12 mo. *N* (%)
Major and complete molecular response												
Evaluable, n	79	75	72	69	79	70	60	57[b]	78	73	68	66
MMR	4 (5)	25 (33)	30 (42)	37 (54)	8 (10)	18 (26)	24 (40)	27 (47)	1 (1)	11 (15)	15 (22)	20 (30)
DMR	0 (0)	9 (12)	8 (11)	11 (16)	3 (4)	3 (4)	7 (12)	7 (12)	0 (0)	0 (0)	2 (3)	6 (9)
Complete cytogenetic response												
Evaluable, *n*	79	75	71	69	79	70	60	58	78	73	69	66
CCyR	50 (63)	58 (77)	59 (83)	62 (90)	44 (56)	55 (79)	46 (77)	48 (83)	29 (37)	47 (64)	51 (74)	54 (82)

Abbreviations: bid, twice daily; mo, months; qd, once daily.

[a]Among evaluable patients who had molecular or cytogenetic data at each landmark time point.

[b]One patient completed 12 months of treatment, but molecular data were not available because blood sampling for molecular analysis was not collected at 12 months.

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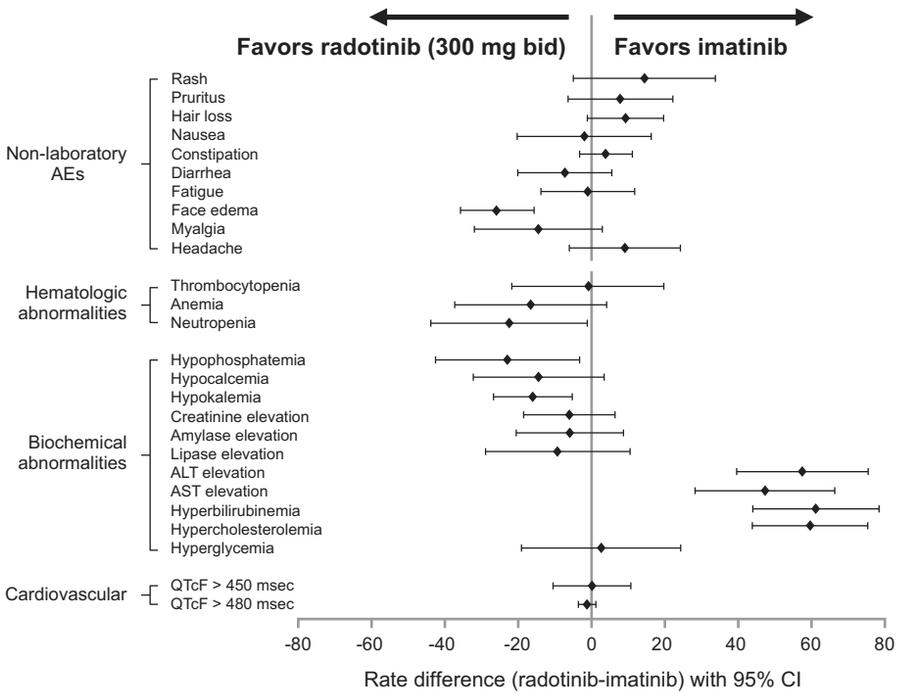

Figure 3.

AEs of interest and laboratory abnormalities: Forest plot comparing differences in rates (all grades) for radotinib 300 mg twice daily (bid) and imatinib 400 mg daily (qd). Adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0). Abbreviations: bid, twice daily; QTcF, QTc Fridericia.

twice-daily, and 1% and 1% in the imatinib group. Dose reduction or interruption due to ALT/AST elevation or hyperbilirubinemia, respectively, occurred 55% and 78% in radotinib 300 mg twice daily, 68% and 82% in radotinib 400 mg twice daily, and 19% and 73% in the imatinib groups. More than 80% of these were resolved and controlled, and severe, irreversible hepatotoxicity was not observed. Grade 3 or 4 hypophosphatemia occurred in 3% of patients receiving radotinib 300 mg twice daily, in 2% receiving radotinib 400 mg twice daily, and in 11% receiving imatinib. In addition, hypercholesterolemia and hyperglycemia (all grades) were relatively higher in radotinib 300 mg (66% and 58%, respectively) and 400 mg (70% and 72%) twice-daily groups than in the imatinib group (6% and 56%). Grade 3 or 4 hypercholesterolemia and hyperglycemia occurred in 1% and 11% in radotinib 300 mg twice daily, 0% and 11% in radotinib 400 mg twice daily, and 0% and 4% in the imatinib group (Fig. 3; Table 3).

The most common any-grade nonlaboratory AEs were skin rash (35% and 31%), nausea (22% and 22%), headache (19% and 31%), and pruritus (16% and 28%) in the radotinib 300 mg and 400 mg twice-daily groups, respectively; most common in the imatinib group were myalgia (28%), edema (25%), nausea (23%), and skin rash (21%; Fig. 3 and Table 3). Overall, grade 3 or 4 non-laboratory AEs were uncommon in all groups with frequency <5%. Patients were closely monitored for QT prolongation and changes during treatment. One patient treated with imatinib had QTcF prolongation (≥480 ms).

Discussion

MMR and CCyR are therapeutic milestones associated with better long-term outcome, and are important endpoints for CML, in which typically low mortality makes survival endpoints impractical (9, 10). In this trial, radotinib was superior to imatinib for all efficacy endpoints. Radotinib treatment resulted in a significantly higher MMR rate by 12 months relative to imatinib for both doses (52% for radotinib 300 mg twice daily, 46% for radotinib 400 mg twice daily, and 30% for imatinib). In addition, radotinib demonstrated significantly higher CCyR and faster MMR rates compared with imatinib. Radotinib 300 mg twice daily had higher MMR and CCyR rates compared with radotinib 400 mg twice daily, due to increased toxicity and dose interruption with the latter dose. Although no head-to-head studies of radotinib, nilotinib, and dasatinib are available, the CCyR and MMR rates observed in this study are generally comparable with that seen in nilotinib or dasatinib studies. MMR rates by 12 months for nilotinib 300 mg twice-daily, dasatinib 100 mg daily, and radotinib 300 mg twice daily were 55%, 46%, and 52%, in their respective studies; CCyR rates by 12 months were 80%, 77%, and 91% (13, 14). However, caution is warranted in making this observation, because radotinib was studied in an Asian population with smaller average body size. In this study, the active control imatinib group showed higher CCyR and MMR than previously reported (15, 16). As a control group, imatinib in this study achieved higher CCyR (77%) and MMR rates than previously reported (13, 14).

The EMR rate at 3 months was significantly higher in the radotinib groups compared with imatinib: 86% of patients who received radotinib 300 mg twice-daily ($P = 0.0111$ vs. imatinib) and 87% of those in the radotinib 400 mg twice-daily group ($P = 0.0206$ vs. imatinib), compared with 71% in the imatinib group. This finding may be important, as EMR at 3 months is an accepted milestone for evaluating optimal response to frontline TKI therapy (8, 9, 17). The high EMR rates observed with radotinib translated into higher MMR and CCyR rates by 12 months. Radotinib treatment was consistently effective regardless of Sokal risk score (Supplementary Fig. S2). However, imatinib demonstrated much lower MMR rates in intermediate-risk and high-risk

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Table 3. AEs occurring in ≥10% of patients, and newly occurring or worsening laboratory abnormalities

	All grade			Grade 3 or 4		
Event	Radotinib 300 mg bid ($n = 79$) No. (%)	Radotinib 400 mg bid ($n = 81$) No. (%)	Imatinib 400 mg qd ($n = 81$) No. (%)	Radotinib 300 mg bid ($n = 79$) No. (0%)	Radotinib 400 mg bid ($n = 81$) No. (%)	Imatinib 400 mg qd ($n = 81$) No. (%)
Non-laboratory adverse event[a]						
Rash	28 (35)	14 (31)	17 (21)	1 (1)	2 (2)	2 (2)
Pruritus	13 (16)	23 (28)	7 (9)	1 (1)	3 (4)	0 (0)
Hair loss	9 (11)	9 (11)	2 (2)	0 (0)	0 (0)	0 (0)
Nausea	17 (22)	18 (22)	19 (23)	3 (4)	2 (2)	1 (1)
Dyspepsia	9 (11)	11 (14)	5 (6)	0 (0)	0 (0)	0 (0)
Constipation	4 (5)	10 (12)	1 (1)	0 (0)	0 (0)	0 (0)
Diarrhea	7 (9)	4 (5)	11 (14)	1 (1)	0 (0)	1 (1)
Fatigue	12 (15)	13 (16)	8 (10)	4 (5)	2 (2)	0 (0)
Face edema	0 (0)	2 (2)	20 (25)	0 (0)	0 (0)	1 (1)
Myalgia	11 (14)	14 (17)	23 (28)	0 (0)	1 (1)	2 (2)
Headache	15 (19)	25 (31)	8 (10)	1 (1)	0 (0)	0 (0)
Hematologic abnormality						
Thrombocytopenia	53 (67)	43 (53)	55 (68)	13 (16)	11 (14)	16 (20)
Neutropenia	32 (41)	29 (36)	51 (63)	15 (19)	19 (24)	24 (30)
Anemia	22 (28)	26 (32)	36 (44)	5 (6)	8 (10)	4 (5)
Biochemical abnormality						
ALT elevation	62 (78)	66 (81)	17 (21)	16 (20)	21 (26)	1 (1)
AST elevation	53 (67)	62 (77)	16 (20)	5 (6)	5 (6)	1 (1)
Hyperbilirubinemia	61 (77)	65 (80)	13 (16)	21 (27)	34 (42)	0 (0)
Hypophosphatemia	16 (20)	17 (21)	35 (43)	2 (3)	2 (2)	9 (11)
Hypocalcemia	12 (15)	15 (19)	24 (30)	3 (4)	0 (0)	0 (0)
Hypokalemia	1 (1)	3 (4)	14 (17)	0 (0)	1 (1)	2 (2)
Creatinine elevation	3 (4)	4 (5)	10 (12)	0 (0)	0 (0)	0 (0)
Amylase elevation	8 (10)	6 (7)	13 (16)	1 (1)	0 (0)	0 (0)
Lipase elevation	19 (24)	28 (35)	27 (33)	9 (11)	6 (7)	2 (2)
Hypercholesterolemia	52 (66)	57 (70)	5 (6)	1 (1)	0 (0)	0 (0)
Hyperglycemia	46 (58)	58 (72)	45 (56)	9 (11)	9 (11)	3 (4)
QTcF						
>450 msec	5 (6)	6 (7)	5 (6)			
>480 msec	0 (0)	0 (0)	1 (1)			

NOTE: Adverse events assessed according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0).
Abbreviation: QTcF, QTc Fridericia.
[a]Regardless of causality.

groups. As some contributing factors can influence EMR (8, 18), high Sokal risk patients may be strong candidates for frontline, second-generation TKI therapies.

The safety profile of radotinib in this study was consistent with a previous phase II study (11). Most AEs were reversible and manageable with transient dose interruption or reduction. The safety profiles of radotinib and imatinib were different. Differences were seen in laboratory abnormalities; liver abnormalities occurred at a higher frequency in the radotinib groups, whereas abnormalities related to hematology parameters and minerals (e.g., hypophosphatemia, hypocalcemia, hypokalemia) were more frequent in the imatinib group. Permanent discontinuation of radotinib due to hepatobiliary abnormalities was low.

The issue of TKI toxicity in Asian populations has been an important topic of discussion. Several subpopulation analyses conducted for major clinical trials have demonstrated that Asian patients with CML-CP frequently have higher response rates to TKI therapy, but have increased toxicity when compared with non-Asian populations (15, 19–22). One of the explanations given for the high efficacy observed in the Chinese population in the ENEST China trial was the larger proportion of low-risk patients (23). However, an alternative explanation may be an increased exposure to the TKI due to smaller body size than Western patients. This highlights the need for a dosing regimen based on body size for TKIs in general, and particularly for radotinib in Asian populations, with the objective of minimizing AEs while maintaining efficacy. In a recent analysis, we obtained clinical data from a fixed radotinib dose of 300 mg twice-daily or 400 mg twice-daily phase III study in 160 Asian patients with CML (24). The radotinib dose was adjusted on the basis of patient body weight, and the probability of dose-limiting toxicity demonstrated a significant positive association. Because lower average body weight was observed in the phase III trial population than in the phase II population for a similar dosing regimen (60.4 kg vs. 65.2 kg in the 400 mg twice-daily cohort), we hypothesize that this may contribute to the increased toxicity. Our study and others may provide the framework for future dose-finding randomized clinical trials (25–28).

QT prolongation was minimal in the radotinib group, with no patients experiencing QTcF > 480 ms. A multicenter, independent assessment of outcomes in patients with CML who were treated with imatinib found a lower prevalence of cardiovascular comorbidities in Korean patients than in other ethnic groups (3.9% vs. 20.9%, $P < 0.001$; ref. 29). Other vascular events with radotinib were carefully monitored because radotinib has a similar structure to nilotinib; however, none were observed. A longer follow-up period is required to assess possible development.

In summary, most patients were able to tolerate and continue therapy with radotinib 300 mg twice daily and 400 mg twice daily; however, radotinib 300 mg twice daily was more effective and more tolerable than radotinib 400 mg twice daily. Radotinib 400 mg twice daily demonstrated numerical superiority on efficacy measures compared with imatinib, but the difference did not reach statistical significance due to the rate of early discontinuation resulting from adverse events. On the basis of the data presented here, radotinib 300 mg twice daily was approved for first-line use.

Disclosure of Potential Conflicts of Interest

S-H. Kim reports receiving speakers bureau honoraria from Dae-Woong Pharmaceutic Company. Y.R. Do reports receiving speakers bureau honoraria and reports receiving commercial research grants from Bristol-Myers Squibb and Novartis. C.W. Choi reports receiving commercial research grants from Il-Yang Pharm. D-Y. Kim reports receiving commercial research grants from Ilyang Co. and Roche. A.H. Reksodiputro reports receiving commercial research grants from Il-Yang Pharm. D-W. Kim reports receiving speakers bureau honoraria from Ilyang Co. and Novartis, is a consultant/advisory board member for Bristol-Myers Squibb, Ilyang Co., Novartis and Pfizer, and reports receiving commercial research grants from Ariad Co., Ilyang Co., Novartis and Pfizer. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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Phase III Clinical Trial (RERISE study) Results of Efficacy and Safety of Radotinib Compared with Imatinib in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia

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