

Efficacy and safety of radotinib in chronic phase chronic myeloid leukemia patients with resistance or intolerance to BCR-ABL1 tyrosine kinase inhibitors

Sung-Hyun Kim,¹ Hari Menon,² Saengsuree Jootar,³ Tapan Saikia,⁴ Jae-Yong Kwak,⁵ Sang-Kyun Sohn,⁶ Joon Seong Park,⁷ Seong Hyun Jeong,⁷ Hyeoung Joon Kim,⁸ Yeo-Kyeong Kim,⁸ Suk Joong Oh,⁹ Hawk Kim,¹⁰ Dae Young Zang,¹¹ Joo Seop Chung,¹² Ho Jin Shin,¹² Young Rok Do,¹³ Jeong-A Kim,¹⁴ Dae-Young Kim,¹⁵ Chul Won Choi,¹⁶ Sahee Park,¹⁷ Hye Lin Park,¹⁸ Gong Yeal Lee,¹⁸ Dae Jin Cho,¹⁸ Jae Soo Shin,¹⁸ and Dong-Wook Kim^{17,19}

¹Dong-A University Medical Center, Busan, South Korea; ²Tata Memorial Hospital, Parel, Mumbai, India; ³Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; ⁴Prince Aly Khan Hospital, Mazagaon, Mumbai, India; ⁵Chonbuk National University Medical School & Hospital, Jeonju, South Korea; ⁶Kyungpook National University Hospital, Daegu, South Korea; ⁷Ajou University Hospital, Suwon, South Korea; ⁸Chonnam National University, Hwasun Hospital, Hwasun, South Korea; ⁹Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea; ¹⁰Ulsan University Hospital, Ulsan, South Korea; ¹¹Hallym University Sacred Heart Hospital, Anyang, South Korea; ¹²Pusan National University Hospital, Pusan, South Korea; ¹³Dongsan Medical Center, Keimyung University, Daegu, South Korea; ¹⁴St. Vincent Hospital, The Catholic University of Korea, Suwon, South Korea; ¹⁵Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; ¹⁶Korea University, Guro Hospital, Seoul, South Korea; ¹⁷Cancer Research Institute, The Catholic University of Korea, Seoul, South Korea; ¹⁸Central Research Institute, IL-YANG Pharm. Co. Ltd., Yongin, South Korea; and ¹⁹Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea

ABSTRACT

Radotinib (IY5511HCL), a novel and selective BCR-ABL1 tyrosine kinase inhibitor, has shown pre-clinical and phase I activity and safety in chronic myeloid leukemia. This phase II study investigated the efficacy and safety of radotinib in Philadelphia chromosome-positive chronic phase-chronic myeloid leukemia patients with resistance and/or intolerance to BCR-ABL1 tyrosine kinase inhibitors. Patients received radotinib 400 mg twice daily for 12 cycles based on results from the phase I trial. The primary end point was rate of major cytogenetic response by 12 months. A total of 77 patients were enrolled. Major cytogenetic response was achieved in 50 (65%; cumulative 75%) patients, including 36 (47%) patients with complete cytogenetic response by 12 months. Median time to major cytogenetic response and complete cytogenetic response were 85 days and 256 days, respectively. Major cytogenetic response and complete cytogenetic response rates were similar between imatinib-resistant and imatinib-intolerant patients, but were higher in patients without BCR-ABL1 mutations. Overall and progression-free survival rates at 12 months were 96.1% and 86.3%, respectively. All newly-occurring or worsening grade 3/4 hematologic abnormalities included thrombocytopenia (24.7%) and anemia (5.2%); grade 3/4 drug-related non-hematologic adverse events included fatigue (3.9%), asthenia (3.9%), and nausea (2.6%). The most common biochemistry abnormality was hyperbilirubinemia (grade 3/4 23.4%), and 12 of 18 cases were managed with dose modification. Study findings suggest radotinib is effective and well tolerated in chronic phase-chronic myeloid leukemia patients with resistance and/or intolerance to BCR-ABL1 tyrosine kinase inhibitors and may represent a promising alternative for these patients. (*clinicaltrials.gov* identifier: 01602952)

Introduction

Chronic myeloid leukemia (CML) is characterized by the presence of the Philadelphia chromosome, which forms as a result of a reciprocal translocation between chromosomes 9 and 22 and leads to production of the BCR-ABL1 fusion protein.^{1,2} The first BCR-ABL1 tyrosine kinase inhibitor, imatinib, has been recommended for the first-line treatment of chronic phase CML and has dramatically improved survival rates since its introduction.^{3,4} Nonetheless, some patients with chronic phase-CML have shown imatinib resistance, in most patients due to mutation in BCR-ABL1 that affects the imatinib binding site.⁵⁻⁷ Additionally, some patients have developed intolerance due to adverse events associated with imatinib treatment.⁸⁻¹⁰ In an attempt to overcome imatinib resistance, 2nd-generation tyrosine kinase inhibitors were devel-

oped, including dasatinib, nilotinib, bosutinib, and ponatinib.¹¹⁻¹⁴ However, the costs of 2nd-generation tyrosine kinase inhibitors may be prohibitive, particularly in emerging regions such as the Asia-Pacific countries, and new, lower cost alternatives are necessary.¹⁵⁻¹⁸

Radotinib (SupectTM; C27H21F3N8OHCl, 4-Methyl-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyrazin-2-yl-pyrimidin-2-ylamino)-benzamide hydrochloride; IL-YANG Pharm. Co. Ltd., Seoul, Korea) is an oral tyrosine kinase inhibitor.¹⁹ *In vitro*, radotinib binds BCR-ABL1 and reduces phosphorylation of CrkL, a BCR-ABL1 target protein. Furthermore, pre-clinical studies demonstrated superiority of radotinib to imatinib in both wild-type and mutant BCR-ABL1 positive CML cell lines.²⁰ In a phase I clinical trial, no dose-limiting toxicities were observed with a dose of up to 1000 mg/day.²¹ This study evaluated the efficacy and safety of

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The online version of this article has a Supplementary Appendix.

Manuscript received on August 15, 2013. Manuscript accepted on March 31, 2014.

Correspondence: dwkim@catholic.ac.kr

radotinib in Philadelphia chromosome-positive chronic phase-CML patients with resistance and/or intolerance to prior BCR-ABL1 tyrosine kinase inhibitors. (*clinicaltrials.gov* identifier: 01602952)

Methods

Additional details of the study design and methods can be found in the *Online Supplementary Appendix*.

Patients

Eligible patients were at least 18 years of age with Philadelphia chromosome-positive chronic phase-CML and resistance and/or intolerance to imatinib. Patients were also eligible if they were intolerant to dasatinib and/or nilotinib, provided that they were also resistant or intolerant to imatinib. Patients with partial cytogenetic response (PCyR) or T315I mutation at screening were excluded. Intolerance was defined as failure to achieve major cytogenetic response (MCyR) and having a grade ≥ 3 or persistent (lasting more than 2 weeks) grade ≥ 2 drug-related adverse event during imatinib treatment of ≥ 300 mg/day. Suboptimal response and failure with imatinib were defined according to the criteria of the European LeukemiaNet 2009 recommendations, with the exception of molecular suboptimal response.²²

This clinical trial was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The study protocol was approved by the institutional review boards at each center and all patients provided informed consent.

Study design

This was a multicenter phase II clinical trial conducted at 12 sites in South Korea, India, and Thailand; the accrual period was between July 2009 and November 2011. Patients were treated with radotinib 400 mg twice daily based on the results of the phase I trial.²¹ Dose modification was allowed based on response and adverse events. The primary efficacy end point of the study was the rate of MCyR by 12 months. Secondary end points included time to MCyR, duration of response, progression-free survival (PFS), and overall survival (OS). Adverse events were classified according to the Common Terminology Criteria for Adverse Events Version 3.0.

Efficacy assessments

Cytogenetic assessments required the evaluation of at least 20 metaphases. To evaluate molecular response to treatment, real-time quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) was performed to measure BCR-ABL1 transcript copy number in International Scale (IS) units. Major molecular response (MMR) was defined as a BCR-ABL1 transcript level of 0.1% or lower on the IS. The ABL1 kinase domain (region equivalent to amino acids 237-486) of BCR-ABL1 was directly sequenced after nested PCR amplification. Cytogenetic, qRT-PCR, and mutation analysis were performed at baseline, every three months, and at treatment failure.

Statistical analysis

Efficacy variables were summarized using descriptive statistics, including response rates with 95% confidence intervals and Kaplan-Meier curves. Time to MCyR was calculated from the first day of radotinib administration to the date of response. Duration of response was calculated from the first date of response to the first date of confirmed loss of response. Disease progression was defined as progression to the accelerated or blast phase in patients

who started the trial while in the chronic phase. OS was calculated from the first day of treatment to the date of death, and PFS was calculated from the first day of treatment to the date of disease progression or death. The safety analysis population was defined as all patients in the intention-to-treat population who had at least one post-baseline safety evaluation.

Results

Patients

A total of 77 patients with a median age of 43 years (range 22-75 years) were enrolled in the study; 65 (84.4%) were imatinib-resistant and 12 (15.6%) were imatinib-intolerant (Table 1). Four patients were also intolerant to dasatinib: 3 with imatinib resistance and intolerance and one with imatinib intolerance. BCR-ABL1 kinase domain mutation was detected at baseline in 12 patients: 4 *P-loop* [*G250E*, *Y253F+E355G*, *E255K*, *E255V*], 2 *F359V*, and one each of *M244V*, *M244V+H396R*, *L387M*, *F317L*, *M351T*, *E355G*. Other kinase domain abnormalities were detected at baseline in 2 patients (between exons 8 and 9, and deletion of amino acids 363-386).

Patient disposition

As of the data cut off for this analysis on October 9, 2012, the minimum follow up was 12 months and the median duration of follow up was 23.4 months (Table 2). The median duration of radotinib exposure was 378 days (range 8-1050 days), and median dose intensity was 730 mg/day. Dose interruption was required by 55 (71.4%) patients and 53 (68.8%) patients required dose reductions. Overall, 33 (42.9%) patients permanently discontinued treatment before the end of 12 cycles. Reasons for treatment discontinuation were non-hematologic adverse events ($n = 3$, including hepatitis flare, gastrointestinal bleeding, and muscle pain), abnormal laboratory tests ($n = 15$, including hyperbilirubinemia $n=6$, thrombocytopenia $n=7$, including 1 patient with liver enzyme elevation; and liver enzyme elevation $n=2$), disease progression ($n=8$), death ($n=2$, sepsis), and other reasons ($n=5$).

Table 1. Demographic and base-line characteristics.

Characteristic	N = 77*
Age, year	
Median (range)	43 (22-75)
Duration of CML before enrollment, months	
Median (range)	11.8 (2.3-182.9)
Duration of prior total imatinib therapy, months	
Median (range)	9.2 (1.2-110.4)
Imatinib resistance, n. (%)	65 ^a (84.4)
Imatinib intolerance, n. (%)	12 ^c (15.6)
Prior therapy, n. (%)	
Dasatinib or nilotinib	4 (5.2)
Interferon- α	4 (5.2)
Stem cell transplantation	1 (1.3)
Previous imatinib dose ≥ 600 mg/day, n. (%)	23 (29.9)

CML: chronic myeloid leukemia; ELN: European LeukemiaNet. *Last patient was enrolled in November 2011 and completed 12 cycles of treatment by the data cut off for this analysis on October 9, 2012. ^aIncludes 11 patients with suboptimal response according to ELN 2009 guidelines and 3 patients with dasatinib intolerance with imatinib resistance and intolerance. ^cIncludes 1 patient with dasatinib intolerance and imatinib intolerance.

Efficacy

MCyR was achieved in 50 (cumulative 75%) patients, including 36 (cumulative 47%) patients with complete cytogenetic response (CCyR) by 12 months (Figure 1). At baseline, 4 of 77 patients were in PCyR, which was among the exclusion criteria for study entry. Therefore, patients in PCyR at baseline were only considered eligible for CCyR and were assessed as not responding if they remained in PCyR. According to these criteria, 3 patients achieving CCyR were assessed as responding, and one patient discontinued prior to assessment. Of the patients who achieved CCyR, 11 (30.5%) achieved major molecular response. The median time to MCyR and CCyR were 85 days and 256 days, respectively. By 24 months, 6 of 50 patients in MCyR lost the response, and the probability of remaining in MCyR was 86.8%. The rates of MCyR, CCyR, and MMR for the overall population and for subgroups of patients according to base-line BCR-ABL1 mutation or kinase domain abnormality are shown in Figure 2. Among the 14 patients with known BCR-ABL1 mutation or kinase domain abnormality at baseline, 43% achieved MCyR and 21% achieved CCyR; MCyR and CCyR rates were higher in patients without mutation.

Among 14 patients with BCR-ABL1 mutation (n=12) or ABL1 kinase domain abnormalities (n=2) at baseline, these were no longer detectable after 12 months of treatment in 3 patients (1 patient with base-line M351T point mutation and 2 patients with base-line ABL1 kinase domain abnormalities between exons 8 and 9, del 363-386). On treatment, 6 patients retained their base-line mutation(s) and 4 patients had variable mutation dynamics. On the other hand, 6 of 63 patients without base-line mutation had a newly detectable single mutation (E255V, F317L, T315I, F359V, E459K, and E255V) during treatment.

The 12-month estimated OS and PFS rates were 96.1% and 86.3%, respectively (Figure 3). The probability of PFS was significantly higher in patients without base-line

mutations (P=0.0397). The PFS rate was higher among patients without a base-line mutation compared with those who had base-line mutations at 12 months (90.3% vs. 69.6%; *Online Supplementary Figure S1*). In total, disease progression or death occurred 9 times: 7 disease progression events (at 0.9, 3.9, 5.2, 6.1, 8.1, 9.4, and 9.8 months) and 2 deaths (at 2.6 and 4 months).

Safety

All newly-occurring or worsening grade 3/4 hematologic abnormalities included thrombocytopenia (24.7%) and anemia (5.2%) (Table 3). Grade 3/4 drug-related non-

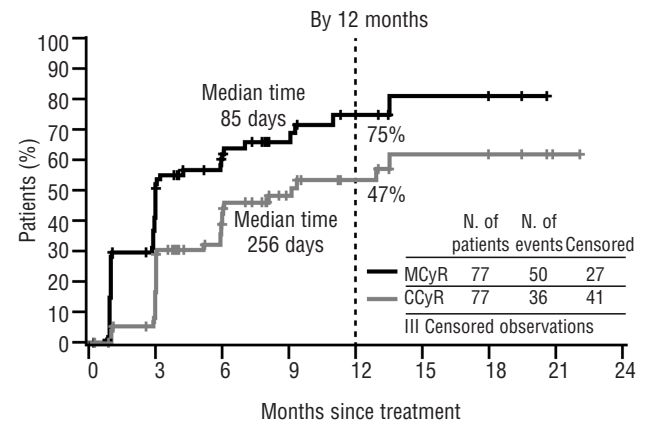


Figure 1. Cumulative incidence of cytogenetic response. CCyR: complete cytogenetic response; MCyR: major cytogenetic response.

Table 2. Patient treatment and follow up.

Completed 12 cycles, ^a n. (%)	44 (57.1)
Discontinued treatment before 12 cycles, n. (%)	33 (42.9)
Disease progression ^b	8 (10.4)
Adverse events	3 (3.9)
Abnormal test/laboratory value	15 (19.5)
Other ^c	5 (6.5)
Death ^d	2 (2.6)
Duration of radotinib exposure, d	
Median (range)	378 (8-1.050)
Duration of follow up, mo	
Median (range)	23.4 (0.9-41.3)
Dose intensity, mg/d	
Median (range)	730 (354.4-907.1 ^e)
Dose interruption, ^f n. (%)	55 (71.4)
Dose reduction, n. (%)	53 (68.8)

CHR: complete hematologic response; CyR: cytogenetic response; MCyR: major cytogenetic response. ^aA total of 36 patients remained on treatment since completion of 12 cycles by the data cut off for this analysis on October 9, 2012. ^bDisease progression was defined as progression to the accelerated or blast phase in patients who started the trial while in the chronic phase. ^cIncludes protocol violation, withdrawal of consent, lost to follow up, and administrative problems. ^dIncludes only those patients for whom death was reported as the primary reason for discontinuation of therapy. ^eDose escalation to radotinib 1,000 mg/day was permitted for lack of efficacy (no CHR by 3 months, no CyR by 6 months, or no MCyR by 12 months, or loss of CHR or CyR). ^fDose interruption was defined as >1 day of interruption regardless of reason.

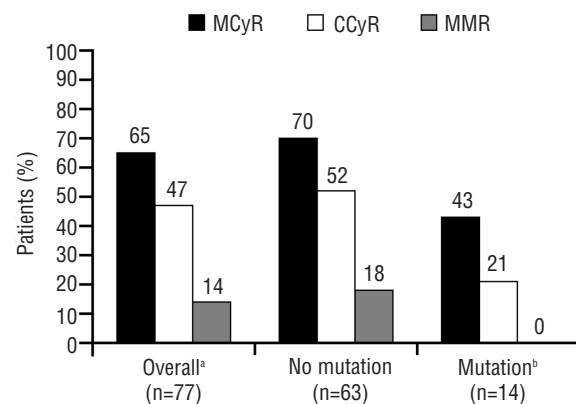


Figure 2. Cytogenetic and molecular response in patients with and without base-line BCR-ABL1 kinase domain abnormality. CCyR: complete cytogenetic response; MCyR: major cytogenetic response; MMR: major molecular response. ^aAt baseline, 4 of 77 patients had PCyR, which was among the exclusion criteria for study entry. Therefore, patients with PCyR at baseline were only considered eligible for CCyR and were assessed as not responding if they remained in PCyR. According to these criteria, 3 patients achieving CCyR were assessed as responding. ^bType of mutation included 1 M244V, 1 M244V+H396R, 4 P-loop (1 G250E, 1 Y253F+E355G, 1 E255K, 1 E255V), 1 A-loop (1 L387M), and 7 other (1 F317L, 1 M351T, 1 E355G, 2 F359V, 1 35bp INS between exons 8 and 9, 1 del 363-386).

hematologic adverse events included fatigue (3.9%), asthenia (3.9%), nausea (2.6%), myalgia (1.3%), rash (1.3%), and pruritus (1.3%). The most common biochemical abnormality was hyperbilirubinemia (all grade 70.1%; grade 3/4 23.4%) (Table 3). Hyperbilirubinemia generally occurred in the early period of treatment and was managed by dose reduction or transient interruption; however, 6 patients permanently discontinued treatment due to hyperbilirubinemia. Overall elevations of alanine transaminase (ALT) and aspartate transaminase (AST) were observed in 85.7% and 72.7% of patients, respectively. Grade 3/4 ALT and AST abnormalities were experienced by 11.7% and 2.6% of patients, respectively. Hyperglycemia was observed in 68.8% of patients, including 19.5% of patients with grade 3/4 hyperglycemia. One (1.3%) patient developed diabetes during the study, but it was not considered drug-related; 8 (10.4%) patients had a history of diabetes at baseline. However, no patients with diabetes interrupted or discontinued study drug due to aggravation of hyperglycemia or required an increase in treatment for their diabetes. Lipase elevation was observed in 37.7% of patients, including 10.4% of patients with grade 3/4 lipase elevation. Although 7 (9.1%) patients had a lipase abnormality at baseline, symptoms related to pancreatitis were not observed in any patients during the treatment period. The incidence of hematologic or biochemical laboratory abnormalities at baseline and after treatment is shown in *Online Supplementary Table S4*. QT interval prolongation (>30 ms change from baseline) was reported in 6 (7.8%) patients; 5 (6.5%) patients had a QT interval over 450 ms but none had an interval over 480 ms. There were 2 deaths during the study, both caused by sepsis. One patient died at 2.6 months with soft tissue cellulitis due to disease progression and one patient died at four months with febrile neutropenia due to pulmonary fungal infection; these patients had minimal cytogenetic response (66-95%) and no cytogenetic response (>95%), respectively, when they died.

Table 3. Drug-related adverse events (frequency >5%) and newly-occurring or worsening hematologic or biochemical laboratory abnormalities (frequency >5%; n = 77)

Adverse event, n. (%)	All grades	Grade 3/4
Drug-related non-hematologic adverse events		
Rash	18 (23.4)	1 (1.3)
Fatigue	13 (16.9)	3 (3.9)
Pruritus	11 (14.3)	1 (1.3)
Headache	10 (13.0)	0 (0)
Decreased appetite	8 (10.4)	0 (0)
Myalgia	8 (10.4)	1 (1.3)
Nausea	8 (10.4)	2 (2.6)
Asthenia	7 (9.1)	3 (3.9)
Arthralgia	5 (6.5)	0 (0)
Pyrexia	5 (6.5)	0 (0)
Vomiting	5 (6.5)	0 (0)
Dyspepsia	5 (6.5)	0 (0)
Alopecia	4 (5.2)	0 (0)
Pain in extremities	4 (5.2)	0 (0)
Diarrhea	4 (5.2)	0 (0)
Hematologic abnormality*		
Thrombocytopenia	46 (59.7)	19 (24.7)
Anemia	29 (37.7)	4 (5.2)
Neutropenia	1 (1.3)	0 (0)
Biochemical abnormality*		
ALT elevation	66 (85.7)	9 (11.7)
AST elevation	56 (72.7)	2 (2.6)
Hyperbilirubinemia	54 (70.1)	18 (23.4)
Hyperglycemia	53 (68.8)	15 (19.5)
Lipase elevation	29 (37.7)	8 (10.4)
Hypophosphatemia	27 (35.1)	7 (9.1)
Alkaline phosphatase elevation	23 (29.9)	1 (1.3)
Hypomagnesemia	21 (27.3)	0 (0)
Hyponatremia	17 (22.1)	7 (9.1)
Hyperkalemia	11 (14.3)	1 (1.3)
Hypoalbuminemia	10 (13.0)	0 (0)
Hypocalcemia	10 (13.0)	0 (0)
Hypokalemia	10 (13.0)	0 (0)
Amylase elevation	7 (9.1)	0 (0)
Hypercalcemia	7 (9.1)	0 (0)
Creatinine elevation	6 (7.8)	0 (0)
Hypermagnesemia	5 (6.5)	1 (1.3)

*Newly-occurring or worsening after treatment, regardless of causality.

inase (ALT) and aspartate transaminase (AST) were observed in 85.7% and 72.7% of patients, respectively. Grade 3/4 ALT and AST abnormalities were experienced by 11.7% and 2.6% of patients, respectively. Hyperglycemia was observed in 68.8% of patients, including 19.5% of patients with grade 3/4 hyperglycemia. One (1.3%) patient developed diabetes during the study, but it was not considered drug-related; 8 (10.4%) patients had a history of diabetes at baseline. However, no patients with diabetes interrupted or discontinued study drug due to aggravation of hyperglycemia or required an increase in treatment for their diabetes. Lipase elevation was observed in 37.7% of patients, including 10.4% of patients with grade 3/4 lipase elevation. Although 7 (9.1%) patients had a lipase abnormality at baseline, symptoms related to pancreatitis were not observed in any patients during the treatment period. The incidence of hematologic or biochemical laboratory abnormalities at baseline and after treatment is shown in *Online Supplementary Table S4*. QT interval prolongation (>30 ms change from baseline) was reported in 6 (7.8%) patients; 5 (6.5%) patients had a QT interval over 450 ms but none had an interval over 480 ms. There were 2 deaths during the study, both caused by sepsis. One patient died at 2.6 months with soft tissue cellulitis due to disease progression and one patient died at four months with febrile neutropenia due to pulmonary fungal infection; these patients had minimal cytogenetic response (66-95%) and no cytogenetic response (>95%), respectively, when they died.

Discussion

Radotinib is a BCR-ABL1 specific 2nd-generation tyrosine kinase inhibitor. According to recently conducted *in vitro* kinase assays, the IC₅₀ value for radotinib against wild-type BCR-ABL1 kinase was 34 nM, which is relatively lower compared with the IC₅₀ levels of c-kit (1,324 nM), PDGFR (PDGFR α , 75.5 nM; PDGFR β , 130 nM) and src (>2,000 nM). Also, radotinib effectively inhibited the proliferation of common mutant clones of BCR-ABL1, with the exception of T315I. In an off-target kinase assay to assess safety, DDR, EPHB, LYN, and PDGFR kinases

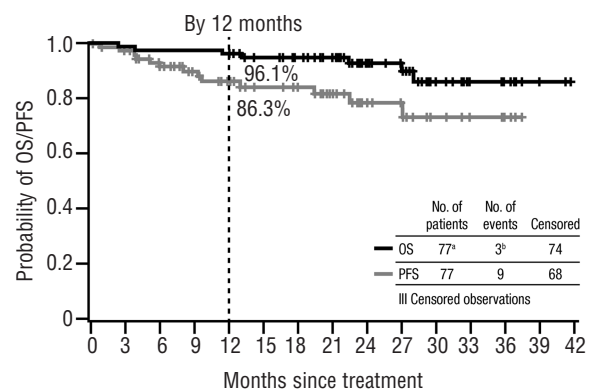


Figure 3. Kaplan-Meier curves of OS and PFS. OS: overall survival; PFS: progression-free survival. *By 12 months. ^bTwo patients died due to sepsis during treatment and 1 patient died after discontinuation due to disease progression.

were inhibited below the 180 nM level (Kim *et al.*, unpublished data, 2014).^{20,21}

This study was designed to evaluate the efficacy and safety of radotinib in patients with chronic phase-CML after resistance and/or intolerance to BCR-ABL1 tyrosine kinase inhibitors. Based on the analysis of the primary end point, a cumulative 75% of patients achieved MCyR by 12 months. Additionally, 47% of patients achieved CCyR, and 22% of patients with MCyR also achieved MMR. OS and PFS rates at 12 months were 96.1% and 86.3%, respectively, and 9 (11.7%) patients experienced disease progression during treatment at a median follow up of 23.4 months. In the current study, 5 of 12 (42%) patients having base-line BCR-ABL1 mutations had less sensitive mutation to nilotinib or dasatinib. Among them, 2 patients achieved MCyR, and PFS was higher in patients with no base-line BCR-ABL1 mutations.

Efficacy results from this study of radotinib are comparable, and in some cases favorable, to those observed with other 2nd-generation BCR-ABL1 tyrosine kinase inhibitors used in similar treatment settings. In a phase II study of dasatinib in 186 patients with imatinib-resistant or imatinib-intolerant chronic phase-CML, MCyR and CCyR rates at eight months were 45% and 33%, respectively.²⁵ A phase II study of nilotinib in 280 patients with chronic phase-CML and resistance or intolerance to imatinib reported MCyR and CCyR rates of 48% and 31%, respectively, in patients with ≥ 6 months or longer follow up or who prematurely discontinued the study.²⁴

In this study, the rates of MCyR and CCyR with radotinib treatment were similar but slightly higher in imatinib-intolerant patients *versus* imatinib-resistant patients. In the phase II study of nilotinib, MCyR and CCyR rates were also similar but generally higher in imatinib-intolerant patients. MCyR and CCyR rates with dasatinib treatment were also higher in imatinib-intolerant patients. A summary of the efficacy of radotinib, dasatinib, and nilotinib is shown in *Online Supplementary Table S2*.

The rates of MCyR and CCyR observed in this study with radotinib were generally higher than those seen in studies of other tyrosine kinase inhibitors. This difference may be due to the patient population in this study; compared with other studies, patients in this study had a shorter duration of CML, had used lower doses of imatinib prior to study entry, and, taken together, had a smaller proportion of patients with mutation of BCR-ABL1. Moreover, according to European LeukemiaNet 2009 guidelines,²² 11 patients with suboptimal response to imatinib were included in this study; however, these patients would be considered to have treatment failure according to European LeukemiaNet 2013 guidelines.²⁵ Considering the limitations of this patient population, these data suggest the overall response rate with radotinib is comparable with other 2nd-generation tyrosine kinase inhibitors.

Adverse events were generally transient and managed

by dose reduction or interruption. Overall adverse events were somewhat different than with other BCR-ABL1 tyrosine kinase inhibitors. For example, the incidence of hematologic adverse events was lower and the incidence of hyperbilirubinemia was higher with radotinib compared with other 2nd-generation BCR-ABL1 tyrosine kinase inhibitors.^{23,24} Moreover, some of the troublesome adverse events associated with other BCR-ABL1 tyrosine kinase inhibitors (e.g, fluid retention, pulmonary arterial hypertension, and increased risk of bleeding with dasatinib; vascular events with nilotinib)^{23,26-30} were not observed with radotinib in the current study. Although grade 3/4 hyperglycemia and lipase elevation were observed in 19.5% and 10.4% of patients, respectively, the metabolic and vascular complications associated with other BCR-ABL1 tyrosine kinase inhibitors were not observed with radotinib. However, as the duration of follow up in this study was relatively short, a longer follow-up period will be required to more completely assess possible additional complications with radotinib treatment. Likewise, while nilotinib has been associated with occasional cases of QT interval prolongation,^{24,31} there were no patients with a QT interval over 480 msec at baseline, and no patients experienced a QT interval over 480 msec with radotinib treatment during this study.

In conclusion, the response to radotinib was rapid, deep, and durable, and it was comparable to that observed in phase II trials of other 2nd-generation BCR-ABL1 tyrosine kinase inhibitors. The results of this study suggest that radotinib is effective and well tolerated in chronic phase-CML patients with resistance and/or intolerance to BCR-ABL1 tyrosine kinase inhibitors and may represent a promising alternative treatment for these patients. Moreover, a cost-effective tyrosine kinase inhibitor, which can improve accessibility to the drug and increase compliance and adherence to treatment, may be necessary in emerging regions, such as the Asia-Pacific countries.¹⁸

Acknowledgments

The authors would like to thank all of the patients who participated in this trial and their families and all of the investigators and clinical research staff from all the clinical centers. This trial was sponsored by IL-YANG Pharm., South Korea, and supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of South Korea (A084899). Editorial support was provided by Allison Michaelis, PhD, of Medergy and was funded by IL-YANG Pharm. These data were previously presented in part at the 54th Annual Meeting and Exposition of the American Society of Hematology (ASH), December 8-12, 2012, Atlanta, Georgia.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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