Optimizing olverembatinib dose in chronic phase chronic myeloid leukemia

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Abstract

Optimizing olverembatinib dose in people with chronic phase chronic myeloid leukemia is important to increase safety without compromising efficacy. We designed a multicenter, retrospective study comparing safety and efficacy of olverembatinib between the recommended dose of 40 mg every other day (QOD; N=216) and a reduced dose of 30 mg QOD (N=66) in subjects failing to have benefited from other tyrosine kinase inhibitors. The cohorts were similar with regard to baseline

co-variates and adjusted for by propensity score matching. There were no significant differences in cytogenetic and molecular responses, or in outcomes between the two dose cohorts. However, the proportion of subjects receiving the original olverembatinib dose at the last follow-up was significantly higher in the 30 mg cohort: 64% (95% confidence interval [95% CI]: 53-75%) *versus* 44% (95% CI: 37-51%; *P*=0.004). Furthermore, the proportion of subjects receiving a reduced dose or permanently discontinuing because of adverse events was significantly lower in the 30 mg cohort: 21% (95% CI: 9-33%) *versus* 41% (95% CI: 34-48%; *P*=0.003). In summary, a starting dose of olverembatinib 30 mg QOD is as effective as a 40 mg starting dose but better tolerated in people with chronic phase chronic myeloid leukemia in whom other tyrosine kinase inhibitors have failed.

Introduction

The recommended and/or approved dose of most anti-cancer drugs is usually derived from studies of maximum tolerated dose.[1] However, the United States Food and Drug Administration and other health authorities have increasingly emphasized the identification of the lowest effective dose to enhance safety, with gemtuzumab ozogamicin in acute myeloid leukemia serving as a recent example.[2] In the instance of tyrosine kinase inhibitors (TKI) in chronic phase chronic myeloid leukemia (CML), the recommended starting dose may not provide the best balance of safety and efficacy, especially in the context of long-term use, as in TKI therapy of CML.[3] For example, about 30% of people receiving the third-generation TKI, ponatinib 45 mg/day, develop cardiovascular events.[4,5] Starting ponatinib at a dose of 45 mg/day or 30 mg/day with dose reduction to 15 mg/day on achieving ≤1% *BCR::ABL1*^{IS} increases safety without compromising efficacy.[6,7]

Olverembatinib, a structurally optimized third-generation TKI, is approved in China for patients with chronic or accelerated phase CML resistant or intolerant to other TKI.[8] The approved starting dose is 40 mg every other day (QOD). At this dose, 52% of subjects had therapy interruptions and 30% required a dose reduction because of therapy-related adverse events (TRAE). More than 70% had grade ≥3 TRAE including thrombocytopenia, hyperpigmentation, increased triglycerides and/or proteinuria and others. Cardiovascular adverse events occurred in 32% of subjects.[8] Consequently, it is important to optimize the dose of this TKI.

To determine whether 40 mg QOD was the best compromise between safety and efficacy, we designed a respective, multicenter study using propensity score matching (PSM) to compare the safety and efficacy of a 40 mg starting dose of olverembatinib with a starting dose of 30 mg QOD. We found that the 30 mg QOD starting dose was safer, better tolerated and comparably effective.

Methods

Olverembatinib was given as a third-line therapy or beyond in CML subjects with a *BCR::ABL1*^{T315I} mutation at any time. Medical records of 282 subjects ≥18 years old with TKI-resistant and/or intolerant chronic phase CML with *e14a2* and/or *e13a2 BCR::ABL1* transcripts who received a starting dose of olverembatinib 30 or 40 mg QOD from 36 Chinese hospitals from October, 2016 to August, 2024 with regular follow-up during TKI therapy were investigated. Among them, 145 subjects were in phase I/II olverembatinib trials,[8] while the remaining 137 subjects were treated in a real-world setting after olverembatinib had been approved in November 2021 in China. Co-variates studied, including sex, age, complete blood counts, percentages of blood blasts and basophils, spleen size below the left costal margin, co-morbidities, olverembatinib dose, results of hematologic, cytogenetic and molecular analyses, responses and adverse events during olverembatinib therapy were extracted from the medical records. Olverembatinib dose was adjusted according to responses and/or adverse events based on European LeukemiaNet (ELN) recommendations.[9-12] This study was approved by the Ethics Committee of Peking University People's Hospital (N. 2024PHB336-001). Subjects gave written informed consent consistent with the precepts of the revised Declaration of Helsinki.

Diagnosis and monitoring were done according to ELN recommendations.[9-12] TRAE were assessed continuously, graded and reported according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[13] The definitions of therapy responses were based on the ELN recommendations.[9-12] TKI resistance was defined by therapy failure according to the ELN recommendations.[9] Progression-free survival was calculated from the start of olverembatinib therapy to transformation to the accelerated or blast phase, death or censoring at a transplant or the last follow-up. Survival was calculated from the start of olverembatinib therapy to death or censoring at a transplant or the last follow-up. The last follow-up was November 20, 2024.

Plasma concentrations in subjects receiving olverembatinib for ≥1 month at Peking University People's Hospital were determined using ultra-high performance liquid chromatography and tandem mass spectrometry before dosing (C_0) and 6 hours after dosing (C_6). In subjects with multiple determinations the average concentration was used.

Statistical analyses

A Pearson χ^2 test was used to analyze categorical co-variates. A Student *t* test or Mann-Whitney U test was used to

analyze continuous co-variates. Cumulative incidences of therapy responses, including major cytogenetic response (MCyR), complete cytogenetic response (CCyR), major molecular response (MMR) and a 4-log reduction in molecular response (MR^4), were calculated using the competing risk model and compared by the Fine-Gray test considering competing events, including withdrawal from study for any reason, transplant or death. Progression-free survival and survival were calculated by the Kaplan-Meier method and compared by the log-rank test. A Cox regression model was used to identify the co-variates associated with therapy responses and outcomes. PSM was used to adjust for differences in baseline co-variates between the two dose cohorts.[14] A two-sided $P<0.05$ was considered statistically significant. SPSS 22.0 (SPSS, Chicago, IL, USA), R version 4.0.2 (R Core Team, Vienna, Austria) and GraphPad Prism 8 (GraphPad Software Inc., La Jolla, CA, USA) were used for analyses and graphical representations.

Results

Subjects' co-variates

Two hundred and eighty-two subjects with chronic phase CML receiving olverembatinib 30 mg (N=66) or 40 mg (N=216) QOD as the starting dose were studied. These subjects' baseline co-variates are displayed in Table 1. One hundred and ninety-four (69%) of the study subjects were male. The median age at the start of olverembatinib therapy was 39 years (interquartile range [IQR], 25-46 years). The median interval from CML diagnosis to starting olverembatinib was 47 months (IQR, 25-80 months). One hundred and thirty (46%) subjects had received three or more prior TKI. The median duration of prior TKI therapy was 45 months (IQR, 25-75 months). As regards mutational status, 126 subjects (45%) had $ABL1^{T315I}$, 35 (12%) had $ABL1^{T315I}$ and another mutation, 37 (13%) had other mutations and 61 (22%) had no mutation. Forty-nine (17%) subjects had additional cytogenetic abnormalities in Philadelphia (Ph) chromosome-positive cells, 30 (11%) of whom had high-risk additional cytogenetic abnormalities. Two-hundred and sixty-five (94%) subjects switched to olverembatinib because of TKI resistance. There were no significant differences in baseline co-variates between the dose cohorts except better responses to prior TKI therapy in the 30 mg cohort (P=0.04).

Subjects' disposition

As of November 20, 2024, the median duration of the follow-up was 28 months (IQR, 9-76 months) in the 30 mg cohort and 25 months (IQR, 8-56 months) in the 40 mg cohort (P=0.05). At the last follow-up, 224 (79%) subjects were receiving olverembatinib therapy at doses of 10 mg (N=8; 3%), 20 mg (N=30; 11%), 30 mg (N=88; 31%), 40 mg (N=96; 34%) and 50 mg (N=2; <1%) QOD (Table 2).

Thirty-seven subjects (56%) in the 30 mg cohort and 125 (58%) in the 40 mg cohort had a transient reduction in olverembatinib dose or discontinued therapy because of TRAE (P=0.80). The median interval from the start of olverembatinib to dose-reduction or discontinuation was 8 months (IQR, 3-22 months) in the 30 mg cohort compared with 2 months (IQR, 1-6 months) in the 40 mg cohort (P=0.02). The most common TRAE resulting in transient dose reductions in both cohorts was severe thrombocytopenia (grade ≥3): 30 mg cohort: N=33, 50%; 40 mg cohort: N=92, 44% (P=0.29). In the 30 mg cohort, nine (14%) subjects permanently discontinued olverembatinib because of TRAE (N=2) or disease progression (N=7); in the 40 mg cohort, 49 (23%) subjects permanently discontinued olverembatinib because of TRAE (N=17; 8%), treatment failure (N=6; 3%), disease progression (N=24; 11%) or withdrawal of consent (N=2; 1%). The percentage of subjects with permanent dose reductions or discontinuation because of TRAE was significantly lower in the 30 mg cohort than in the 40 mg cohort (N=14 [21%] *vs.* N=89 [41%]; P=0.003). At the last follow-up the proportion of subjects receiving the original starting dose was significantly higher in the 30 mg cohort (N=42, 64%) than in the 40 mg cohort (N=94, 44%; P=0.004).

Therapy responses and outcomes

In the 30 mg cohort, 58 of 62 (94%) evaluable subjects achieved a complete hematologic response within 3 months. Of 57 subjects without a MCyR at baseline, 43 (75%) and 38 (67%) achieved MCyR and CCyR at a median of 3 months (IQR, 2-5 months) and 4 months (IQR, 2-10 months), respectively. Among 61 subjects evaluable for molecular responses, 27 (44%) obtained a MMR and 17 (28%) achieved MR^4. Ten subjects (15%) progressed to accelerated (N=4) or blast (N=6) phase CML. Seven (11%) subjects died of disease progression. The 6-year cumulative incidences of MCyR, CCyR, MMR and MR^4 were 84% (95% CI: 75-93%), 84% (95% CI: 73-95%), 57% (95% CI: 45-69%) and 36% (95% CI: 18-54%), respectively. The 6-year probabilities of progression-free survival and survival were 78% (95% CI: 64-92%) and 82% (95% CI: 67-97%), respectively.

In the 40 mg cohort, 178 of 200 (89%) evaluable subjects achieved a complete hematologic response within 3 months. Of 186 subjects without MCyR at baseline, 129 (69%) and 112 (60%) achieved MCyR and CCyR at a median of 3 months (IQR, 2-6 months) and 3 months (IQR, 2-9 months), respectively. Among 194 subjects evaluable for molecular responses, 87 (45%) had a MMR and 66 (34%) achieved a MR^4. Twenty-seven subjects (13%) progressed into accelerated (N=12) or blast (N=15) phase CML. Twenty-four (11%) subjects died of disease progression (N=23) or severe infection (N=1). The 4-year cumulative incidences of MCyR, CCyR, MMR and MR^4 were 84% (95% CI: 77-91%), 71% (95% CI: 63-79%), 59% (95% CI: 51-67%) and 51% (95% CI: 35-67%), respectively. The 4-year probabilities of progression-free survival and survival were 82%

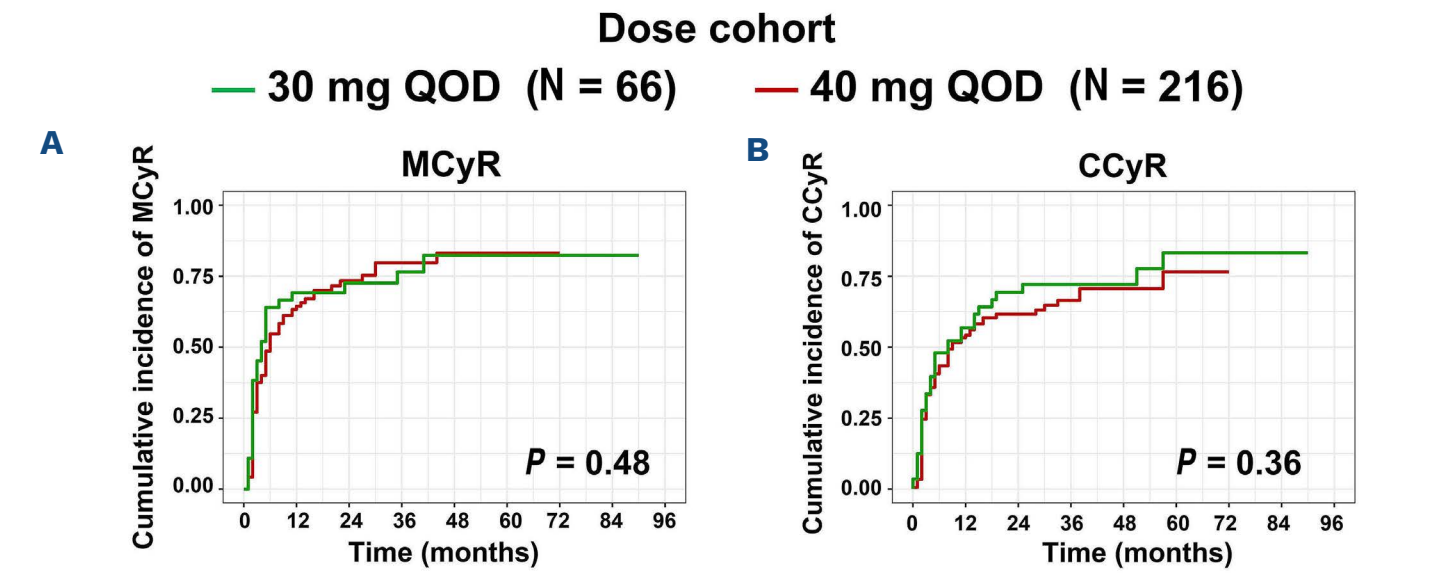
Table 1. Subjects' characteristics.

Co-variates	Before propensity-score matching			After propensity-score matching		
	30 mg QOD N=66	40 mg QOD N=216	*P*	30 mg QOD N=66	40 mg QOD N=154	*P*
Age, years, median (IQR)	39 (24-45)	39 (28-49)	0.79	39 (24-45)	37 (27-37)	0.43
Male, N (%)	49 (74)	145 (67)	0.28	49 (74)	108 (70)	0.54
Comorbidity(ies), N (%)	16 (24)	60 (28)	0.57	16 (24)	35 (23)	0.81
Lines of prior TKI therapy, N (%)			0.10			0.60
1	18 (27)	37 (17)		18 (27)	32 (21)	
2	26 (39)	71 (33)		26 (39)	59 (38)	
3	17 (26)	81 (38)		17 (26)	52 (34)	
≥4	5 (8)	27 (12)		5 (8)	11 (7)	
Best prior TKI-therapy responses ≥CCyR, N (%)	26 (39)	56 (26)	0.04	26 (39)	54 (35)	0.65
Duration of previous TKI therapy, months, median (IQR)	46 (26-74)	45 (24-76)	0.65	46 (26-74)	44 (25-71)	0.58
Grade ≥3 hematologic adverse events on prior TKI therapy, N (%)	34 (52)	96 (44)	0.31	34 (52)	72 (47)	0.52
WBC, $\times 10^9$/L, median (IQR)	6 (4-10)	6 (5-11)	0.26	6 (4-10)	7 (5-11)	0.39
Hemoglobin, g/L, median (IQR)	128 (97-141)	122 (109-140)	0.53	128 (97-141)	125 (105-144)	0.67
Platelets, $\times 10^9$/L, median (IQR)	166 (88-270)	166 (108-234)	0.66	166 (88-270)	167 (113-234)	0.81
Blood blasts, %, median (IQR)	0 (0-0)	0 (0-0)	0.66	0 (0-0)	0 (0-0)	0.92
Bone marrow blasts, %, median (IQR)	2 (1-3)	1 (0-1)	0.18	2 (1-3)	1 (0-2)	0.56
Blood basophils, %, median (IQR)	0 (0-1)	0 (0-2)	0.12	0 (0-1)	0 (0-1)	0.80
Ph^+ ACA, N (%)	7 (11)	42 (19)	0.10	7 (11)	28 (18)	0.16
High-risk ACA, N (%)	6 (9)	24 (11)	0.64	6 (9)	17 (11)	0.67
100% Ph^+ cells, N (%)	33 (50)	96 (44)	0.43	33 (50)	68 (44)	0.43
BCR::ABL mutation status			0.69			0.53
Single *T315I* mutation	29 (44)	97 (45)		29 (44)	72 (47)	
T315I + additional mutations	10 (15)	25 (12)		10 (15)	20 (13)	
Other mutations	8 (12)	29 (13)		8 (12)	21 (14)	
No mutation	16 (24)	45 (21)		16 (24)	26 (17)	
Not detected	3 (5)	20 (9)		3 (5)	15 (10)	
Clinical trials, N (%)	33 (50)	112 (52)	0.79	33 (50)	73 (47)	0.72
Reasons for switching to olverembatinib, N (%)			0.56			0.35
Resistance	61 (92)	204 (94)		61 (92)	147 (95)	
Intolerance	5 (8)	12 (6)		5 (8)	7 (5)	
Median follow-up, months, median (IQR)	28 (9-76)	25 (8-56)	0.05	26 (9-72)	25 (8-54)	0.27

QOD: every other day; IQR: interquartile range; TKI, tyrosine kinase inhibitor; CCyR: complete cytogenetic response; WBC: white blood cells; Ph^+: Philadelphia chromosome-positive; ACA: additional cytogenetic abnormalities.

(95% CI: 76-88%) and 84% (95% CI: 78-90%), respectively. There were no significant differences in achieving complete hematologic response by 3 months (*P*=0.30). Cumulative incidences of MCyR (*P*=0.48), CCyR (*P*=0.36), MMR (*P*=0.39) and MR^4 (*P*=0.14), as well as probabilities of progression-free survival (*P*=0.95) and survival (*P*=0.46) were similar between the 30 mg and 40 mg QOD cohorts (Figure 1).

Results of univariable Cox analyses are displayed in *Online Supplementary Table S1*. Multivariable Cox analyses in all olverembatinib-treated subjects showed that olverembatinib doses were not significantly correlated with therapy responses and outcomes. Increasing numbers of prior TKI therapies, best prior TKI-therapy response less than CCyR, longer duration of prior TKI therapy, grade ≥3 hematologic toxicity on prior TKI therapy, 100% Ph-chromosome-positive cells, and no *ABL1* mutation were significantly associated with lower cytogenetic and/or molecular responses (Table 3). Initial therapy with a second-generation TKI, higher percentages of blood blasts and basophils and Ph-chromosome-positive additional cytogenetic abnormalities were associated with worse progression-free survival and survival (Table 3). Additionally, age and the source of subjects (from clinical trials or post marketing real-world cohorts) did not have an impact on therapy responses and outcomes of olverembatinib treatment.



Cumulative incidences of MCyR (%)					
Dose cohort	1-year	2-year	3-year	4-year	5-year
— 30 mg QOD	67	73	77	84	84
— 40 mg QOD	64	73	82	85	85

Cumulative incidences of MCyR (%)					
Dose cohort	1-year	2-year	3-year	4-year	5-year
— 30 mg QOD	56	68	73	73	84
— 40 mg QOD	53	62	70	71	76

Cumulative incidences of MMR (%)					
Dose cohort	1-year	2-year	3-year	4-year	5-year
— 30 mg QOD	36	40	52	52	57
— 40 mg QOD	43	53	59	59	61

Cumulative incidences of MR⁴ (%)					
Dose cohort	1-year	2-year	3-year	4-year	5-year
— 30 mg QOD	22	29	32	32	32
— 40 mg QOD	27	38	44	51	54

Probabilities of PFS (%)					
Dose cohort	1-year	2-year	3-year	4-year	5-year
— 30 mg QOD	89	89	87	81	78
— 40 mg QOD	92	89	86	82	78

Probabilities of Survival (%)					
Dose cohort	1-year	2-year	3-year	4-year	5-year
— 30 mg QOD	95	95	92	86	82
— 40 mg QOD	94	91	87	84	78

Figure 1. Comparison of therapy responses and outcomes between the cohorts of patients who started treatment with 30 or 40 mg olverembatinib every other day before propensity score matching (A-F). QOD: every other day; MCyR: major cytogenetic response; CCyR: complete cytogenetic response; MMR: major molecular response; MR⁴: 4-log reduction in molecular response; PFS: progression-free survival.

Table 2. Subjects' disposition.

Disposition	Total	30 mg QOD	40 mg QOD	*P*
N of subjects	282	66	216	-
Follow-up, months, median (IQR)	26 (9-77)	28 (9-76)	25 (8-56)	0.05
Ongoing olverembatinib therapy, N (%)	224 (79)	57 (86)	167 (77)	0.11
Olverembatinib 10 mg	8 (3)	3 (5)	5 (2)	
Olverembatinib 20 mg	30 (11)	9 (14)	21 (10)	
Olverembatinib 30 mg	88 (31)	42 (64)	46 (21)	
Olverembatinib 40 mg	96 (34)	2 (3)	94 (44)	
Olverembatinib 50 mg	2 (<1)	1 (2)	1 (<1)	
Ongoing initial olverembatinib dose, N (%)	136 (48)	42 (64)	94 (44)	0.004
Permanently discontinued treatment, N (%)	58 (21)	9 (14)	49 (23)	0.11
Treatment-related adverse events	19 (7)	2 (3)	17 (8)	
Treatment failure	6 (2)	0	6 (3)	
Disease progression	31 (11)	7 (11)	24 (11)	
Consent withdrawal	2 (1)	0	2 (1)	

QOD: every other day; IQR: interquartile range.

Safety

Olverembatinib was well-tolerated at both doses. Detailed safety profiles are presented in Table 4. There were no significant differences in incidences of hematologic (grade ≥3) and non-hematologic (any grade) TRAE between the 30 mg and 40 mg cohorts. Thyroid dysfunction was not observed in the 30 mg cohort, whereas six subjects in the 40 mg cohort had elevated thyroid-stimulating hormone levels, with one exhibiting decreased free triiodothyronine and another decreased free thyroxine. None of these six subjects had any clinical symptoms related to hypothyroidism. Proteinuria was observed in 79 (28%) subjects, with 73 (26%) cases identified as grade 1-2, and only six (2%) cases classified as grade 3. The proteinuria persisted during olverembatinib therapy, and dose reductions did not reduce the proteinuria concentrations.

Propensity score matching analyses

Using PSM we identified 66 subjects in the 30 mg cohort and 154 in the 40 mg cohort with matches (Table 1). In the PSM analyses we found no significant differences in therapy responses (*P*=0.21-0.89) or outcomes (*P*=0.60-0.88) between the dose cohorts (Figure 2). The percentage of subjects still receiving the starting dose of olverembatinib at the last follow-up was significantly higher in the 30 mg cohort (N=44, 67%) than in the 40 mg cohort (N=73, 47%; *P*=0.009). There were significantly fewer subjects who had transient dose reductions or discontinuations because of TRAE in the 30 mg cohort (N=12, 18%) than in the 40 mg cohort (N=59, 38%; *P*=0.003). The median interval from starting olverembatinib treatment to a dose reduction or discontinuation was 7 months (IQR, 4-22 months) in the 30 mg cohort, compared with 3 months (IQR, 2-6 months) in the 40 mg cohort (*P*=0.02). In PSM safety profiles of both dose cohorts were similar (*Online Supplementary Table S2*).

Plasma concentrations

Plasma concentrations at C_0 C_6 were measured in 88 subjects including 57 in the 30 mg cohort and 31 in the 40 mg cohort. The median number of measurements per subject was 2 (IQR, 1-3). The median C_0 concentration in the 30 mg cohort was 5.3 ng/mL (IQR, 3.4-7.9 ng/mL) *versus* 8.0 ng/mL (IQR, 6.5-9.1 ng/mL) in the 40 mg cohort (*P*=0.01). The median C_6 concentration in the 30 mg cohort was 18.2 ng/mL (IQR, 13.2-23.9 ng/mL) *versus* 26.6 ng/mL (IQR, 18.2-33.1 ng/mL) in the 40 mg cohort (*P*<0.001).

Sensitivity analyses

Sensitivity analyses were conducted in the clinical trial cohort and the real-world post-marketing cohort. Treatment responses, outcomes, and safety profiles were similar across both doses in both the clinical trial and real-world cohorts (*Online Supplementary Figures S1* and *S2*, *Online Supplementary Tables S3* and *S4*).

Discussion

In this study, we found that the initial olverembatinib dose of 30 mg QOD was as effective as the 40 mg QOD dose but was better tolerated in TKI-resistant and/or intolerant subjects with chronic phase CML. There were significantly lower plasma concentrations of olverembatinib at C_0 and C_6 in the 30 mg cohort than in the 40 mg cohort. These data suggest that the plasma concentrations achieved with 30 mg QOD are adequate for efficacy and higher concentrations decrease safety.

These findings are consistent with those of previous studies on dasatinib and ponatinib in chronic phase CML.[6,7,15] Dasatinib 50 mg once daily (QD) demonstrated similar efficacy to 100 mg QD, but was associated with reduced pleural effusion and hematologic toxicity.[15] In the OPTIC

Table 3. Results of multivariable Cox analyses for therapy responses and outcomes in all olverembatinib-treated subjects.

Co-variates	MCyR		CCyR		MMR		MR[4]		PFS		Survival	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Male (Female as Ref)	-	-	-	-	-	-	-	-	-	-	-	-
Age	-	-	-	-	-	-	-	-	-	-	-	-
Comorbidity(ies)	-	-	-	-	-	-	-	-	-	-	-	-
Prior TKI-therapy lines	0.7 (0.5-0.9)	0.006	0.7 (0.6-1.0)	0.069	-	-	-	-	-	-	-	-
Best prior TKI-therapy response < CCyR (≥ CCyR as Ref)	0.6 (0.4-0.9)	0.038	0.4 (0.3-0.7)	0.001	0.3 (0.2-0.5)	<0.001	0.5 (0.3-0.9)	0.020	4.3 (1.0-19.2)	0.051	4.4 (1.0-19.4)	0.052
Duration of prior TKI therapy	-	-	0.9 (0.9-1.0)	0.023	0.9 (0.9-0.9)	0.002	-	-	-	-	-	-
Experienced ≥ grade 3 hematologic toxicity on prior TKI therapy (Not experienced as Ref)	0.7 (0.4-0.9)	0.047	-	-	-	-	0.5 (0.3-0.9)	0.011	-	-	-	-
Initial 2nd-generation TKI therapy (Imatinib as Ref)	-	-	-	-	-	-	-	-	3.4 (1.2-9.6)	0.024	4.3 (1.5-12.5)	0.008
Blood blasts	0.6 (0.3-1.0)	0.093	-	-	-	-	-	-	1.2 (1.0-1.3)	0.008	1.2 (1.0-1.3)	0.042
Blood basophils	-	-	-	-	-	-	-	-	1.2 (1.0-1.2)	0.002	1.2 (1.1-1.3)	0.001
Ph+ ACA (No ACA as Ref)	0.6 (0.3-1.1)	0.076	-	-	-	-	-	-	2.9 (1.3-6.6)	0.009	3.5 (1.5-8.0)	0.003
100% Ph+ cells (<100% Ph+ cells as Ref)	0.4 (0.3-0.6)	<0.001	0.4 (0.3-0.6)	<0.001	0.4 (0.2-0.7)	<0.001	0.4 (0.2-0.7)	0.002	-	-	-	-
BCR::ABL1 mutation status		0.023		0.004		<0.001		0.027	-	-	-	-
Single *T315I* mutation (Ref)	1		1		1		1		-	-	-	-
T315I + additional mutations	0.5 (0.2-0.9)	0.018	0.6 (0.3-1.1)	0.103	0.8 (0.4-1.5)	0.430	0.7 (0.3-1.4)	0.291	-	-	-	-
Other mutations	0.9 (0.5-1.6)	0.816	1.1 (0.6-1.8)	0.827	1.0 (0.6-1.7)	0.961	0.9 (0.5-1.7)	0.805	-	-	-	-
No mutation	0.6 (0.3-0.9)	0.032	0.4 (0.2-0.7)	0.001	0.1 (0.1-0.3)	<0.001	0.1 (0.1-0.5)	0.001	-	-	-	-
Not detected	0.7 (0.2-1.3)	0.235	0.6 (0.3-1.1)	0.460	0.9 (0.6-1.3)	0.582	0.8 (0.4-1.2)	0.673	-	-	-	-
Olverembatinib 40 mg QOD as initial dose (30 mg QOD as Ref)	-	-	-	-	1.6 (0.9-3.0)	0.103	-	-	-	-	-	-
Clinical trials (Real-world post-marketing as Ref)	-	-	-	-	-	-	-	-	-	-	-	-

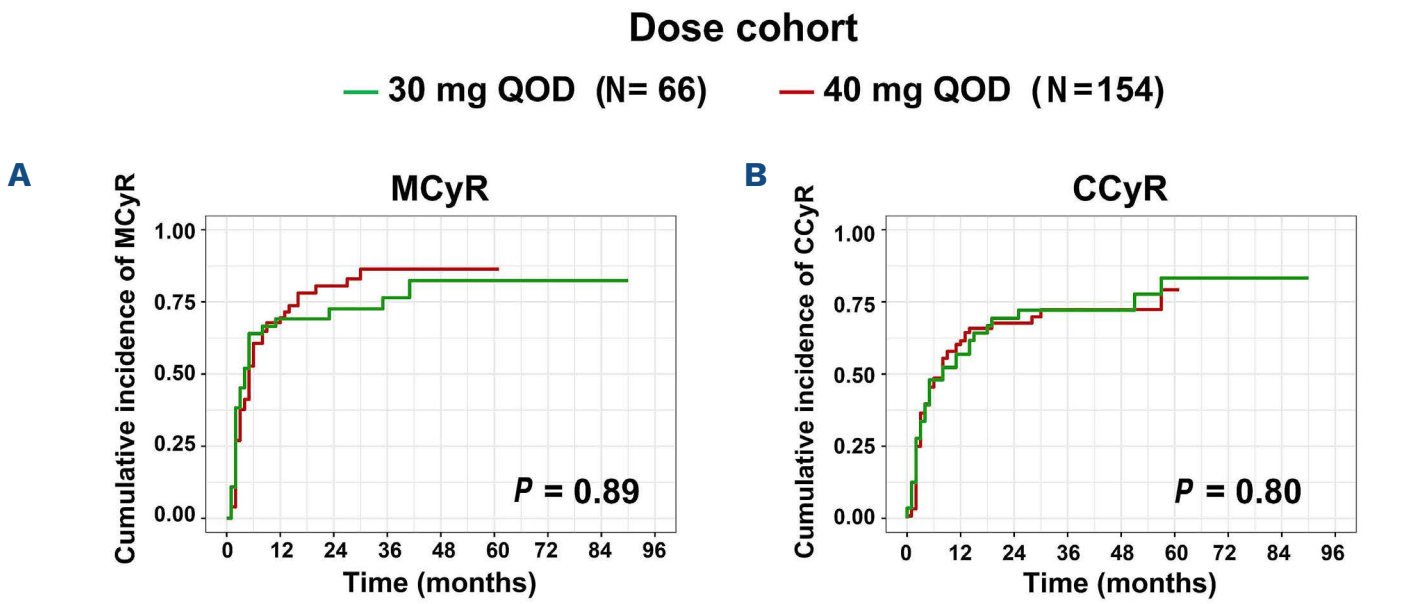
Co-variates listed without corresponding values were included in the initial multivariable Cox model but excluded during the final stepwise selection; therefore, hazard ratios and *P* values are not reported for them. MCyR: major cytogenetic response; CCyR: complete cytogenetic response; MMR: major molecular response; MR[4]: 4-log reduction in molecular response; PFS: progression-free survival; HR: hazard ratio; 95% CI: 95% confidence interval; Ref: reference; TKI: tyrosine kinase inhibitor; Ph+: Philadelphia chromosome-positive; ACA: additional cytogenetic abnormalities.

study, subjects were randomly assigned two three arms of ponatinib treatment at 45 mg, 30 mg or 15 mg, with mandatory dose reduction to 15 mg in the 45 mg and 30 mg arms once *BCR::ABL1*^{IS} levels dropped below 1%.[6] The 1-year CCyR rates were 44%, 29% and 23% in the three arms, respectively, while severe arterial occlusive events occurred less frequently than in the PACE study with ponatinib 45 mg.[4,6,7] Additionally, patients in the OPTIC study had a lower

Table 4. Treatment-related adverse events (before propensity score matching).

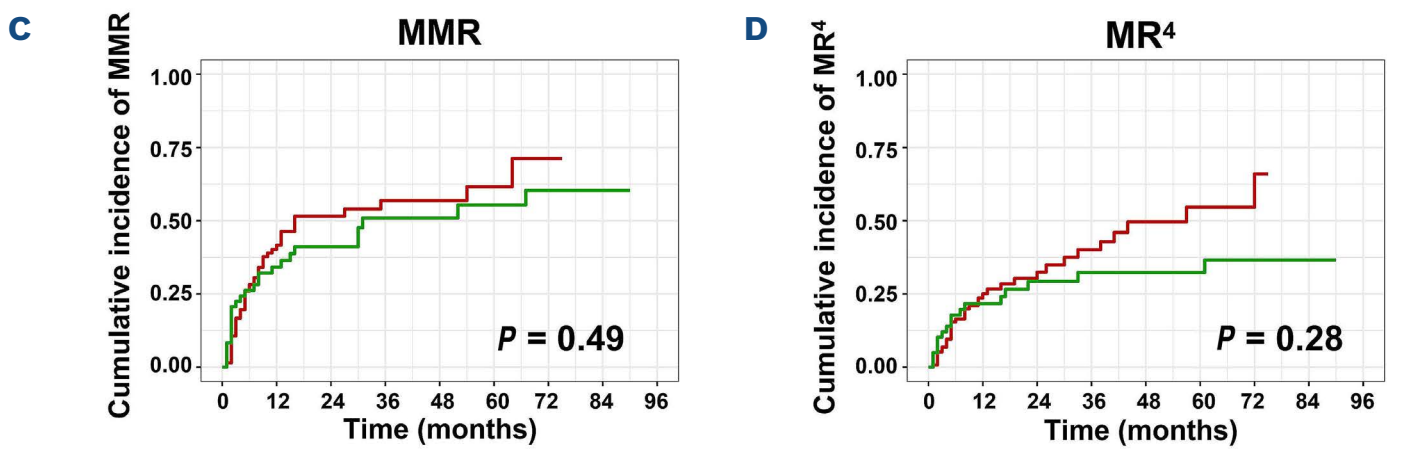
Treatment-related adverse events	30 mg QOD N=66	30 mg QOD N=216
	N of patients with event/total N of available patients (%)	
Hematologic (grade ≥3)		
Thrombocytopenia	33/66 (50)	92/211 (44)
Leukopenia	12/66 (18)	29/211 (14)
Neutropenia	9/66 (14)	21/211 (10)
Non-hematologic (any grade)		
Cardio- and cerebro-vascular toxicity	18/62 (29)	55/184 (30)
Hypertension	8/62 (13)	37/200 (19)
Sinus tachycardia	7/66 (11)	14/184 (8)
Arterial and/or venous obstructive events	3/66 (5)	17/213 (8)
Pericardial effusion	2/66 (3)	5/184 (3)
Sinus bradycardia	1/66 (2)	4/184 (2)
Atrial fibrillation	1/66 (2)	4/184 (2)
Heart failure	1/66 (2)	4/184 (2)
Pulmonary arterial hypertension§	1/66 (2)	3/184 (2)
Hepatic and renal toxicity	35/60 (58)	112/200 (56)
Alanine aminotransferase increased	21/63 (33)	59/201 (29)
Aspartate aminotransferase increased	21/63 (33)	54/201 (27)
Proteinuria	19/60 (32)	60/200 (30)
Glutamyl transferase increased	19/63 (30)	45/201 (22)
Alkaline phosphatase increased	8/63 (13)	26/201 (13)
Endocrine and metabolic toxicity	32/53 (60)	101/160 (63)
Hypertriglyceridemia	25/63 (40)	73/197 (37)
Hypocalcemia	14/62 (23)	33/200 (17)
Hypokalemia	14/62 (23)	27/200 (14)
Hyperglycemia	14/63 (22)	45/201 (22)
Hyponatremia	10/62 (16)	18/200 (9)
Hypoproteinemia	6/63 (10)	32/201 (16)
Lipase increased	6/60 (10)	15/184 (8)
Thyroid dysfunction*	0/53 (0)	6/160 (4)
Gastrointestinal toxicity	4/63 (6)	11/194 (6)
Nausea and/or vomiting	4/63 (6)	9/195 (5)
Diarrhea	3/63 (5)	7/194 (4)
Pancreatitis	0/66 (0)	1/216 (<1)
Others		
Skin pigmentation	40/62 (65)	121/200 (61)
Creatine kinase increased	14/62 (23)	50/198 (25)
Sexual dysfunction#	14/62 (23)	29/161 (18)
Fatigue	10/63 (16)	27/196 (14)
Muscle and/or joint pain	9/63 (14)	44/194 (23)
Fever	8/59 (14)	18/208 (9)
Rash	8/63 (13)	30/194 (15)
Pneumonia	4/60 (7)	8/200 (4)
Hemorrhage	4/66 (6)	5/197 (3)

§Pulmonary arterial hypertension was identified as highly suspected based on echocardiographic screening. *Thyroid dysfunction was characterized by elevated thyroid-stimulating hormone levels, with or without reduced free triiodothyronine/free thyroxine hormone levels in this study. #Sexual dysfunction was assessed through follow-up inquiries and patients' self-reports. All reported cases occurred in male patients, presenting primarily as erectile dysfunction and decreased libido. QOD: every other day.



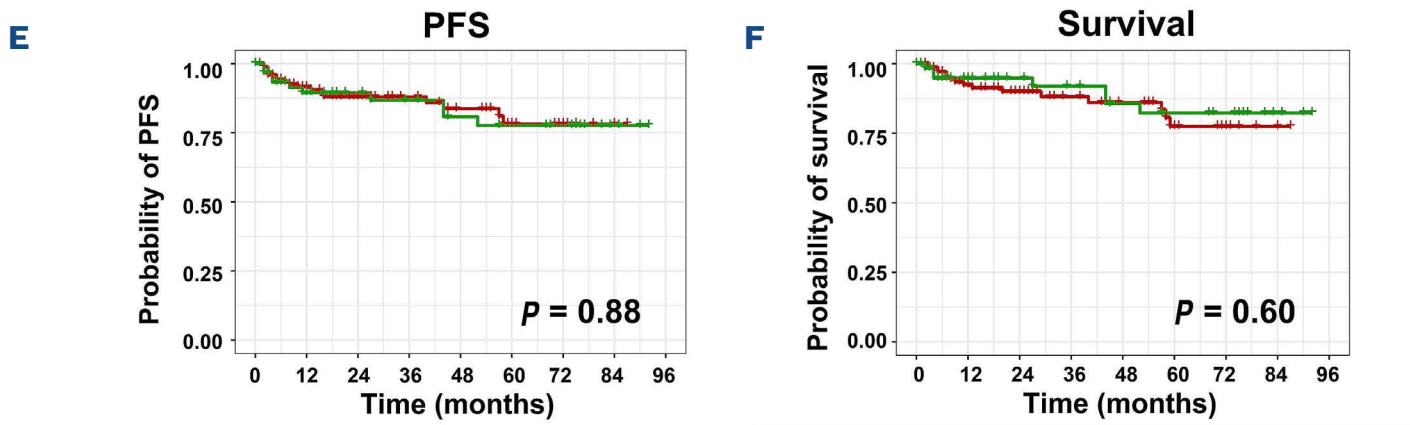
Cumulative incidences of MCyR (%)					
Dose cohort	1-year	2-year	3-year	4-year	5-year
— 30 mg QOD	67	73	77	84	84
— 40 mg QOD	69	81	86	86	86

Cumulative incidences of CCyR (%)					
Dose cohort	1-year	2-year	3-year	4-year	5-year
— 30 mg QOD	56	68	73	73	84
— 40 mg QOD	61	67	72	72	79



Cumulative incidences of MMR (%)					
Dose cohort	1-year	2-year	3-year	4-year	5-year
— 30 mg QOD	36	40	52	52	57
— 40 mg QOD	42	51	57	57	61

Cumulative incidences of MR4 (%)					
Dose cohort	1-year	2-year	3-year	4-year	5-year
— 30 mg QOD	22	29	32	32	32
— 40 mg QOD	25	32	40	50	55



Probabilities of PFS (%)					
Dose cohort	1-year	2-year	3-year	4-year	5-year
— 30 mg QOD	89	89	87	81	78
— 40 mg QOD	92	88	88	84	78

Probabilities of Survival (%)					
Dose cohort	1-year	2-year	3-year	4-year	5-year
— 30 mg QOD	95	95	92	86	82
— 40 mg QOD	92	90	88	86	77

Figure 2. Comparison of therapy responses and outcomes between the cohorts of patients who started treatment with 30 or 40 mg olverembatinib every other day after propensity score matching (A-F). QOD: every other day; MCyR: major cytogenetic response; CCyR: complete cytogenetic response; MMR: major molecular response; MR^4: 4-log reduction in molecular response; PFS: progression-free survival.

exposure-adjusted incidence of arterial occlusive events compared to those in the PACE study.[4-7] These precedents highlight the importance of TKI dose optimization and support our findings that olverembatinib 30 mg QOD provides comparable efficacy with improved tolerability compared to 40 mg QOD.

It is common that the incidence of TRAE increases with age.[16] The strategy of dose reduction is perhaps best suited to older persons who constitute the majority of people with CML. Although the median age of subjects in our study was 39 years, which is substantially younger than that of people of European descent, multivariate analyses revealed that age was not an independent predictor of therapy responses or outcomes. However, whether dose-reduction is equally effective in all age cohorts needs further study.

The incidences of TRAE in the 40 mg and 30 mg cohorts were similar, likely due to early dose reduction or discontinuation in approximately half of the subjects in the 40 mg cohort at a median of only 2 months on olverembatinib therapy. Nevertheless, the C_0 and C_6 levels of plasma concentrations in the 40 mg cohort remained significantly higher than those in the 30 mg cohort.

Recently, Jabbour *et al*. reported similar efficacy of olverembatinib at 40 and 30 mg doses with fewer severe adverse events and dose interruptions and discontinuations in the 30 mg cohort.[17] Our study with a larger sample size confirms these observations. Jabbour *et al*. also reported that a higher concentration of olverembatinib was needed to inhibit leukemia cells with BCR::*ABL1*^{T315I} than need for unmutated cells.[17] In contrast, we found no difference clinically.

Given that patients with CML require long-term or even lifelong treatment with TKI, cost-effectiveness is an essential consideration, especially in resource-limited and/or low-income regions.[18,19] Our findings indicate that the dose of 30 mg QOD might serve as a more cost-effective dosing strategy rather than 40 mg QOD as later-line TKI therapy for patients with CML. Our data indicate a 25% cost-reduction in China using the 30 mg QOD dose.

Our study has important limitations. First, the sources of the subjects' data were heterogeneous, including on and off clinical trials. In sensitivity analyses we found no differences. Second, our subjects were relatively young with a median age of 39 years and with few co-morbidities. The added safety benefit of the 30 mg QOD starting dose may be even greater in older persons. Third, the sample size is relatively small and follow-up brief. Larger samples with longer follow-up are needed to validate our conclusions. Fourth, we could not monitor compliance strictly because of the diverse contributing centers. However, this heterogeneity increases generalizability of our conclusions. Finally, PSM analyses can only adjust for known co-variates and, although useful, are not a substitute for randomized controlled trials.

In conclusion, olverembatinib 30 mg QOD as a starting dose has equivalent efficacy but better tolerability compared with 40 mg QOD in people with chronic-phase CML who are TKI-resistant and/or intolerant. Our data suggest that 30 mg QOD should be the starting dose of olverembatinib.

Disclosures

RPG is a consultant to Antengene Biotech LLC and Shenzen TargetRx; is Medical Director of FFF Enterprises Inc.; is a speaker for Janssen Pharma, BeiGene and Hengrui Pharma; sits on the Board of Directors of the Russian Foundation for Cancer Research Support; and is a member of the Scientific Advisory Board of StemRad Ltd.

Contributions

QJ designed the study. QJ, XZ, YY, BL, XD,[4] XW, LZ and YanlZ analyzed the data and prepared the typescripts. RPG provided valuable insights on data analyses and assisted in preparing the typescript. QJ, YF, BL, XD,[4] XW, HZ, LuY, ZoL, SZ, LinY, YM, LM, YanqZ, GL, LijY, BW, XR, JH, NG, QW, YW, YuxZ, YuZ, YH, ZhL, XD,[20] JW, LZ and YanlZ provided subjects' data and revised the typescript. All the authors approved the final typescript, take responsibility for its content and agreed to its submission for publication.

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Data-sharing statement

Data are available from the corresponding authors on reasonable request and in compliance with the laws of China.

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