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Phase 2 study of subcutaneous omacetaxine mepesuccinate for chronic-phase chronic myeloid leukemia patients resistant to or intolerant of tyrosine kinase inhibitors

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Abstract

Omacetaxine mepesuccinate (omacetaxine) is a first-in-class cephalotaxine with a unique mode of action, independent of BCR-ABL, that has shown promising activity in patients with chronic myeloid leukemia (CML). This multicenter, noncomparative, open-label phase 2 study evaluated the efficacy and safety of subcutaneous omacetaxine in CML patients with resistance or intolerance to two or more tyrosine kinase inhibitors (TKIs); results in patients in chronic phase are reported here. Patients received subcutaneous omacetaxine 1.25 mg/m² twice daily days 1–14 every 28 days until hematologic response (up to a maximum of six cycles), then days 1–7 every 28 days as maintenance. Primary endpoints were rates of hematologic response lasting >8 weeks and major cytogenetic response (MCyR). Forty-six patients were enrolled: all had received imatinib, 83% had received dasatinib, and 57% nilotinib. A median 4.5 cycles of omacetaxine were

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administered (range, 1–36). Hematologic response was achieved or maintained in 31 patients (67%); median response duration was 7.0 months. Ten patients (22%) achieved MCyR, including 2 (4%) complete cytogenetic responses. Median progression-free survival was 7.0 months [95% confidence interval (CI), 5.9–8.9 months], and overall survival was 30.1 months (95% CI, 20.3 months—not reached). Grade 3/4 hematologic toxicity included thrombocytopenia (54%), neutropenia (48%), and anemia (33%). Nonhematologic adverse events were predominantly grade 1/2 and included diarrhea (44%), nausea (30%), fatigue (24%), pyrexia (20%), headache (20%), and asthenia (20%). Subcutaneous omacetaxine may offer clinical benefit to patients with chronic-phase CML with resistance or intolerance to multiple TKI therapies.

Introduction

Despite the overall success of small-molecule tyrosine kinase inhibitors (TKIs) in the treatment of chronic myeloid leukemia (CML), a subset of CML patients demonstrate TKI resistance or intolerance. By 6 years, approximately one-third of patients discontinued first-line imatinib due to unsatisfactory therapeutic effect, safety, or other reasons [1]. Patients failing first-line TKI therapy typically receive another TKI as second-line treatment; rates of major cytogenetic response (MCyR) with dasatinib and nilotinib are 50–60% after failure of imatinib [2,3].

Patients who experience treatment failure with a second TKI may receive another TKI or undergo allogeneic hematopoietic stem cell transplantation (HSCT). The efficacy of dasatinib or nilotinib in patients who have failed prior treatment with two TKIs has been evaluated in several trials, in which MCyR rates have ranged from 24 to 50%; the highest rates are in series with a predominance of patients with intolerance to prior therapy [4–7]. These responses are relatively short in duration and discontinuation rates are high. The utilization of allogeneic HSCT is limited by donor availability and significant treatment-related mortality, particularly in older patients [8]. Thus, new therapies are needed for patients with treatment failure after multiple TKIs.

Omacetaxine mepesuccinate (hereafter omacetaxine) is a first-in-class cephalotaxine with a unique mode of action that has shown promising activity in CML [9–11]. Omacetaxine is not a TKI and as such is not dependent on BCR-ABL binding for its activity; instead, it binds to the A-site cleft of ribosomes, resulting in a profound but transient inhibition of protein synthesis [12]. In preclinical studies, omacetaxine selectively reduced levels of BCR-ABL as well as other short-lived oncoproteins that are upregulated in leukemic cells, such as Mcl-1 and c-Myc [13–16], inducing apoptosis in human CML cell lines and prolonging survival in BCR-ABL-expressing mice [17].

Here, we report the outcomes for chronic-phase patients enrolled in a phase 2 study to evaluate the clinical efficacy and safety of subcutaneous omacetaxine in patients with CML who had developed resistance and/or intolerance to two or more previous TKIs.

Methods

Study design

This was an open-label, single-arm study conducted at 28 sites in 10 countries. The study was conducted in accordance with the standards of Good Clinical Practice and the principles of the Declaration of Helsinki. The study protocol was approved by the relevant institutional review boards. This study is registered at clinicaltrials.gov as NCT00462943.

Patients

Male and female patients aged ≥ 18 years with Philadelphia chromosome-positive (Ph⁺) CML in chronic phase who experienced resistance or intolerance to prior treatment with ≥ 2 TKIs were eligible for inclusion (with the exception of patients enrolled in India, who were required to have failed ≥ 1 TKI). TKI resistance was defined as any of the following: no complete hematologic response at 12 weeks (whether lost or never achieved), no cytogenetic response at 24 weeks (whether lost or never achieved), no MCyR at 52 weeks (whether lost or never achieved), or progressive leukocytosis (defined as increasing white blood cell [WBC] count measured at least 2 weeks apart and doubling from nadir to $\geq 20,000/\mu\text{L}$ or absolute increase in WBC count by $\geq 50,000/\mu\text{L}$ above the post-treatment nadir). Intolerance to TKI therapy included any grade 3/4 nonhematologic toxicity not resolving with adequate intervention, any grade 4 hematologic toxicity lasting more than 7 days, or any grade ≥ 2 toxicity that was unacceptable to the patient. Patients were required to have bilirubin levels ≤ 2.0 times the upper limit of normal, alanine aminotransferase levels ≤ 3 times the upper limit of normal, creatinine levels ≤ 1.5 times the upper limit of normal, and an Eastern Cooperative Oncology Group performance status of 0–2. Written informed consent for participation was obtained from all patients prior to enrollment.

The main criteria for study exclusion were New York Heart Association class III or IV heart disease, active ischemia or any other uncontrolled cardiac condition, myocardial infarction within the last 12 weeks, interfering concurrent illness (such as malignancy or infection), and lymphoid Ph⁺ blast phase. Prior transplantation was allowed. Patients were also required to have completed all previous antileukemic therapy at least 2 weeks prior to the first planned dose of omacetaxine. Patients with rapidly proliferating disease could receive hydroxyurea immediately prior to and during the first two cycles of treatment.

Study treatment

Omacetaxine was either self-administered or administered by a nurse or caregiver at home on an outpatient basis. Patients were provided with a diary in which to record the time and location of injection and any reactions that occurred. Compliance was assessed based upon diary entries.

During induction therapy, patients received subcutaneous omacetaxine $1.25 \text{ mg}/\text{m}^2$ twice daily for up to 14 days, every 28 days. In patients with rapidly proliferating disease, concomitant hydroxyurea could be administered immediately prior to and during the first two cycles of treatment, and in subsequent cycles after approval from the Medical Monitor. Patients with no evidence of clinical response after six induction cycles were considered for

discontinuation from study drug; patients achieving hematologic response, hematologic improvement, or any cytogenetic response were converted to maintenance treatment. Maintenance treatment consisted of omacetaxine 1.25 mg/m² twice daily for up to 7 days every 28 days for up to 24 months; maintenance therapy could be continued beyond 24 months at the physician's discretion with the approval of the Medical Monitor. Patients with loss of response during maintenance therapy could revert to induction treatment at the highest previously tolerated dose, if clinically indicated.

In the event of toxicity, adjustments were made to the number of consecutive days of treatment within each 28-day dosing cycle while keeping the daily dose constant. In patients who developed grade 4 neutropenia (absolute neutrophil count $<0.5 \times 10^9/L$) or grade 3 thrombocytopenia (platelet count $<50 \times 10^9/L$), treatment was delayed until recovery to absolute neutrophil count $>1.0 \times 10^9/L$ and platelet count $>50 \times 10^9/L$, and the number of consecutive days of treatment reduced by 2 days in subsequent cycles with further reductions in the number of daily doses per cycle allowed in cases of recurrent myelosuppression. Omacetaxine dose was not modified for myelosuppression in patients with WBC count $>10 \times 10^9/L$ and/or absolute blast count $>5 \times 10^9/L$. Nonhematologic toxicity was managed similarly. For grade 2 adverse events unresponsive to supportive care, treatment could be interrupted until resolution to grade 1. For grade 2 adverse events, treatment was then resumed at full dose; for grade 3 adverse events, the number of treatment days was reduced by 2 in subsequent cycles.

Assessments

Patients were evaluated every 7 days during induction treatment, every 14 days during the first 3 maintenance treatment cycles, and every 28 days thereafter. Assessments included physical examination, a complete blood cell count with WBC differential, and serum chemistry. Electrocardiogram, bone marrow aspiration, and cytogenetic analysis (involving at least 20 metaphases) were performed every 3 months, or earlier if clinically indicated. *BCR-ABL* kinase domain mutation analysis was performed in peripheral blood by two central reference laboratories: in the United States the ABL kinase domain was amplified by reverse transcriptase polymerase chain reaction and sequenced, and in Europe mutations were detected by denaturing high-performance liquid chromatography followed by direct sequencing.

An independent data monitoring committee was responsible for adjudicating the response of each patient. Achievement of hematologic response or MCyR during induction therapy was confirmed by repeat complete blood count, bone marrow aspiration, and cytogenetics, as appropriate, 8 weeks after initial detection. A follow-up evaluation was conducted in all patients at the completion of study treatment. Upon study discontinuation, patient survival data were collected via telephone follow-up every 3 months. Toxicities were assessed and graded according to the National Cancer Institute Common Terminology for Adverse Events version 3.0 where applicable, or otherwise graded as mild, moderate, severe, life-threatening, or fatal. Adverse events were classified by body system using the MedDRA Thesaurus and categorized by body system.

Study endpoints

The primary endpoint was the proportion of patients with hematologic response lasting for >8 weeks or MCyR. Hematologic response was defined as a WBC count $<10 \times 10^9/L$, a platelet count $<450 \times 10^9/L$, <20% basophils in peripheral blood, the absence of blasts or promyelocytes in peripheral blood, the presence of <5% myelocytes plus metamyelocytes in peripheral blood, and no extramedullary involvement (including a normal-sized liver and spleen on physical examination). In patients who received hydroxyurea during the first two cycles of treatment, only hematologic response that was sustained for 8 weeks after discontinuation of hydroxyurea was documented as a response. MCyR was defined as a complete (CCyR) or partial (PCyR) cytogenetic response (CCyR: 0% Ph⁺ cells, PCyR: 1–35% Ph⁺ cells), based on standard cytogenetic analysis with at least 20 metaphases counted. Secondary endpoints included other hematologic and cytogenetic responses, the number of induction cycles required for response, duration of response, failure-free survival (FFS), overall survival (OS) including long-term follow-up by telephone survey after study discontinuation, and safety.

Statistical analysis

Descriptive statistics (number of patients, mean, minimum, median, maximum, and standard deviation) were used to summarize continuous variables; for categorical variables, number and percent of total were tabulated.

All enrolled patients were treated with the study drug and included in the safety population. All efficacy and safety analyses were performed in the safety population. Exact 1-sided lower 95% binomial confidence limits were calculated for primary response endpoints (hematologic response and MCyR). For time-to-event variables (duration of response, FFS, and OS), the median and 95% confidence interval (CI) were calculated using Kaplan-Meier product limit estimates. Duration of response was defined as the time from the onset of hematologic or cytogenetic response until the date of objective evidence of disease progression, relapse, or death. FFS was defined as the time from initiation of treatment until the date of death from any cause, development of accelerated-phase or blast-phase CML, loss of hematologic response or MCyR, or discontinuation due to toxicity or disease progression; patients without progression were censored at the time of study discontinuation or data cut-off, whichever came first. OS was defined as the time from initiation of treatment until death from any cause.

Results

Patient demographics and treatment

Forty-six patients with CML in chronic phase were enrolled from March 2007 through June 2009 (Table I). Median patient age was 58 years (range, 20–78 years) and median time from initial diagnosis was 6.2 years (range, 0.66–18.4 years). Among 33 patients with mutational analysis, 13 had a *BCR-ABL* kinase domain mutation prior to therapy with omacetaxine. The most common mutations detected were F395V ($n = 4$) and V299L ($n = 3$).

Eighty-five percent of patients had received treatment with two or more TKIs and 59% of patients had received three or more TKIs (Table I). The most common previous non-TKI antileukemia treatments were hydroxyurea (52% of patients), cytarabine (37%), and interferon (28%). Eight patients (17%) were in hematologic response at baseline. Twenty-one patients, none of whom were in hematologic response at baseline, received hydroxyurea to control their WBC count within 48 hr of treatment initiation; 18 patients received hydroxyurea after treatment initiation, including five patients who received treatment after cycle 2.

At the cut-off for data analysis (January 2011), 41 patients (89%) had discontinued the study drug; the most common reason for discontinuation was disease progression (Table II). Five patients (11%) continued treatment, having received a median of 30 treatment cycles (range, 12–36) to date. Overall, patients received a median of 4.5 treatment cycles (range, 1–36 cycles), and the median duration of omacetaxine exposure was 5.1 months (range, 0.2–33.3 months).

Efficacy

Of the 46 patients enrolled in this study, 31 [67%; 95% lower confidence limit (LCL), 52.0%] achieved or maintained hematologic response (Table III), with a median duration of 70 months (range, 1.4–35.0 months). Among the 38 patients not in hematologic response at the start of omacetaxine therapy, the rate of hematologic response was 61% (23/38). Ten patients (22%; 95% LCL, 11.0%) achieved MCyR, including two (4%) with CCyR and eight (17%) with PCyR (Table III). In addition, seven patients (15%) achieved a minor cytogenetic response. The median duration of MCyR was 6.0 months (range, 1–25 months). In an ad hoc analysis, the arithmetic median time to onset of MCyR among patients who achieved this response ($n = 10$) was 2.5 months (range, 0.0–5.7 months).

After a median follow-up of 19.1 months (range, 0.3–35.3 months), estimated median progression-free survival was 7.0 months (95% CI, 5.9–8.9 months) and estimated median OS was 30.1 months (95% CI, 20.3 months—not reached) (Fig. 1). Of 13 patients who discontinued the study due to disease progression, nine were reported by the investigators to have progressed to accelerated phase ($n = 5$) or blast phase ($n = 4$). Median OS was not reached in patients with a major or minor cytogenetic response, and was 27.8 months (95% CI, 14.4–33.9 months) in patients with no response or inevaluable for response (Fig. 2).

Safety

Toxicities associated with omacetaxine were primarily hematologic. Grade 3/4 myelosuppression was common, with grade 3/4 adverse events of thrombocytopenia, neutropenia, and anemia occurring in 54, 48, and 33% of patients, respectively (Table IV). Nonhematologic adverse events were predominantly grade 1 or 2 in severity; the most common events of any grade were diarrhea (44%), nausea (30%), fatigue (24%), pyrexia (20%), headache (20%), and asthenia (20%) (Table IV). Grade 3/4 nonhematologic events occurring in >1 patient were fatigue (4%), pneumonia (4%), and hypokalemia (4%). Infection was reported in 27 patients (59%) and was of grade 3/4 severity in eight patients (17%). Administration site conditions, which included erythema ($n = 8$ patients), injection

site reaction ($n = 5$), rash ($n = 3$), induration ($n = 2$), and inflammation, bruising, irritation, pruritus, and pain ($n = 1$ each), were all reported as grade 1 or 2 in severity.

Serious adverse events were reported in 25 patients (54%). Eighteen patients (39%) experienced serious adverse events considered possibly or probably related to study drug or with unknown relationship to study drug; these included pancytopenia ($n = 7$), thrombocytopenia ($n = 3$), pancytopenia associated with fever ($n = 2$), pneumonia ($n = 2$), and single cases each of anemia, neutropenia, febrile neutropenia, gastrointestinal hemorrhage (in the presence of grade 4 thrombocytopenia), injection site infection, localized edema, sepsis, lung infection, and back pain.

Delays to treatment cycles occurred in 32 patients (70%), with a median delay duration of 10 days (range, 2–79 days). The most common reasons for delay were related to myelosuppression, namely thrombocytopenia (47% of those with delay), pancytopenia (31%), and neutropenia (28%); 34% of delays were due to patient availability.

Six deaths occurred on study or within the first 30 days of follow-up. The causes of death were disease progression ($n = 2$) and sepsis, multiorgan failure, failure to thrive, and cause unknown ($n = 1$ each); none of the patients were in remission at the time of death. One death, due to sepsis, was considered probably related to study drug. In this patient, pancytopenia developed during the first cycle of treatment and study drug was discontinued; the pancytopenia was not resolved and the patient died 7 months after the last dose of study drug. The death due to unknown causes occurred 34 days after the last dose of study drug and was considered possibly related to study drug. An additional 12 deaths were reported during long-term follow-up by telephone survey.

Discussion

Treatment options for CML patients after failure of multiple TKI therapies are limited. In this study, omacetaxine produced and/or maintained a hematologic response for 8 weeks in 67% of patients with heavily pretreated CML in chronic phase, more than half (59%) of whom had been previously treated with three or more TKIs. Furthermore, the rate of MCyR with omacetaxine treatment in this population was 22%, and the overall cytogenetic response rate (including minor responses) was 37%. The responses observed were durable, with a median duration of 6.0 months for MCyR. Notably, the median OS was 30 months, which is higher than might have been expected in this patient group based on historical data from the literature. Although the clinical value of MCyR has been long recognized, achievement of hematologic response and lesser cytogenetic responses (partial and minor) has also been shown to correlate with improved survival in patients receiving second and later lines of therapy [18], indicating that the responses achieved in the current study may have had significant clinical value.

The observed tolerability profile of omacetaxine was acceptable. Hematologic toxicity comprised the most common grade 3/4 adverse events and was the most frequent reason for treatment delay. Hematologic adverse events could usually be managed with adequate monitoring and dose adjustment (reducing the number of days of omacetaxine

administration). Nonhematologic toxicities were mainly grade 1/2, and most commonly included diarrhea, nausea, and fatigue. Grade 3/4 nonhematologic events were relatively uncommon, with no event occurring in more than 4% of patients. Omacetaxine was administered on an intermittent schedule (14 days on, 14 days off during induction; 7 days on, 21 days off during maintenance), a schedule that was well accepted by patients.

Omacetaxine has a unique mechanism of action, providing a non-TKI treatment alternative for patients who have failed multiple prior TKI therapies or are intolerant of these agents. Responses reported from studies of additional TKI therapy after failure of two or more TKIs have been few and of relatively short duration [4–7], and few options are available for patients who have failed three TKIs other than HSCT for select patients. In addition, early clinical data suggest that treatment of TKI-resistant disease with omacetaxine may allow successful subsequent rechallenge with TKIs [19]. Furthermore, the disease suppression achieved with omacetaxine may provide a window of opportunity in which to perform allogeneic HSCT; three patients in this study discontinued omacetaxine therapy to undergo transplantation.

Limitations of the current study include the noncomparative design and relatively small sample size. In addition, the dose and dosing regimen used in this trial were based on past experience with the intravenous administration of omacetaxine; investigation of different doses and/or dosing schedules and individualization of treatment might be an area for future studies. Also, no patients with the *BCR-ABL* T315I mutation were included in this trial due to concurrent enrollment of a “sister” study in which subcutaneous omacetaxine treatment was assessed in patients with CML with a history of the T315I mutation. Among 62 chronic-phase patients enrolled in the sister study (75% of whom had failed two TKIs), MCyR was achieved in 24% and OS was 65% at 2 years [20].

Overall, the findings of the current study indicate that subcutaneously administered omacetaxine can produce clinically meaningful hematologic and cytogenetic responses with an acceptable safety profile in patients with chronic-phase CML after treatment failure with multiple TKIs, potentially providing a valuable new therapeutic option in a population with few treatment choices.

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Figure 1. Failure-free (A) and overall survival (B) in patients with chronic-phase CML treated with omacetaxine ($n = 46$).

Figure 2. Overall survival according to best cytogenetic response (major response versus minor response versus no response/inevaluable) in patients with chronic-phase CML.

TABLE I

Demographics and Baseline Characteristics

<i>n</i> = 46	
Age, years	
Median	58
Youngest, oldest	20, 78
Gender, <i>n</i> (%)	
Male	26 (57)
Female	20 (43)
Hematologic response at baseline, <i>n</i> (%)	
Yes	8 (17)
No	38 (83)
Hydroxyurea use at study entry, <i>n</i> (%)	
Yes	21 (46)
No	25 (54)
<i>BCR-ABL</i> mutation, <i>n</i> (%)	
Yes ^a	13 (28)
No	20 (44)
Not available	13 (28)
Previous TKIs received, <i>n</i> (%)	
Imatinib	46 (100)
Dasatinib	38 (83)
Nilotinib	26 (57)
Other ^b	4 (9)
No. of prior TKIs, <i>n</i> (%)	
1	7 (15)
2	12 (26)
3	25 (54)
>3	2 (4)

^a Includes eight patients with a single mutation (F395V [*n* = 2], G250E, V299L, F317I, F317L, H396R, E453K) and five patients with multiple mutations (M244V/G250E, M244V/E255Q, V299L/F359C, V299L/F359V, L248V/M351T/F359V).

^b Includes investigational TKIs MK0457 (tozasertib), INNO406, SKI606 (bosutinib), and KW2449.

TKI, tyrosine kinase inhibitor.

TABLE II**Patient Disposition and Reasons for Study Discontinuation**

Patients (<i>n</i> = 46)	<i>n</i> (%)
Disposition	
Participation ongoing	5 (11)
Discontinued study	41 (89)
Primary reason for discontinuation	
Disease progression	13 (28)
Patient, physician, or sponsor request	8 (17)
Failure to achieve response	5 (11)
Death	5 (11)
Adverse event	4 (9)
Patient noncompliance	1 (2)
Other	5 (11)

TABLE III**Best Clinical Response to Omacetaxine Treatment**

Hematologic response, <i>n</i> (%)	
Overall	31 (67)
Complete ^a	31 (67)
Partial	0
Hematologic improvement	0
No response	10 (22)
Inevaluable ^b	5 (11)
Cytogenetic response, <i>n</i> (%)	
Overall	17 (37)
Major ^a	10 (22)
Complete ^c	2 (4)
Partial ^c	8 (17)
Minor	7 (15)
No response	18 (39)
Inevaluable ^d	11 (24)

^aPrimary endpoint.

^bInevaluable due to missing data; all inevaluable patients discontinued treatment in cycle 1.

^cIncludes confirmed and unconfirmed responses. An unconfirmed response is based on a single bone marrow cytogenetic evaluation where a confirmatory evaluation is not available.

^dInevaluable due to absence of post-baseline bone marrow assessment.

TABLE IV

Treatment-Emergent Adverse Events: Hematologic and Nonhematologic (15% Incidence)

Event	All grades <i>n</i> (%)	Grade 3/4 <i>n</i> (%)
Hematologic		
Thrombocytopenia	31 (67)	25 (54)
Anemia	25 (54)	15 (33)
Neutropenia	23 (50)	22 (48)
Leukopenia	9 (20)	9 (20)
Pancytopenia	8 (17)	8 (17)
Febrile neutropenia	7 (15)	7 (15)
Nonhematologic		
Diarrhea	20 (44)	0
Nausea	14 (30)	0
Fatigue	11 (24)	2 (4)
Headache	9 (20)	1 (2)
Asthenia	9 (20)	1 (2)
Pyrexia	9 (20)	0
Epistaxis	8 (17)	0
Injection site erythema	8 (17)	0
Pain in extremity	8 (17)	1 (2)
Peripheral edema	7 (15)	0
Vomiting	7 (15)	0