Omacetaxine mepesuccinate for patients with accelerated phase chronic myeloid leukemia with resistance or intolerance to two or more tyrosine kinase inhibitors

Accelerated phase chronic myeloid leukemia (AP-CML) is characterized by tyrosine kinase inhibitor (TKI) resistance, additional cytogenetic abnormalities, and tyrosine kinase mutations.[1,2] Although the recently approved TKI ponatinib may be effective in some patients with TKI-resistant AP-CML, patients with resistance or intolerance to multiple TKIs may benefit from a non-TKI approach.

Omacetaxine mepesuccinate ("omacetaxine") provides a unique mechanistic approach to the treatment of relapsed/refractory CML that, unlike TKIs, does not require binding to BCR-ABL and is not affected by resistance-conferring mutations in BCR-ABL.[3-6] Functioning as a protein synthesis inhibitor;[7,8] omacetaxine reduces levels of multiple oncoproteins, including BCR-ABL, and induces apoptosis in leukemic stem cells.[3-6] Omacetaxine has demonstrated clinical activity in chronic phase (CP)-CML patients previously treated with TKIs.[9] Here we report the efficacy and safety of omacetaxine in patients with AP-CML who have demonstrated intolerance or resistance to two or more approved TKIs.

Patients with AP-CML enrolled in two international open-label phase II studies of omacetaxine (CML-202 and CML-203) were included in this pooled analysis if they had previously received imatinib and had documented resistance or intolerance to dasatinib and/or nilotinib. AP-CML was defined as: 15-30% blasts, 30% or over blasts and promyelocytes, or 20% or over basophils in peripheral blood or bone marrow; platelet count less than 100×10^9/L unrelated to therapy; or clonal evolution. Primary end points were rates of major hematologic response (MaHR) and major cytogenetic response (MCyR). Treatment and assessments were identical in the two studies. Patients received induction therapy with omacetaxine 1.25 mg/m^2 administered subcutaneously twice daily (BID) Days 1 to 14 every 28 days for up to six cycles or until hematologic or cytogenetic response. Patients who achieved hematologic or cytogenetic response were switched to maintenance omacetaxine therapy 1.25 mg/m^2 BID for 7 consecutive days every 28 days. In patients who developed grade 4 neutropenia or grade 3 or over thrombocytopenia, treatment was delayed until recovery to values of grade 2 or under, and the number of consecutive days of treatment was reduced by two days in subsequent treatment cycles. Similar adjustments were made for treatment-related non-hematologic toxicities that did not respond to supportive care.

Forty-one patients with AP-CML met inclusion criteria for this analysis; base-line characteristics are shown in Table 1. At the time of data cut off (January 2011), 39 patients (95%) had discontinued the study due to progressive disease (49%), lack of efficacy (17%), death (12%), adverse events (5%), or withdrawal by request (12%). Median duration of follow up was 11.5 months (95%CI: 6.8-16.0 months).

Patients received a median of two treatment cycles (range 1-29 cycles); median duration of omacetaxine exposure was 1.9 months (range 0.03-30 months). Two patients remained on study treatment at the time of this analysis, having received 13 and 14 treatment cycles over a period of 31.2 months and 18.1 months, respectively. The median number of treatment days per cycle was 14 (range 1-17 days) in cycles 1 to 3, consistent with induction dosing. The number of patients receiving 14 days of treatment each cycle gradually decreased, from 85% (35 of 41 patients) in cycle 1 to 50% (10 of 20 patients) in cycle 3, with a median of 7 to 8 treatment days in cycles 4 to 6, consistent with a transition to maintenance dosing.

Table 1. Patients' baseline characteristics.

Baseline characteristics	All patients (n=41)
Previously failed approved TKIs, n (%)	
Imatinib and dasatinib	14 (34)
Imatinib and nilotinib	3 (7)
Imatinib, dasatinib, and nilotinib	24 (59)
Reasons for TKI treatment failure, n (%)	
Resistance to ≥2 TKIs	36 (88)
Intolerance ≥2 TKIs	3 (7)
Resistance to 1 TKI and intolerance to 1 TKI	2 (5)
Median time since CML diagnosis to study drug initiation, months (range)	97.8 (23.5-285.6)
Previous stem cell transplant, n (%)	2 (5)
Hydroxyurea use at enrollment, n (%)	26 (63)
ACA present at baseline, n (%)	20 (49)
BCR-ABL mutation status at baseline	
Positive	22 (53)
Multiple mutations	5 (12)
T315I	10 (24)
Negative	9 (22)
No baseline data	10 (24)

ACA: additional chromosomal abnormalities; CML: chronic myeloid leukemia; TKI: tyrosine kinase inhibitor.

MaHR was achieved or maintained in 11 patients (27%) (Table 2). MaHR was 40% (6 of 15) among patients who were not receiving hydroxyurea at baseline and 19% (5 of 26) in those who were. In an *ad hoc* efficacy analysis that excluded 6 patients with MaHR at baseline, the overall rate of MaHR was 14% (5 of 35). Among patients with evidence of clonal evolution at baseline, the MaHR rate was 25% (5 of 20); in 2 of these patients, clonal evolution became undetectable with omacetaxine treatment. The rate of MaHR was 32% (7 of 22) in patients with any mutation in BCR-ABL at baseline, 40% (2 of 5) in patients with multiple mutations, and 50% (5 of 10) in patients with T315I. Six patients (15%) achieved minor CyR (Table 2); the median number of cycles necessary to achieve minor CyR in these patients was 1.5 (range 1-3).

The median duration of MaHR was 9.0 months (95%CI: 3.6-14.1 months). Patients who had received two prior TKIs had a longer median duration of response (13.4 months; 95%CI: 5.6-14.1 months) than those who had received three prior TKIs (6.4 months; 95%CI: 3.6 months-NA). The duration of best CyR was 3.0 months (95%CI: 2.3-3.9 months). Median failure-free survival (FFS) was 4.7 months (95%CI: 2.1-7.0 months) and median overall survival (OS) was 16.0 months (95%CI: 8.2-24.6 months). Patients who achieved MaHR had longer median FFS (9.0 *vs.* 3.5 months) and OS (24.6 *vs.* 8.9 months) than those without MaHR. Among patients with minor CyR (n=6), median FFS was 7.9 months (95%CI: 1.7-NA) and median OS was 35.8 months (95%CI: 6.8-57.2 months).

The toxicity profile associated with omacetaxine was primarily hematologic. Grade 3/4 hematologic adverse events were reported in 78% of patients (thrombocytopenia 51%; anemia 37%; neutropenia 22%). Febrile neutropenia was reported in 6 patients (15%). Granulocyte-stimulating factors were administered in 5% of patients and erythropoiesis-stimulating agents in 17%. Thirty-one patients

Table 2. Best DMC-adjudicated hematologic and cytogenetic responses to omacetaxine.

Response, n (%)	All patients (n=41)
Best hematologic response	
Major hematologic response	11 (27)
Complete hematologic response	10 (24)
No evidence of leukemia	1 (2)
Return to chronic phase	2 (5)
Hematologic improvement	3 (7)
Partial hematologic response	1 (2)
No response	19 (46)
Not evaluable	5 (12)
Best cytogenetic response	
Complete	0
Partial	0
Minor	6 (15)
No response	19 (46)
Not evaluable	16 (39)

DMC: Data Monitoring Committee.

(76%) received red blood cells and 24 patients (59%) received platelets. The most common non-hematologic adverse events were infection (all grades, 59%; grade ≥3, 27%), diarrhea (37%), pyrexia (29%), fatigue (24%), asthenia (24%), and nausea (22%). Of the 32 patients receiving at least two cycles of treatment, 20 (63%) had at least one cycle delay during the study. The most common reasons for treatment delays were thrombocytopenia (36% of delays) and neutropenia (20% of delays).

In conclusion, omacetaxine may be a feasible and tolerable treatment option for this patient population. Subcutaneous omacetaxine induced or maintained hematologic response and minor cytogenetic response in a minority of patients with AP-CML who had failed multiple TKIs. Although response duration was limited, the achievement of response may serve as a bridge to allogeneic stem cell transplantation, which remains the best possibility for long-term survival in patients with advanced CML.

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