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

Franck E. Nicolini, Centre Hospitalier Lyon Sud
H Jean Khoury, Emory University
Luke Akard, St. Francis Health
Delphine Rea, Hôpital Saint-Louis
Hagop Kantarjian, University of Texas
Michele Baccarani, University of Bologna
Janis Leonoudakis, Powered 4 Significance LLC
Adam Craig, ChemGenex Pharmaceuticals
Annie-Claude Benichou, ChemGenex Pharmaceuticals
Jorge Cortes, University of Texas

Journal Title: Haematologica
Volume: Volume 98, Number 7
Publisher: Ferrata Storti Foundation | 2013-07-01, Pages E78-E79
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.3324/haematol.2012.083006
Permanent URL: https://pid.emory.edu/ark:/25593/s7728

Final published version: http://dx.doi.org/10.3324/haematol.2012.083006

Copyright information:
© Ferrata Storti Foundation

Accessed December 25, 2019 11:30 PM EST
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. 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. Functioning as a protein synthesis inhibitor, omacetaxine reduces levels of multiple oncoproteins, including BCR-ABL, and induces apoptosis in leukemic stem cells. Omacetaxine has demonstrated clinical activity in chronic phase (CP)-CML patients previously treated with TKIs. 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 x 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/m² 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/m² 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.

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); 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.

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

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.

Franck E. Nicolini,1 H. Jean Khoury, b Luke Akard,2 Delphine Rea,4 Hagop Kantarjian,5 Michele Bacaccarla,6 Janis Leonoudakis,7 Adam Craig,8 Annie-Claude Benichou,9 and Jorge Cortes10

Hematology department 1G, Centre Hospitalier Lyon Sud, Pierre Béline, France; Emory University School of Medicine, Atlanta, Georgia, USA; Indiana Blood and Marrow Transplantation at St. Francis Health, Indianapolis, Indiana, USA; Service des Maladies du Sang, EA3518 and CIC, Hôpital Saint-Louis, Paris, France; University of Texas MD Anderson Cancer Center, Houston, Texas, USA; University of Bologna, Bologna, Italy; Powered 4 Significance LLC, Bloomsbury, New Jersey, USA; formerly of ChemGenex Pharmaceuticals, an indirect wholly owned subsidiary of Teva Pharmaceuticals, an indirect wholly owned subsidiary of Teva Pharmaceutical Industries Ltd., Petach Tikva, Israel.

Key words: omacetaxine, homoharringtonine, advanced chronic myeloid leukemia, tyrosine kinase inhibitors, imatinib, dasatinib, nilotinib.

Correspondence: franck-emanuel.nicolini@chu-lyon.fr

Acknowledgments: the authors would like to thank the investigators who contributed accelerated-phase patients to this study: Maria Baer, Ragahundharathi Digomari, Laurence Legros, Armín Leitner, Jeffrey Lipton, David Mann, Tamas Masszi, Mauricette Michellet, Candido Rivera, Philippe Rousselet, and Krzysztof Warzocha. We would also like to thank Madeleine Eniene and Elda Gaullet, CRAs, Hematology department 1G in Pierre Béune, France, for assistance with study enrollment at this site. The authors would like to thank ChemGenex Pharmaceuticals, now an indirect wholly owned subsidiary of Teva Pharmaceutical Industries Ltd., for study funding and Teva Branded Pharmaceutical Products R&D, Inc. for funding of medical writing assistance. The authors would also like to thank Peter Brown, PhD, of Teva Pharmaceuticals for his critical review of the data and manuscript and Glen Davis of Teva Pharmaceuticals for his dedicated support in the collection and review of additional clinical data.

Funding: FEN reports grants from Novartis and Bristol-Myers Squibb (BMS), and personal fees from Pfizer, Novartis, Teva, Aran, and BMS, outside the submitted work. HKJ has nothing to disclose. LA reports grants and personal fees from Teva/Cephalon during the conduct of the study, and personal fees from BMS, grants and personal fees from Aran, grants from Merc, grants and personal fees from Novartis, grants from Pfizer, personal fees from Celgene, and grants from Millennium, outside the submitted work. DR reports personal fees from BMS, Novartis, and Teva, outside the submitted work. HK reports grants from ChemGenex during the conduct of the study and grants from Novartis, BMS, Aran, and Pfizer, outside the submitted work. MB reports other support from Teva, outside the submitted work. AC reports personal fees from ChemGenex, outside the submitted work. AC-B reports other support from ChemGenex during the conduct of the study. JL reports personal fees from Teva Branded Pharmaceutical Products R&D during the conduct of the study. JEC reports grants and non-financial support from ChemGenex during the conduct of the study, and grants and personal fees from Aran, grants from BMS, grants and personal fees from Pfizer, and grants from Novartis, outside the submitted work.

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.

References

3. Allan KE, Holyoake TL, Craig AR, Jorgensen HG. Omacetaxine may have a role in chronic myeloid leukaemia eradication through downregulation of McI-1 and induction of apoptosis in stem/progenitor cells. Leukemia. 2011;25(8):985-95.