Omacetaxine for chronic or accelerated phase CML in patients with resistance or intolerance to TKIs

See Commentary on page 193

Omacetaxine mepesuccinate has been granted accelerated approval for the treatment of adult patients with chronic phase (CP) or accelerated phase (AP) chronic myeloid leukemia (CML) with resistance or intolerance to 2 or more tyrosine kinase inhibitors (TKIs).[1,2] Approval was based on response rates observed in a combined cohort of adult CML patients from 2 clinical trials. As yet, no clinical trials have verified improved disease-related symptoms or increased survival with omacetaxine treatment.

The mechanism of action of omacetaxine is not fully known, but it includes inhibition of protein synthesis and activity that is independent of direct BCR-ABL binding.[2,3] The agent was shown to have activity in CML patients in the pre-TKI era. In studies in vitro, omacetaxine reduces levels of the BCR-ABL oncoprotein and Mcl-1 (an anti-apoptotic BCL-2 family member), and its activity is not affected by presence of BCR-ABL mutations. It exhibits activity in animal models of wild-type and T315I-mutant BCR-ABL CML and in CML patients with the T315I mutation.

The combined cohort in which efficacy of omacetaxine was assessed consisted of 111 patients (76 with CP CML and 35 with AP CML) who had received 2 or more approved TKIs and had documented evidence of resistance or intolerance to dasatinib and/or nilotinib.[2] Resistance was defined as one of the following: no complete hematologic response (CHR) by 12 weeks (whether lost or never achieved); no cytogenetic response by 24 weeks (ie, 100% Philadelphia chromosome positive [Ph+] – whether lost or never achieved); no major cytogenetic response (MCyR) by 52 weeks (ie, ≥ 35% Ph+ – whether lost or never achieved); or progressive leukocytosis. Intolerance was defined as one of the following: grade 3 to 4 nonhematologic toxicity that did not resolve with adequate intervention; grade 4 hematologic toxicity lasting more than 7 days; or any grade 2 or higher toxicity that was unacceptable to the patient. Patients with New York Heart Association class III or IV heart disease,

What's new, what's important

The approval of omacetaxine mepesuccinate as a therapy for adults with chronic myeloid leukemia who are resistant or intolerant to tyrosine kinase inhibitors was based on response rates seen in a combined cohort of patients from 2 clinical trials. Although omacetaxine's mechanism of action of is not fully known, it includes the inhibition of protein synthesis and activity that is independent of direct BCR-ABL binding. The combined cohort in which efficacy of omacetaxine was assessed consisted of 111 patients with CP or AP CML (76 and 35, respectively) who had documented evidence of resistance or intolerance to dasatinib and/or nilotinib. Patients received omacetaxine 1.25 mg/m^2 SC twice daily for 14 consecutive days every 28 days in induction cycles. Responding patients received the same dose for 7 consecutive days every 28 days in maintenance cycles for up to 24 months.

Major cytogenetic response (MCyR), the primary efficacy endpoint in patients with CP CML, occurred in 14 patients (18.4%; 95% CI, 10.5%-29.0%); mean time to onset of response was 3.5 months and median response duration was 12.5 months. The primary efficacy endpoint in AP CML patients was MCyR or major hematologic response (MaHR). MaHR occurred in 5 patients (14.3%; 95% CI, 4.5%-30.3%), with none having MCyR. Among patients with MaHR, mean time to onset of response was 2.3 months and median duration of response was 4.7 months. Grades 3 and 4 adverse events included thrombocytopenia, neutropenia, and anemia for CP and AP patients. Serious adverse events occurred in 51% of CP patients and in 60% of AP patients. As Dr. Matt Kalaycio writes on page 193, it is important to note that to date, no trial has shown improvements in disease-related symptoms or survival with the drug.

— Jame Abraham, MD

Report prepared by Matt Stenger, MS

Commun Oncol 2013;10:194-196
DOI: 10.12788/j.cmonc.0045

How I treat CML

Four randomized, controlled trials demonstrate faster and deeper molecular remissions when patients with chronic myeloid leukemia (CML) in chronic phase are treated with second-generation TKIs (sgTKI) compared with imatinib.[1-4] Although none of these trials have shown improved survival with sgTKIs, the early reduction in the number of patients transforming to more advanced disease in at least 3 of the trials persuades me that sgTKIs are the treatment of first choice for patients with CML. I do not foresee the impending loss of patent protection for imatinib, which will result in the availability of generic and less costly formulations, changing my predilection for sgTKIs. Although I see no clear therapeutic advantage for one sgTKI over any other, I tend to prefer nilotinib over the others.

Regardless of the agent that is used first, emerging data demonstrate that long-term prognosis is predicted by the results of molecular testing 3 months after starting treatment.[5,6] According the latest iteration of the National Comprehensive Cancer Network Guidelines 7, patients who fail to meet the goal of a reduction in BCR-ABL/ABL transcripts to < 10% by the international scale are candidates for a change in therapy and should also be evaluated for the possibility of allogeneic transplantation.

Assuming patients achieve a suitable reduction in BCR-ABL transcripts, I monitor qPCR every 6 months indefinitely. I reserve a 12-month bone marrow aspirate and biopsy to those patients who develop myelosuppression with treatment as they are most prone to treatment failure and the development of cytogenetic abnormalities in the Ph-negative clone. In the absence of rising transcripts, I continue treatment indefinitely as long as treatment is tolerated.

References

1. O'Brien S, Kantarjian H, Keating M, et al. Homoharringtonine therapy induces responses in patients with chronic myelogenous leukemia in late chronic phase. *Blood*. 1995;86(9):3322-3326.
2. Kantarjian HM, O'Brien S, Cortes J. Homoharringtonine/Omacetaxine Mepesuccinate: The long and winding road to Food and Drug Administration approval. *Clin Lymphoma Myeloma Leuk*. 2013.
3. Cortes J, Lipton JH, Rea D, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation. *Blood*. 2012;120(13):2573-2580.
4. Cortes J, Digumarti R, Parikh PM, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate for chronic-phase chronic myeloid leukemia patients resistant to or intolerant of tyrosine kinase inhibitors. *Am J Hematol*. 2013;88(5):350-354.
5. Nicolini FE, Khoury HJ, Akard L, et al. Omacetaxine mepesuccinate for patients with accelerated phase chronic myeloid leukemia with resistance or intolerance to two or more tyrosine kinase inhibitors. *Haematologica*. 2013;98(7):e78-e79.
6. Cortes JE, Kantarjian H, Shah NP, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2012;367(22):2075-2088.

— Matt Kalaycio, MD

active ischemia, or other uncontrolled cardiac conditions were excluded from the studies.

Patients received omacetaxine 1.25 mg/m^2 SC twice daily for 14 consecutive days every 28 days in induction cycles. Responding patients received the same dose for 7 consecutive days every 28 days in maintenance cycles. Patients could receive maintenance treatment for up to 24 months.

Among the 76 patients with CP CML, median age was 59 years, 62% were men, 30% were aged 65 years or older, 80% were white, 5% were African-American, 4% were Asian, and 4% were Hispanic. Nearly half (47%) had failed treatment with imatinib, dasatinib, and nilotinib. Most patients had also received prior non-TKI treatments, most commonly hydroxyurea (54%), interferon (30%), or cytarabine (29%).

MCyR, the primary efficacy end point in patients with CP CML, occurred in 14 patients (18.4%; 95% CI, 10.5%-29.0%). Among the patients with MCyR, mean time to onset of response was 3.5 months and median response duration was 12.5 months.

Among 35 patients with AP CML, median age was 63 years, 57% were men, 46% were aged ≥ 65 years, 68% were white, 23% were African-American, 3% were Asian, and 3% were Hispanic. More than half (63%) had failed treatment with imatinib, dasatinib, and nilotinib. Most had received prior non-TKI treatments, most commonly hydroxyurea (43%), interferon (31%), and cytarabine (29%).

The primary efficacy endpoint in AP CML patients was MCyR or major hematologic response (MaHR), defined as CHR or no evidence of leukemia. MaHR occurred in 5 patients (14.3%; 95% CI, 4.5%-30.3%), with none having MCyR. Among patients with MaHR, mean time to onset of response was 2.3 months and median duration of response was 4.7 months.

Safety data are from 163 patients receiving omacetaxine in 3 clinical trials. Among 108 patients with CP CML included in the analysis, median duration of exposure to omacetaxine was 7.4 months (range, 0-43 months). The median total cycles of treatment was 6 (range, 1-41), and the median total dose delivered was 131 mg/m^2 (range, 1.2-678 mg/m^2). Overall, 87% of patients received 14 days

of treatment during cycle 1. By cycles 2 and 3, the percentages of patients receiving 14 days of treatment decreased to 42% and 16%, respectively. Of the 91 patients who received at least 2 cycles of treatment, 87% had at least 1 cycle delay. The median number of days of cycle delays was greatest for cycle 2 (17 days) and cycle 3 (25 days), when many patients were still receiving induction cycles.

Among the patients with CP CML, 87% had grade 3 or 4 adverse events, including thrombocytopenia in 67%, neutropenia in 45%, anemia in 36%, bone marrow failure in 16%, and febrile neutropenia in 10%. The most common grade 3 or 4 nonhematologic adverse events were infections or infestations (11%) and fatigue (5%). Serious adverse events occurred in 51% of patients, including bone marrow failure in 10%, thrombocytopenia in 10%, infection in 8%, and febrile neutropenia in 6%. Discontinuation of treatment due to adverse events occurred in 18% of patients, with the most common reasons being pancytopenia, thrombocytopenia, and increased ALT (2% each). Five patients (5%) died, as a result of cerebral hemorrhage in 2, multi-organ failure in 1, disease progression in 1, and unknown cause in 1.

Among 55 patients with AP CML included in the analysis, the median duration of treatment exposure was 1.9 months (range, 0-30 months). The median total cycles of exposure was 2 (range, 1-29), and the median total dose delivered was 70 mg/m^2. Overall, 86% of patients received 14 days of treatment during cycle 1. By cycles 2 and 3, the percentages of patients receiving 14 days of treatment decreased to 55% and 44%, respectively. Of the 40 patients who received at least 2 cycles of treatment, 68% had at least 1 cycle delay during the trials. The median number of days of cycle delays was greatest for cycle 3 (31 days) and cycle 8 (36 days).

Among the patients with AP CML, 84% had grade 3 or 4 adverse events, including thrombocytopenia in 49%, anemia in 36%, neutropenia in 18%, and febrile neutropenia in 16%. The most common grade 3 or 4 nonhematologic adverse events were infections or infestations (20%), fatigue (9%), and diarrhea (7%). Serious adverse events occurred in 60% of patients, including febrile neutropenia in 18%, infection in 11%, thrombocytopenia in 9%, anemia in 7%, diarrhea in 6%, and convulsions in 6%. Discontinuation of treatment due to adverse events occurred in 33% of patients, with the most common causes being leukocytosis (6%) and thrombocytopenia (4%). Death occurred in 5 patients (9%), due to cerebral hemorrhage in 2 and disease progression in 3.

References

1. US Food and Drug Administration. Approved drugs. Omacetaxine Mepesuccinate. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm325990.htm.
2. Synribo [product characteristics]. North Wales, PA: Teva Pharmaceuticals; 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203585lbl.pdf.
3. Cortes J, Lipton JH, Rea D, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation. *Blood*. 2012;120:2573-2580.