Other therapy options may relegate omacetaxine to last-line choice for chronic or accelerated phase CML

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Many oncologists remember the storied history of homoharringtonine (HHT) and wonder whatever happened to it. HHT showed initial promise for myeloid leukemias, particularly for chronic myelogenous leukemia (CML) where it seemed to induce more cytogenetic remissions than did interferon alpha.[1] Unfortunately for HHT investigators, but fortunately for everybody else, these studies coincided with those being done with imatinib. The phenomenal introduction of imatinib contributed to the shelving of HHT in the mid to late 1990s.[2]

As is often the case, though, imatinib is not perfect. Some patients with CML develop resistance and approximately half of these do so through the acquisition of binding site mutations. One mutation in particular, T315I, rendered patients with CML resistant to all available tyrosine kinase inhibitors (TKI). In the meantime, a semisynthetic version of HHT, omacetaxine mepesuccinate, was developed. With the help of partners in industry, investigators at MD Anderson Cancer Center initiated new studies of omacetaxine in TKI resistant CML patients. Among 62 CML patients with a T315I mutation, complete hematologic response was achieved in 77% with median response duration of 9.1 months.[3] Further, cytogenetic response was also achieved in a portion of patients, complete in 16%. These data prompted application for approval by the Food and Drug Administration, but were rejected for lack of a standardized test for T315I mutations. The additional data presented in the Community Translations article on page 194 formed the basis of a second application, this time for an indication in patients with CML resistant to 2 or more TKIs.

The data speak to omacetaxine's safety in patients with advanced CML. Myelosuppression is by far the most common and serious toxicity of treatment. The myelosuppression may be delayed and profound. Otherwise, the subcutaneous injections are well tolerated.

Omacetaxine's efficacy is modest with 18%-20% major cytogenetic response in CML patients in chronic phase but none in those in accelerated phase.[4,5] Hematologic responses were more frequent and one obvious role for omacetaxine in clinical practice is as a therapeutic bridge to allogeneic transplant when patients are progressing on second- or third-line TKI therapy.

Are there any other roles? The availability of an orally administered third-generation TKI, ponatinib, that is also active after resistance to two or more other TKIs, even when the T315I mutation is present,[6] suggests that omacetaxine will be relegated to last-line therapy when all or most TKIs have already been tried. Even then, in the absence of a plan for transplant, treatment goals are largely palliative since the cytogenetic responses induced by omacetaxine are of relatively short duration (median, 12 months). Hydroxyurea may provide more convenient and less expensive palliation. All other roles for omacetaxine are currently investigational.

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