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Omacetaxine: The FDA Decision

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H&O Could you provide some background on omacetaxine?

EB Omacetaxine (Omapro, ChemGenex) is a new formulation of an older drug, homoharringtonine. Because it is a different formulation, it does not have the side effects that were seen with homoharringtonine. Omacetaxine is well tolerated. It was initially tested in patients with chronic myeloid leukemia (CML) who have the *BCR-ABL* T315I mutation, which is associated with a very high risk of disease progression. Most, if not all, patients with this mutation progress fairly rapidly. Up until now, there has been no good drug that has been useful in patients with the T315I mutation, and the activity with omacetaxine looked promising. In one trial, omacetaxine was associated with a response rate of approximately 35%, which was a cytogenetic and hematologic response.

H&O Why are new agents needed for CML patients?

EB Not all patients respond to the standard of care, which is imatinib (Gleevec, Novartis). In addition, there is a proportion of patients who either cannot tolerate imatinib or who progress through standard-dose and even high-dose imatinib. Approximately 50% of patients who progress through imatinib have a detectable mutation in the *BCR-ABL* protein, the protein that causes the disease. The mechanism of action of imatinib is that it fits into a pocket in that CML protein and inhibits the protein function. The mutation changes the conformation of the CML protein, and imatinib no longer fits into the pocket. Patients who progress on imatinib may receive treatment with the alternative tyrosine kinase inhibitors dasatinib (Sprycel, Bristol-Myers Squibb) and nilotinib (Tasigna, Novartis), but these agents also may not work in patients with a mutation. For CML patients with the T315I mutation, nothing works.

H&O What were the results of the omacetaxine clinical trial CML-202?

EB In the CML-202 trial, the major cytogenetic response rate was 25% in chronic phase. Out of that 25% major cytogenetic response rate, 15% of patients had a complete cytogenetic response, and 10% of patients had a partial cytogenetic response. Overall, 85% of patients had a complete hematologic response, although hematologic response is less important than cytogenetic response. Overall survival was approximately 68–70% at 3 years in chronic-phase patients.

The toxicities were mostly blood-related and included neutropenic fevers in 11% of patients, thrombocytopenia in 11% of patients, bone marrow failure—meaning low blood count—in 8% of patients, progression while on the drug in 8% of patients, anemia in 4% of patients, sepsis in 3% of patients, low white blood cell count in 2% of patients, pneumonia in 2% of patients, and diarrhea in 2% of patients.

H&O Could you discuss the recent FDA decision regarding omacetaxine?

EB For the first time, the US Food and Drug Administration (FDA) decided that approval of a drug would be predicated upon the submission of a companion diagnostic, which is a "proven test" that is used in the setting of drugs, such as omacetaxine, that have specific targets. A companion diagnostic confirms that the target is present. The problem is, in CML—as in many other diseases that have specific targets—there are no agreed upon method-

ologies for discerning or detecting the target. There are different methodologies used for detecting the *BCR-ABL* protein, and there are different methodologies used for detecting the particular mutation of T315I. Although these methodologies are different, that does not mean that one is less accurate or reliable than the others.

The question that the FDA asked the reviewers to decide was not about the drug's efficacy or side effects, but whether a companion diagnostic test should have been submitted with the drug's application. The question began with a review of the data: "A well-characterized in vitro diagnostic test is defined as a test for which analytical performance characteristics—eg, sensitivity, specificity, limit of detection, reproducibility—have been adequately demonstrated and shown to support clinical use. The information has not been provided to the FDA at this time. Two different in-vitro tests were used in CML-202. The comparability of these tests is unknown. Furthermore, 23 of the 66 patients, including 5 of 11 responders, did not have central laboratory confirmation of the mutation at enrollment at either site. Should a well-characterized in-vitro diagnostic to identify patients with a T315I mutation be required and reviewed by the FDA and correlated to clinical trial results prior to approval of omacetaxine for the proposed indication?"

The vote was 13 to 1 that a companion diagnostic test should be required, and the drug was turned down for approval. The one dissenting vote was mine, and I made it because I did not think that the question was the proper question. I think this view was shared by many of the CML experts in the audience, as well as by oncologists across the country. There were a number of CML experts at the meeting who spoke about the fact that there are no standardized tests for looking at the CML protein or the mutation. It would be ideal to have a standardized test, but that is not how science is. There are many approaches, and not one approach is used at all centers. My concern is whether future studies will be made much more difficult by this requirement of a companion diagnostic.

In addition, the FDA's statement that "23 of the 66 patients did not have central laboratory confirmation," is not accurate. What those patients lacked were correlative studies, which are completely irrelevant to whether the drug is active. Correlative samples are usually frozen in a laboratory and reviewed as needed months or years later. All patients had testing for T315I, but the correlative samples were not drawn in 23 of the 66 patients. I believe this misinterpretation was an unintentional error on the FDA's part.

H&O Do you think this decision will have implications for other drugs in development?

EB I do. Smaller startup companies, which might not have extensive resources but are interested in a specific drug for a certain disease, cannot begin to answer a question like "Is there one best method of determining *BCR-ABL* in CML?" Even larger drug companies are going to have trouble doing that. The requirement that standardized tests be used within a clinical trial will divert money that would have been allocated to investigating the study objective. Although that approach might be fine when standardized tests are available, that is not always the case. I think the FDA will have to allow some flexibility here: there are some tests for targets that are not standardized. It would be a huge undertaking for any drug company to prove there is one standard test. In addition, even if the FDA—or a pharmaceutical company—determines that one test is the standard, that does not mean that the test will be used by all laboratories across the country.

Hamberg and Collins addressed the issues surrounding personalized medicine in a recent editorial in the *New England Journal of Medicine*. I do not think it is one size fits all for all diseases.

Suggested Readings

ClinicalTrials.gov. Homoharringtonine (omacetaxine mepesuccinate) in treating patients with chronic myeloid leukemia (CML) with the T315I BCR-ABL gene mutation. http://clinicaltrials.gov/ct2/show/NCT00375219?term=cml-202&rank=2. December 21, 2010. ClinicalTrials.gov Identifier: NCT00375219.

Hamburg MA, Collins FS. The path to personalized medicine. *N Engl J Med*. 2010;363:301-304.