New Drug for Chronic Myeloid Leukemia Might Stimulate the Market

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Summary: The evolution of treatment options over the past 20 years has provided for a normal life expectancy for most patients with chronic myeloid leukemia. Currently approved tyrosine kinase inhibitors mainly differ in potency and side effect profile. Flumatinib goes for deep responses and good tolerability.

Text: In this issue of CLINICAL CANCER RESEARCH, Zhang and colleagues report results of a phase 3, randomized, open-label, multi-center trial comparing the new compound flumatinib with well-known imatinib in newly diagnosed chronic phase chronic myeloid leukemia (CP-CML) patients (1). The design of the study was comparable to other trials testing 2nd generation TKIs versus imatinib, e.g. ENESTnd and ENESTChina (nilotinib), DASISION (dasatinib), BELA and BFORE (bosutinib). 394 patients were randomized 1:1 to flumatinib 600mg once daily after fasting (n=196) or imatinib 400mg once daily with meal (n=198). Sponsor of the trial is Hansoh Pharmaceuticals who developed flumatinib.

The primary endpoint in the intention-to-treat population was met by showing significantly higher rates of major molecular response (MMR) at 6 months in the flumatinib arm. In addition, molecular response of different depth (MR1, MR2, MMR (MR3), MR4, MR4.5) and complete cytogenetic remission rates at all considered timepoints (3, 6, 9, 12 months) revealed significantly deeper responses. No progressions to accelerated phase on flumatinib versus 4 progressions on imatinib were counted within 12 months. However, one patient of the flumatinib arm died of cerebral hemorrhage independent of disease progression or thrombocytopenia. The side effect profiles were different with lower event rates of edema, pain in extremities, rash, neutropenia, anemia, and hypophosphatemia, and on the other side, higher rates of diarrhea and alanine transaminase elevation in the flumatinib arm. Adverse events were primarily grade 1 or 2 according to CTCAE. Diarrhea was mostly grade 1 (93%) and 62% of these events lasted shorter than two days. No treatment discontinuation occurred due to diarrhea. Cardiac events in the form of QTc interval prolongation were recorded in 3 patients on imatinib and in none on flumatinib. The percentage of patients remaining on treatment after 12 months was identical between the two therapy arms (81%).

In view of the advent of tyrosine kinase inhibitors like imatinib and its derivatives, CML has largely lost its terror in the last two decades. Patients usually face an optimistic hematologist at initial diagnosis classifying the disease no longer a death sentence as it has been before the turn of the millennium. More and more patients develop the justified hope for a “functional cure”, in other
words it has become likely after several years to reach a situation of very deep response without the need to continue TKI therapy even though a fair number of leukemic cells survive under immunologic control. This perspective is especially important for patients who suffer from long-term low-grade side effects diminishing their quality of life. Furthermore, younger patients eventually hope to fulfill the desire to have children. This positive outlook is justified for CML in general, on the other hand this disease still is deadly if not managed properly. Firstly, adherence to swallow the daily pill is a well-known challenge in chronic diseases. According to Marin and colleagues adherence in CML is closely associated to the achievement of adequate responses. They used intelligent, but normal-looking, pill bottles tracking each time the bottle has been opened. Patients with less than 90% adherence only had a negligible chance to achieve deep molecular responses (2). Side effects might decrease adherence if no proper action is taken, e.g. consultation with practitioner, dose adaptation, or switch to a different drug. Secondly, standardized molecular monitoring has proven to be an essential tool for response assessment incorporating the ability to predict the outcome in CML patients. Particularly early molecular responses at 3 and 6 months after starting TKI treatment are associated with deep molecular responses after 5 years and might indicate patients at risk for progressive disease like accelerated phase or blast phase (3). Second-generation TKIs like nilotinib, dasatinib, and bosutinib have shown to achieve deeper responses than imatinib at early timepoints (3 and 6 months) trending to lower progression events on the long run (4).

Flumatinib is a derivative of imatinib with two changes in chemical structure which were intended to increase the specificity of BCR-ABL1 inhibition (Fig. 1). Thereby a higher potency together with lower rates of side effects should be achieved. In fact, preclinical data showed 50-fold lower IC_{50} values for flumatinib in the BCR-ABL1 positive cell line K562 compared to imatinib, 5-fold lower IC_{50} values compared to nilotinib, and 5-fold higher IC_{50} values compared to dasatinib (5).

The efficacy results of the phase 3 trial clearly show superiority of flumatinib over imatinib which is comparable to the results of previous phase 3 trials testing nilotinib, dasatinib, or bosutinib versus imatinib (1). It is likely that better responses will translate to a higher rate of patients achieving MR4.5 in the years thereafter. The short follow-up of 12 months is a weak point of the trial. Hopefully follow-up data will be made available soon. The plausible consequence of more patients achieving MR4.5 is that more patients will be candidates for treatment-free remission (TFR) attempts under intensified monthly molecular monitoring. So far, the minimum requirements for testing a treatment stop include MR4.5 achievement over a period of at least 2 years applying quarterly tests (4). Future studies should prove that flumatinib safely leads patients to TFR as shown for other TKIs. Furthermore, new trials with larger patient numbers are desirable in order to focus on the so far underrepresented group of high Sokal risk patients as well as on side effects which in competing drugs also did not fully disclose in the first year of treatment. For instance, a stringent cardiovascular follow-up should be considered having in mind the experience gained with other 2^{nd}-generation TKIs. In addition, it is expected to find BCR-ABL1 mutations in patients with progressive disease or treatment failure providing valuable information for a salvage therapy.

The data presented by Zhang and colleagues raise a promising alternative in the treatment of chronic-phase CML indicating high response rates and a reasonable side effect profile. These characteristics increase the chance to maintain optimum adherence, and in turn, achieve high efficacy of the drug leading to future TFR candidates. The data convinced Chinese authorities to approve flumatinib as first-line treatment recently. Larger trials with longer follow-up will be helpful to convince other countries as well.
References


Figure 1

The chemical structures of imatinib and flumatinib are depicted. The phenyl ring of imatinib was replaced with a pyridine group and a trifluoromethyl group was introduced (indicated by arrows). These changes led to higher BCR-ABL1 specificity with less potency against c-kit and PDGFR than imatinib. Further the activity of flumatinib was shown to be higher in in-vitro screens towards wildtype BCR-ABL1 as well as towards several clinically relevant BCR-ABL1 mutants (5).
Flumatinib

Imatinib
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