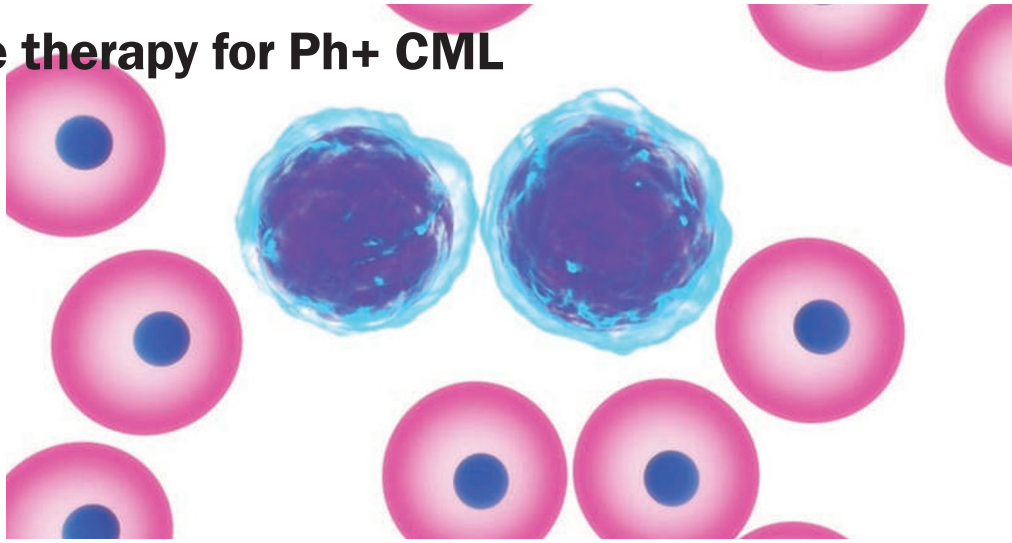
HEMATOLOGY

Nilotinib as first-line therapy for Ph+ CML



The prognosis and outcomes of patients with Philadelphia chromosome (Ph) chronic myeloid leukemia (CML) has been revolutionized by the development of the small-molecule targeted therapy imatinib. This drug targets the protein tyrosine kinase encoded by the *BCR-ABL* gene, which is located on the Ph. Up to 85% of patients treated with 400 mg imatinib achieve a complete cytogenetic response (CCR) and 40–60% achieve a major molecular response (MMR). These responses are stable in many patients; however, 15–20% of patients can become resistant to imatinib and develop residual disease.

The second-generation tyrosine kinase inhibitors nitotinib and dasatinib have already been registered for the treatment of patients who are resistant or intolerant to imatinib, and might represent an important advance as frontline treatment. Now a study from the GIMEMA CML Working Party has shown that nilotinib is safe and effective in patients with early-stage chronic-phase Ph+ CML. The results of this study support the role for this drug as first-line therapy for CML.

Nilotinib is more selective at inhibiting BCR-ABL than any other protein tyrosine kinases, and the concentration required to inhibit cell growth *in vitro* is many fold lower than for imatinib. Therefore, a phase II clinical study was undertaken to evaluate the activity of nilotinib as first-line treatment for patients with previously untreated, early-stage chronic-phase Ph+ CML. In total, 73 patients aged 18 or older with chronic-phase Ph+ CML received 400 mg nilotinib twice daily. The primary end point of the trial was the CCR rate after 1 year of treatment.

At a median follow-up period of 15 months, the CCR rate was 96% at 6 months and 12 months, with only one patient relapsing after an initial response at 3 months. The MMR rate was 66% at 6 months and 85% at 12 months. The responses were rapid as noted by 78% of patients achieving a CCR at 3 months and 52% of patients achieving a MMR at 3 months. Treatment was interrupted in 38 (52%) of the 73 patients during the first year. These dose interruptions were mainly because of nonhematologic adverse effects such as skin rash, pruritis, and bone, muscle and joint pain. Anemia, neutropenia and thrombocytopenia were extremely rare. The mean daily dose of nilotinib ranged between 600 and 800 mg in 74% of patients, and was less than 400 mg in only 8% of patients. The frequency and degree of nonhematologic and biochemical adverse effects was as expected based on the results of previous phase II studies.

"This study provides important new information on the early therapeutic effects of nilotinib, 400 mg twice daily, in previously untreated, early-stage, chronic-phase Ph+ CML patients" comment the researchers. The investigators also noted that the magnitude and rapidity of the response to nilotinib when used as first-line therapy was greater than expected. As the patients were enrolled from 18 clinical centers, the outcomes observed were not considered to be suggestive of a single-center effect, although the researchers noted that all centers participating in this study were experienced in the management of CML with tyrosine kinase inhibitors in the second-line setting. The mean blood trough levels achieved with the 400 mg twice daily dose of nilotinib is many fold higher than concentrations needed to inhibit the growth of 50% of cultured Ph+ cells with either mutated ot wild-type *BCR-ABL*. The authors of this study commented that even though this relatively small single-arm study cannot provide sufficient evidence or conclusions about the efficacy of this drug compared with other targeted therapies, the results do indicate that a prospective randomized study of nilotinib vesus imatinib may reveal that nilotinib is superior to imatinib in the short-term. An ongoing study by the NIH is assessing whether nilotinib is superior to imatinib in this patient population.

The researchers conclude that "Nilotinib 400 mg twice daily is safe and highly effective, in early chronic-phase, previously untreated Ph+ CML patients, provided that the dose is properly adjusted to account for nonhematologic and biochemical side effects". This study provides data in support of the use of nilotinib as first-line therapy for the treatment of CML. "The response rates are such that nilotinib is expected to be more effective and more rapid than imatinib in the short term", comment the researchers.

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Original article Rosti, G. *et al.* Nilotinib for the frontline treatment of Ph+ chronic myeloid leukemia. *Blood* **114**, 4933–4938 (2009)