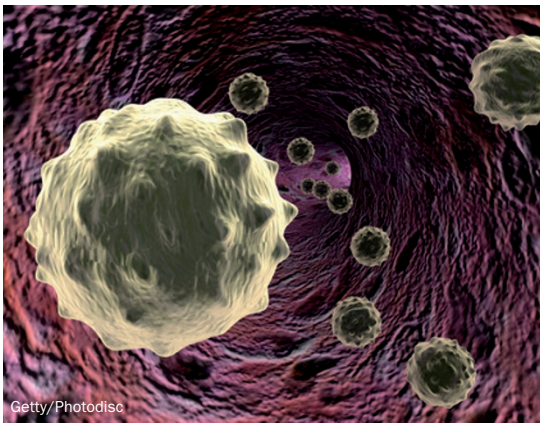
Nature Reviews Clinical Oncology **10**, 248 (2013); published online 2 April 2013; doi:10.1038/nrclinonc.2013.51

HAEMATOLOGICAL CANCER

Nilotinib reduces emergence of BCR–ABL mutations in CML



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Chronic myeloid leukaemia (CML) is characterized by the presence of the Philadelphia chromosome (Ph) and its oncogenic product, the constitutively activated tyrosine kinase BCR–ABL. Following development of the selective BCR–ABL tyrosine kinase inhibitor (TKI) imatinib, the inhibition of BCR–ABL has become the standard of care for patients with CML. Imatinib has been shown to have efficacy in patients with Ph-positive (Ph^+) CML in chronic phase. However, around 15% of patients develop resistance to imatinib or relapse after initially responding to treatment. Nilotinib is a second-generation BCR–ABL inhibitor with greater potency and selectivity for BCR–ABL than imatinib. Nilotinib has been widely approved for the treatment of newly diagnosed adults with Ph^+ CML in chronic phase or with imatinib-resistant or imatinib-intolerant Ph+ CML in chronic phase or accelerated phase.

In patients with CML, mutations in the BCR–ABL kinase domain are a common mechanism of TKI resistance and have been found in 40–60% of imatinib-resistant patients. Over 90 distinct mutations have been identified, each resulting in varying levels of resistance to imatinib. Nilotinib is active *in vitro* against all tested imatinib-resistant BCR–ABL mutations, except the T315I mutation. A report by Andreas Hochhaus *et al*. has now been published in which the occurrence of mutations emerging following treatment with nilotinib and imatinib were assessed through a prospective analysis of patients from the phase III study ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients).

To detect mutations in BCR–ABL, the researchers performed long-range reverse transcription PCR and direct sequencing on samples from 846 patients at baseline. No BCR–ABL mutations were detected for any patients at baseline. With a minimum follow-up duration of 3 years, emerging mutations were detected in almost twice as many patients treated with imatinib 400 mg daily compared with patients treated with either nilotinib 300 mg twice daily or nilotinib 400 mg twice daily (21 patients in the imatinib group versus 11 patients in each nilotinib group). Most treatment-emergent mutations in the imatinib group were imatinib-resistant, nilotinib-sensitive mutations. Fewer patients with emergent mutations progressed to accelerated phase or blast crisis in the nilotinib groups (two patients in the nilotinib 300 mg twice daily group and two in the nilotinib 400 mg twice daily group) compared to the imatinib group (seven patients).

These results indicate that treatment with a more-selective and more-active BCR–ABL inhibitor, such as nilotinib, reduces the emergence of BCR–ABL mutations that cause treatment resistance, and reduces the rate of progression to advanced disease. These observations might explain the improved outcomes observed with nilotinib compared with imatinib in the ENESTnd trial and further support nilotinib treatment of patients newly diagnosed with Ph^+ CML in chronic phase.

Vanessa Marchesi

Original article Hochhaus, A. *et al.* Nilotinib is associated with a reduced incidence of BCR-ABL mutations versus imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase. *Blood* doi:10.1182/blood-2012-04-423418