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Nilotinib vs imatinib – molecular mechanism(s) of its better efficiency

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Recently, several reports in *Cancer* focused on better efficacy of nilotinib than imatinib for the treatment of patients with Philadelphia-positive (Ph+) chronic myeloid leukaemia (CML) in chronic phase.[1, 2] We would like to share our experience with imatinib, which could clarify the molecular mechanism(s) of this finding and to give guidance for further improvement of therapeutic strategy. The effectiveness of both pharmaceutics might be a matter of dose and suppression of telomerase activity in addition to suppression of bcr-abl tyrosine kinase. These enzymes are the most powerful key-factors in the proliferation and immortalisation of cancer cells and they might be in a tight cross-signalling.

In the chronic phase of CML, approximately 80% of the patients show reduced telomere length without highly elevated telomerase activity or microsatellite alterations, and in most instance the Philadelphia translocation is the sole chromosomal anomaly.[3] In contrast, in the blast phase of CML, up to 80 % of patients show additional cytogenetic changes, resulting in genome instability, enhanced telomerase activity and telomere dynamics that relate to karyotypic instability. The majority of these patients are already receiving chemotherapy. It has been observed that the telomerase activity has a high prognostic impact in CML and its acceleration associates with shorter survival of the patients.[3] It seems that both abnormalities – bcr-abl fusion and telomerase activity, are equally essential for the outcome of disease.

How about the effect of imatinib on the telomerase activity and cell proliferation?
We found that imatinib has a dual effect on the proliferation of cultured Ph+ cells, derived from CML patients in chronic phase, depending on the dose of medication (Figure 1). In doses above the threshold level, imatinib has an impressive inhibitory effect on cell proliferation, without influence on telomerase activity. In doses below the threshold level, imatinib has a very strong stimulating effect on cell proliferation, which is accompanied with strong telomerase activation.
The inhibition of bcr-abl tyrosine kinase in Ph+ cells by imatinib has a potential for indirect induction of telomerase activity through regulation of telomeric associated proteins – overexpression of tankyrase and downregulation of Tin2/TRF1.[4] This leads to telomere lengthening and enhancement of cell proliferation.
It has been reported that one of the early strategy to overcome initial standard-dose-resistance to imatinib is the use of high doses, which confirms our hypothesis.[5]