ASPECTS OF LONG-TERM TREATMENT WITH TYROSINE KINASE INHIBITORS IN CHRONIC MYELOID LEUKEMIA

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I **Jönsson S**, Olsson B, Ohlsson C, Lorentzon M, Mellström D, Wadenvik H
Increased cortical bone mineralization in imatinib treated patients with chronic myelogenous leukaemia.
Haematologica 2008; 93*:1101-3*

II **Jönsson S**, Hjorth-Hansen H, Olsson B, Wadenvik B, Sundan A, Standal T
Second-generation TKI dasatinib inhibits proliferation of mesenchymal stem cells and osteoblast differentiation *in vitro*
Leukemia 2010; 24:1357-9

III **Jönsson S**, Olsson B, Jacobsson S, Palmqvist L, Ricksten A, Ekeland-Sjöberg K, Wadenvik H
BCR-ABL1 transcript levels increase in peripheral blood but not in granulocytes after physical exercise in patients with chronic myeloid leukemia
Scand J Clin Lab Invest 2010; 71: 7-11

IV **Jönsson S**, Hjorth-Hansen H, Olsson B, Wadenvik H, Sundan A, Standal T
Imatinib inhibits proliferation of human mesenchymal stem cells and promotes early but not late osteoblast differentiation *in vitro*
J Bone Miner Metab, in press

V **Jönsson S**, Olsson B, Söderberg J, Wadenvik H
Good adherence to imatinib therapy among patients with chronic myeloid leukemia – a single-center observational study
Ann Hematol, in press

VI **Jönsson S**, Standal T, Olsson B, Wadenvik H, Mellström D.
Secondary hyperparathyroidism but stable bone mineral density in patients with chronic myeloid leukemia treated with imatinib
Manuscript

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Abstract

Chronic myeloid leukemia (CML) is caused by the tyrosine kinase activity of the oncoprotein BCR-ABL. The introduction of tyrosine kinase inhibitors (TKIs) targeting BCR-ABL has profoundly changed the prognosis of CML. Currently, there are three TKIs approved for treatment of CML, imatinib, nilotinib and dasatinib. The five-year-survival is about 90 % in CML patients treated with TKI in first chronic phase and the side-effects are generally mild and manageable. However, some concerns remain in CML treatment. Some patients fail TKI therapy. They need to be identified by regular evaluations of hematologic, cytogenetic and molecular response. Moreover, TKI therapy is life-long and the long-term side effects are in part unknown.

The aims of this doctoral thesis were to investigate some aspects of long-term treatment with TKIs in CML, especially side-effects of TKIs on bone *in vitro* and *in vivo*, variations in molecular response and adherence to imatinib therapy.

We showed that CML patients treated with imatinib had stable bone mineral density (BMD) over time despite a high incidence of secondary hyperparathyroidism (Papers I and VI). Imatinib and dasatinib inhibited proliferation of mesenchymal stem cells, i.e. osteoblast progenitors, *in vitro* (Papers II and IV). Dasatinib significantly and dose-dependently inhibited osteoblast differentiation *in vitro* (Paper II), whereas the imatinib-mediated inhibition of osteoblast differentiation was most marked at low concentrations (Paper IV).

Molecular response to TKI therapy is determined by serial measurement of the *BCR-ABL* transcript level in leukocytes from peripheral blood. In CML the *BCR-ABL* fusion gene is predominantly expressed in myeloid leukocytes. We showed that changes in the relative proportion of myeloid and lymphoid leukocytes induced by exercise, significantly affected the *BCR-ABL* transcript level measured in peripheral blood (Paper III).

CML patients treated with imatinib at the Sahlgrenska University Hospital were interviewed in a structured way to assess adherence. Contrary to previous studies from United Kingdom and Belgium, adherence to imatinib was estimated as good in our cohort. The study also revealed factors known to predict adherence to therapy, namely the patients being well-informed and having sufficient access to the treating clinic (Paper V).

In conclusion, imatinib and dasatinib affects osteoblast differentiation *in vitro* and bone metabolism *in vivo*, but the bone quality measured as BMD remains unaffected in imatinib-treated patients. Moreover, variations in molecular response may simply be due to pre-analytic variations in blood counts rather than real changes in CML burden. Thus, small variations in the *BCR-ABL* transcript level should be interpreted cautiously. Finally, good adherence to imatinib can be obtained through simple measures.

Keywords: Chronic myeloid leukemia, tyrosine kinase inhibitors, imatinib, dasatinib, molecular response, qRT-PCR, osteoblast, bone mineral density, parathyroid hormone, adherence

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