MOLECULAR MONITORING OF CHRONIC MYELOID LEUKEMIA TREATED WITH IMATINIB MESYLATE

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Abstract: The *BCR-ABL* fusion gene product is a constitutively activated tyrosine kinase, which is fundamental in the pathogenesis of chronic myeloid leukemia (CML). Imatinib mesylate (imatinib, Glivec® or Gleevec®), a small molecule inhibitor of the BCR-ABL tyrosine kinase, is now the first-line treatment for all newly diagnosed chronic phase CML patients. Imatinib treatment results in a high frequency of complete cytogenetic response (CCgR). Patients in CCgR can be further stratified by the degree of minimal residual disease, measured by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR). The present thesis deals with different aspects on molecular monitoring of imatinib treated CML patients. By serially analyzing peripheral blood and bone marrow *BCR-ABL* transcript levels using qRT-PCR in CML patients commencing imatinib therapy, we found that the major decline in *BCR-ABL* transcripts occurred within 6 months after start of imatinib treatment. An apparent plateau in *BCR-ABL* transcript level seems to have been reached after 12-15 months of imatinib treatment, which indicates a stable number of remaining *BCR-ABL* positive cells. To search for markers associated with molecular response in CML patients treated with imatinib, we studied the mRNA expression of apoptosis-related genes in peripheral blood nucleated cells from chronic phase CML patients commencing imatinib treatment. We found that a lower *BAD* expression at diagnosis correlates with a better molecular response at 12 months of imatinib therapy. Studies of *BCR-ABL* kinase domain mutations in imatinib treated CML patients revealed that point mutations were mainly associated with acquired resistance, but not with cytogenetic or molecular disease persistence in CML patients without signs of increasing leukemia burden. Finally we studied “off-target” effects of imatinib on peripheral blood on T-lymphocytes. We found that therapeutic doses of imatinib alter the expression of apoptosis related genes in CD3+ lymphocytes and change the phenotype of CD4+CD28+ T-helper cells.

Key words: CML, imatinib, *BCR-ABL*, apoptosis, mutation, T-lymphocyte

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II. Wei Y, Stockelberg D, Hullberg S, Ricksten A, Wadenvik H. Changes in expression of apoptosis-related genes are linked to the molecular response to imatinib treatment in chronic-phase chronic myeloid leukaemia patients. *Acta Haematol.* 2007;117(2):83-90.

III. Wei Y, Hardling M, Olsson B, Hezaveh R, Ricksten A, Stockelberg D, Wadenvik H. Not all imatinib resistance in CML are BCR-ABL kinase domain mutations. *Ann Hematol*. 2006 Dec;85(12):841-7.

IV. Wei Y, Olsson B, Jönsson S, Hezaveh R, Stockelberg D, Jacobsson S, Ricksten A, Wadenvik H. Therapeutic doses of imatinib are associated with changes in T-cell phenotype and expression of apoptosis-related genes. *Manuscript*

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