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SHC 1. AN OVERVIEW TO IMATINIB EFFICACY AND RESISTANCE MECHANISMS

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Imatinib is a common therapy in the clinical management of chronic myeloid leukemia (CML). Imatinib, a member of the family of tyrosine kinase inhibitors, is a drug transporter subtrate. It binds expansively to plasma proteins, and can inhibit its own transporters and metabolizing enzymes. The strongest drawback to imatinib treatment is resistance to such a treatment. Even tough response rates are high in imatinib treatment, 70-90% of the patients may manifest nonresponse or disease progression. This observed resistance may be a result of genetic mutations or gene amplifications of drug targets. Cancer cells can develop resistance towards one one drug, to a group of cytotoxic agents or to a number of drugs which are not from the same therapeutic group. There are other resistance mechanisms associated with MDR. One of the fundamental resistance mechanisms in CML patients is mutations in the BCR-ABL1 tyrosine kinase region. However, imatinib resistance may develop independently in some patients. The reason why is the presence of additional factors required for formation of a completely drug resistant phenotype. BCR-ABL positive cells increase the activity of the GLUT 1 glucose transporter thus increase glucose intake. Classical dose regimen during imatinib treatment has revealed differences going up to 4-fold. Drug plasma level determination, and analysis of the impact of transporter protein polymorphic variants on drug levels in CML patients who are receiving imatinib treatment, clinical evaluation of the effects of polymorphisms on imatinib efficacy and resistance development will help enlighten the individual mechanisms behind interindividual differences in imatinib pharmacokinetics.

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