Imatinib (STI571) Inhibits DNA Repair in Human Leukemia Oncogenic Tyrosine Kinase-Expressing Cells

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BCR/ABL oncogene, as a result of chromosome aberration t(9;22), is the pathogenic principle of almost 95% of human chronic myeloid leukemia (CML). Imatinib (STI571) is a highly selective inhibitor of BCR/ABL oncogenic tyrosine kinase used in leukemia treatment. It has been suggested that BCR/ABL may contribute to the resistance of leukemic cells to drug and radiation through stimulation of DNA repair in these cells. To evaluate further the influence of STI571 on DNA repair we studied the efficacy of this process in BCR/ABL-positive and -negative cells using single cell electrophoresis (comet assay). In our experiments, K562 human chronic myeloid leukemia cells expressing BCR/ABL and CCRF-CEM human acute lymphoblastic leukemia cells without BCR/ABL expression were employed. The cells were exposed for 1 h at 37 °C to *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG) at 5 μM, mitomycin C (MMC) at 50 μM or to γ-radiation at 15 Gy with or without a 24 h preincubation at 1 μM of STI571. The MTT cells survival after 4 days of culture showed that STI571 enhanced the cytotoxity of the examined compounds in the K562 line. Further it was found, that the inhibitor decreased the efficacy of DNA repair challenged by each agent, but only in the K562 expressing BCR/ABL. Due to the variety of DNA damage induced by the employed agents in this study we can speculate, that BCR/ABL may stimulate multiple pathways of DNA repair. These results extend our previous studies performed on BCR/ABL-transformed mouse cells onto human cells. It is shown that BCR/ABL stimulated DNA repair in human leukemia cells. In conclusion we report that STI571 was found to inhibit DNA repair and abrogate BCR/ABL-positive human leukemia cells therapeutic resistance.

Key words: BCR/ABL, Drug Resistance, Comet Assay