Abstract

Chronic Myeloid Leukemia is a genetic alteration in premature myeloid cells that results in appearing Philadelphia chromosome. The molecular consequence of this abnormlity is the creation of the fusion protein BCR–ABL. Imatinib is the first drug designed for CML therapy that inhibits tyrosine kinase activity of BCR-ABL, but because of inherent or acquired resistance to Imatinib in patients under treatment, there is a challenge to use TKIs. HSP90 is a kind of molecular chaperone with a role in folding and stability of proteins that control tumor development and malignancies. NVP-AUY922 is a HSP90 inhibitor that can inhibit cancerous cells proliferation and induct apoptosis. Numerous signaling pathways are known to regulate different cell processes. Hippo signaling pathway is known to regulate different physiological processes and its deregulation can result in different diseases such as cancer. Core components of this pathway are SAV1, MST1, MOB1A/B, LATS1/2 kinases. When hippo pathway is on these kinases phosphorylate YAP and TAZ which result in their cytoplasmic retention and inactivation. MicroRNAs are small non-coding RNAs that can regulate their target gene expression after their transcription. Disruption of microRNAs balance in cells can lead to cancer formation. In this study we evaluate expression level of some microRNAs, Hippo signaling components and HSP90 under treatment of NVP-AUY922 with IC50 concentration (250nM) in K562 cell line. Our results showed a decrease in MOB1B, STK3/4, LATS1 expression level after 12hour treatment with NVP-AUY922 and an increase in MOB1A, LATS2, SAV1, YAP expression level. After 48hour treatment with NVP-AUY922, expression level of STK3/4, MOB1A/B, SAV1, LATS1/2 were increased and expression level of YAP was decreased. Also, HSP90 was downregulated after 12 and 48hour treatment with NVP-AUY922. miR-103, miR-182, miR-135 were downregulated after 12hour treatment with NVP-AUY922 and miR-29, miR-590, miR-125 were upregulated. miR-29, miR-182 were upregulated after 48hour treatment with NVP-AUY922 compared to Control group. miR-125, miR-135, miR-590, miR-182 were downregulated after 48hour treatment with NVP-AUY922 compared to Control group. It could be concluded that microRNAs can be used as biomarkers for CML diagnosis and treatment. Furthermore, using HSP90 inhibitors can be a good way to overcome the TKIs resistance in CML patients.

KEYWORDS: Chronic Myeloid Leukemia, Heat-shock Proteins, microRNAs, Hippo signling pthway