ABSTRACT

Chronic myeloid leukemia (CML) is one of the most extensively studied neoplastic disease that can be targeted by molecular therapy with tyrosine kinase inhibitors (TKI). However, despite the introduction of TKI to the therapy of CML, significant proportion of patients may develop resistance and in consequence progress to advanced phase with limited therapeutic options. The main goal of this work was to determine the role of the members of the shelterin complex and the role of metabolism in aberrant telomere maintenance mechanisms in the pathogenesis of CML and identify new mechanisms of disease progression and drug resistance in leukemia cells. CD34+ primary cells from CML patients at different stages of disease, as well as *in vitro* cell lines model (MEG-A2, MOLM-1, LAMA-84, K-562, KU-812), imatinib resistant-cell lines (K-562 and MEG-A2) and acute promyelocytic leukemia cell line (HL-60) were employed. Changes in BCR/ABL1 expression and activity, telomere length, telomeric complex expression, telomerase activity, ALT activation, *TERRA* expression, metabolic profiles, protein posttranslational nonenzymatic modifications, DNA damage were investigated. The study showed that telomere shortening was positively correlated with CML progression. In addition, the negative correlation between mean telomere length and expression of *BCR/ABL1* was observed. Dynamic changes in telomere length were neither associated with enzymatic activity of telomerase nor with ALT in the course of the disease. We showed that the changes in telomere length in CML cells were accompanied by the TRF2 and RAP1 expression changes, as well as metabolic phenotype changes. Therefore, it can be postulated that the increased activity of BCR/ABL1 is associated with elevated glycolytic and oxidative rates leading to metabolic stress in the cell. The member of shelterin complex - RAP1 can act as a molecular linker between cell metabolism and telomere length. RAP1 regulates the expression of *TERRA* and in consequence influence telomere length in CML. This phenomenon may play important role in CML progression, clonal selection and resistance to targeted therapy treatment with TKI.

Keywords: chronic myeloid leukemia, telomeres, shelterin complex;

Dergowska A.