

Introduction: Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. Modern treatment strategies have improved the prognosis of childhood ALL; however, treatment still fails in 20-25% of patients. Further improvement of treatment may depend on the development of targeted therapies. Recently, the mammalian target of rapamycin (mTOR) has gained more attention as a potential therapeutical target in different tumor types including hematological malignancies.

Methods: In our research we studied the mTOR activity in bone marrow/peripheral blood samples from pediatric ALL patients and in lymphoma/leukemia cell lines. The expression of mTOR activity dependent proteins (p-4EBP1, p-S6) were examined by ELISA. We statistically analyzed the expression results in clinical samples before and during the therapy, and at possible relapses. The p-4EBP1 and p-S6 expression, the in vitro effect of rapamycin treatment on lymphoblasts and the expression of mTOR containing complexes were also studied by flowcytometry and immunocytochemistry.

Results: We collected and analyzed more than 250 peripheral blood and bone marrow samples from 49 patients. Significantly elevated p-4EBP1 protein levels were detected in ALL samples at diagnosis. The p-4EBP1 expression levels showed significant correlation with the therapeutic response and prognosis of the patient. Leukemia/lymphoma cell lines also showed significantly increased mTOR activity compared to normal lymphoid cells. In vitro rapamycin inhibited proliferation but could not induce apoptosis in all examined cases. Cell lines and isolated blasts from patients showed different mTOR expressions.

Conclusions: Our results confirm that pediatric ALL cells have high mTOR activity, which could be detected by measuring the p-4EBP1 expression. Recent results suggest that mTOR activity measurements could be useful methods to identify ALL patients with poor prognosis at the diagnosis and to recognize early relapses. However further studies are required to define the best way to sort ALL and other lymphoma patients for future rapalog treatments based on rapalog sensitivity prediction.