Abstract

The molecular basis of different outcomes in pediatric acute lymphoblastic leukemia (ALL) remains poorly understood. We addressed the clinical significance and mechanisms behind in vitro cellular responses to ionizing radiation (IR)-induced DNA double-strand breaks in 74 pediatric patients with ALL. We found an apoptosis-resistant response in 36% of patients characterized by failure to cleave caspase-3, -7, -9, and PARP1 by 24 hours after IR and an apoptosis-sensitive response with the cleavage of the same substrates in the remaining 64% of leukemias. Resistance to IR in vitro was associated with poor early blast clearance at day 7 or 15 and persistent minimal residual disease (MRD) at day 28 of induction treatment. Global gene expression profiling revealed abnormal up-regulation of multiple prosurvival pathways in response to IR in apoptosis-resistant leukemias and differential posttranscriptional activation of the PI3-Akt pathway was observed in representative resistant cases. Importantly, pharmacologic inhibition of selected prosurvival pathways sensitized apoptosis-resistant ALL cells to IR in vitro. We suggest that abnormal prosurvival responses to DNA damage provide one of the mechanisms of primary resistance in ALL, and that they should be considered as therapeutic targets in children with aggressive disease.