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Prevalence and prognostic significance of murine double minute protein-2 overexpression and P53 gene mutations in childhood acute lymphoblastic leukemia

Olfat M Hendy [1], Doaa M Elghannam, Jehan A El-Sharnouby, Enas F Goda, Rasha El-Ashry, Youssef Al-Tonbary

Clinical Pathology Department, National Liver Institute, Menoufiya University, Egypt.

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The murine double minute protein-2 (MDM-2) oncogene is a determinant of embryogenesis, tumorigenesis, and cell cycle progression. The effects of MDM-2 on these processes depend, in part, on its ability to inactivate the p53 tumor suppressor gene. Our goal was to determine whether MDM-2 protein overexpressions or p53 gene mutations are a frequent event in poor outcome pediatric acute lymphoblastic leukemia (ALL). This work was conducted on 46 children with ALL (31 males and 15 females) with age range 2-18 years, 18 children with matched age and sex were enrolled in the study as a control group. The MDM-2 expression by flowcytometry and p53 gene status by PCR were determined in peripheral blood or bone marrow of ALL children (at initial diagnosis) and also of control group. The ALL children were treated by the modified BFM 76179 protocol of therapy, 29 patients (63%) achieved complete remission, while 17 patients (37%) were subsequently failed to achieve complete remission or relapsed within 6 months of achieving complete remission (CR). MDM-2 was significantly overexpressed in 15 ALL patients (32.6%), compared to that of healthy controls, 4 of them (4/15), were out of 29 cases of CR (13.8%), and the other 11 cases were out of 17 relapsed cases (64.7%). In contrast to overexpression of MDM-2, the mutation of p53 was detected in 6 (13%) out of 46 ALL patients at the initial time of diagnosis, 3 of them (10.3%) were out of 29 cases of CR and the other 3 cases (17.6%) were out of 17 of relapsed group, which is significantly higher than CR group ($P < 0.05$). In relapsed group, 2 patients out of 3 cases with p53 mutation were MDM-2 negative, also, all 3 cases of mutant P53 among patients in CR were negative MDM2. A positive correlation was found between the MDM-2 overexpression and initial WBCs count, blast cell counts in peripheral blood and presence of CNS blasts ($p < 0.05$, $p < 0.05$ and $p < 0.05$ respectively). These results indicate that MDM-2 is overexpressed in a significant number of childhood ALL, it is more frequent in relapsed cases and its frequency is not related to p53 status. Thus measuring of MDM-2 as a bad prognostic marker even in cases with non mutant P53 is very important. Moreover, MDM-2 may be a potential molecular target for production of new cancer therapy.