P15 METHYLATION AS A MOLECULAR PROGNOSTIC MARKER IN ACUTE LYMPHOBLASTIC LEUKEMIA

Thesis

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SUMMARY AND CONCLUSION:

Acute lymphoblastic leukemia ALL is one of the commonest malignancies that occur in children. While approximately 75% of children with newly diagnosed ALL are expected to be cured with contemporary treatment regimens, the outcome for children who experience a bone marrow relapse is poor. As important challenge is to define the biologic and genetic basis for this difference in treatment outcome.

TSG, PI5, located at chromosome 9P21, encodes a cyclin dependent kinase (CDK) inhibitor inhibiting the phosphorylation of Rb protein by CDK4/6, resulting in the arrest of G1-S phase transition of the cell cycle. Inactivation of the P15INK4B gene is associated with loss of cell cycle control and aberrant proliferation of tumor cells. In recent studies on hematological malignancies, ALL hypermethylation of the P15INK4B gene was found to be an especially important reason for its inactivation rather than deletion or mutation of the gene.

This study aimed at evaluating the prognostic relevance of P15 gene methylation by correlating it with known clinical and hematological prognostic factors. Moreover, to assess whether P15 gene methylation could be used for detection of MRD or early relapse.

The current study was conducted on 35 randomly newly diagnosed childhood ALL patients. Their ages ranged from 2.5 to 18 years with median value 10 years and male: female ratio 1.2 : 1. P15 methylation was evaluated in patients at time of initial diagnosis as well as time of initial remission (day 28 of chemotherapy) using methylation specific polymerase chain reaction (MSP) technique. Also, patients were followed up as regard their hematological laboratory findings and clinical outcome throughout the period of the study. Then, the clinical significance of P15 gene methylation before and after chemotherapy in association with either the risk group or clinical outcome of every patient was evaluated.

It was found that P15 gene methylation at time of initial diagnosis was high in childhood ALL patients (80%) (100%). Also, P15 methylation remained methylated after chemotherapy in HRG (100%) and in poor clinical outcome patients (80%), while it was turned into unmethylated / partially methylated allele in LRG (77.8%) and in good clinical outcome patients (88.9%).

Monitoring of P15 methylation may have important prognostic implications for clinical monitoring, risk assessment, guiding the selection of therapy and monitoring its efficacy. It also provides the basis for developing novel therapy, which may be useful for ALL patients who are refractory to current therapy.

Conclusions:

(1) P15 methylation has potential value as a molecular prognostic marker in childhood ALL
(2) P15 methylation may putatively be a specific molecular abnormality largely associated with disease recurrence.
(3) P15 methylation has potential value as a molecular prognostic marker in childhood ALL and it may putatively be a specific molecular abnormality largely associated with disease recurrence. Early detection of P15 methylation at apparent remission or its acquisition during follow up may prove valuable for predicting relapse.
(4) The reversibility of this, P15 methylation, epigenetic changes may also provide the basis for developing novel therapies such as demethylating agent leads to re-expression of P15 mRNA. And this may be useful for ALL patients who are refractory to current therapies.