Biological and clinical implications of codon 72 p53 genotypes in Indian chronic myeloid leukemia patients

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Abstract

Chronic myeloid leukaemia (CML) is characterized by the increased and unregulated growth of myeloid cells in the bone marrow and the accumulation of these cells in the blood. In 95% of cases it is caused by the product of the BCR-ABL oncogene, located on the Philadelphia (Ph) chromosome, which is generated as a result of a reciprocal t(9;22) chromosomal translocation. P53 is a tumor suppressor gene involved in DNA repair, induction of growth arrest and apoptosis. The p53 gene is the most commonly mutated tumor suppressor gene in human cancers. In addition to the loss of tumor suppression activity, gain of function mutations in p53 can promote tumorigenesis and drug resistance in various types of human cancers. A common p53 polymorphism occurs at codon 72 of exon 4, with two alleles encoding either arginine(CGC) or proline(CCC). This polymorphism is associated with leukemia susceptibility.

Aim

To evaluate the association between the presence of the Arg/Pro polymorphism at codon 72 of the p53 gene and the risk of chronic myeloid leukemia (CML) and the development of imatinib resistance in Indian patients.

Methods

One hundred CML patients and 100 healthy controls were genotyped for the p53 codon 72 polymorphism by ASO-PCR and PCR-RFLP using restriction enzyme BstU1. The phenotypes were correlated for biological and clinical implications in these patients using Chi X2 test.

Results

Pro/Pro homozygotes were found more frequently in CML patients with imatinib resistance than early phase patients. The proportions of, Pro/Pro, Arg/Arg and Arg/Pro phenotypes in CML patients were 49%, 28%, 23% and in controls 17%, 30%, 53% (P=0.0001). The Pro/Pro phenotype was significantly correlated with higher incidence of imatinib resistance(P=0.001) and higher CML risk (P=0.022). The incidence of Pro/Pro genotype was higher in older CML patients (P=0.0002). The P53 codon 72 polymorphism was found to be a strong predictor of imatinib response. (Odds ratio 17.31, 95% confidence, P=0.0001).

Conclusion

These results suggest that the Pro/Pro genotype of codon 72 p53 represents a risk factor for both development of CML and for molecular resistance to treatment with imatinib. Individuals who are homozygous for Pro p53 allele might benefit from high doses of imatinib or alternative therapeutic options at clinical onset. The codon 72 genotype may be an independent prognostic marker for response to TKIs and apoptosis status.