J Cancer Sci Ther 2017, 9:7 (Suppl)
DOI: 10.4172/1948-5956-C1-109

PDGFRα promoter polymorphisms and their expression pattern influence risk of development of imatinib induced thrombocytopenia in chronic myeloid leukaemia

Sameer Ahmad Guru
Maulana Azad Medical College, India

Background: Platelet derived growth factor receptor (PDGFR) has been implicated in many diseases. PDGFRα is a tyrosine kinase and a side target for imatinib, a revolutionary drug for treatment of chronic myeloid leukaemia (CML) that has dramatically improved the survival of CML patients. Given the importance of PDGFR in platelet development and its inhibition by imatinib, it was intriguing to analyse the role of PDGFRα in relation to imatinib treatment and development of imatinib induced thrombocytopenia in CML patients. We hypothesized that two known functional polymorphisms in the promoter region of the PDGFRA gene may affect the susceptibility of CML patients, receiving imatinib treatment, to the development of thrombocytopenia.

Methods: A case control study was conducted among a cohort of CML patients admitted to the Lok Nayak Hospital, New Delhi, India. A set of 120 patients of CML in different clinical phases (100 chronic phase, 10 accelerated phase and 10 blast crisis) and 100 age and sex matched healthy controls were studied. After initiation of imatinib treatment, the haematological response of CML patients was monitored regularly for two years with development of thrombocytopenia being a primary outcome. PDGFRα promoting polymorphisms were studied by allele specific polymerase chain reaction (AS-PCR) and PDGFRα mRNA expression was evaluated by quantitative real time polymerase chain reaction (qRT-PCR). The mRNA expression results were expressed as fold change+standard deviation.

Results: The distribution of +68GAins/del promoter polymorphism genotypes differed significantly between CML patients and control subjects ($p<0.0001$) and between the thrombocytopenic and non-thrombocytopenic CML patients ($p<0.0001$). Also, +68GA del/del and ins/del genotypes in imatinib treated CML patients were associated with an increased risk for developing thrombocytopenia, with odds ratios 4.93 (95% CI 1.99 to 12.21, $p<0.001$) and 10.24 (95% CI 3.50 to 29.92, $p<0.0001$) respectively. In contrast, the -909C/A promoter polymorphism genotype distribution neither differed significantly between CML patients and control subjects ($p=0.76$), nor between thrombocytopenic and non-thrombocytopenic CML patients ($p=0.15$). Besides, there was no increased risk of imatinib induced thrombocytopenia associated with -909C/A polymorphism mutant homozygous (AA) and heterozygous (CA) genotypes, the odds ratios being 0.97 (95% CI 0.31 to 3.06, $p=0.96$) and 1.05 (95% CI 0.50 to 2.18, $p=0.91$) respectively. PDGFRα mRNA expression was slightly but significantly higher in CML patients compared to controls ($p=0.02$). Moreover, patients with imatinib induced thrombocytopenia had a significantly lower PDGFRα mRNA expression compared to patients without thrombocytopenia ($p=0.03$). A differential expression of PDGFRα mRNA was observed to be associated with +68GA ins/del and -909C/A polymorphism genotypes. The +68GA deletion allele and -909A allele were significantly associated with lower expression of PDGFRαmRNA.

Conclusion: The PDGFRα +68del/del and +68ins/del genotypes are associated with an increased risk of developing thrombocytopenia in imatinib treated CML patients. The differential +68GA ins/del polymorphism genotype specific expression of PDGFRα mRNA associated with down regulated PDGFRα expression and may thereby lead to development of imatinib induced thrombocytopenia in a subset of CML patients receiving imatinib.

sameerahmadguru@gmail.com