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Significance of BCR-ABL mutations, atypical FISH signal patterns and gene amplifications in imatinib resistance - A South Indian study

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Inronic myeloid leukemia (CML) is a hematopoietic stem cell disorder characterized by the BCR-ABL oncogenic fusion gene. Treatment for patients with CML has been greatly improved by the use of imatinib, selective inhibitor of ABL kinase. However, most patients in advanced phase either exhibit primary refractoriness or relapse after an initial response to imatinib. The study was designed to find the major influencing cause of imatinib resistance in south Indian cohort. For this, a total of 182 CML suspects were recruited in the study. The chromosomal abnormalities observed in these cases were validated.Presence of Ph chromosome, being the most common observation apart from various common additional chromosomal abnormalities like trisomy8, double Ph, monosomy Y, ploidy changes etc and with few rare and significant chromosomal alterations with impact on leukemogenesis. The diagnostic confirmation was done using molecular cytogenetics(FISH) and/ or RT-PCR .Several cases showed derivative (9)deletions, which re-directed us to compare and analyze various parameters like hematological ,cytogenetic ,drug dose etc in these cases against controls. The hematological, cytogenetic and follow-up analysis (by FISH) showed some exclusive trends in cases showing der(9) deletions. The next objective was to role of gene amplification and / or BCR-ABL kinase domain mutations((like T315I, F317L and G250E) in resistance. Out of the 35 resistance subjects delineated, the analysis was done on 23 patients (17M:6F). The gene amplification was not frequent, when status checked on 16 /23 resistance suspects, but instead showed FISH patterns like OGGF, OOGF, OGF. On 19/23 cases, ASO-PCR was done to detect three major mutations (T315I ,F317L,G250E) . Mutations T315I (11/19) and F317L (17/19) were common compared to G250E. In one patient, the F317L mutation transcript was atypical. For these cases, the clinical, hematological, socio-demographic parameters were also analyzed. The study is a torchbearer for future investigations on various common and rare observations in CML suspects. Also, on basal screening of resistance suspects, drug resistance is found least associated to gene amplification than mutations.

Biography

Sangeetha Vijay is doing PhD (as Senior research fellow) at Regional Cancer Centre in the area of imatinib resistance in chronic myeloid leukemia patients . she have got two international publications till date and two awards for best paper presentations at national and international level conferences.

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