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Stopping TKI in pediatric chronic myeloid leukemia: Are we there?

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Pediatric chronic myeloid leukemia accounts for less than 2% in < 14 yr old children and less than 9% in 14-19 yr age group. Even though the clinical manifestations and biology of disease is different in Ph+ ALL compared to CML, there are interesting findings to learn from treatment protocols. First generation (Imatinib Mesylate - IM) TKI consistently showed good clinical response in Philadelphia positive acute lymphoblastic leukemia with multi agent chemotherapy. COG study had shown 7 yr EFS of 71% and EsPhALL study had 4 yr EFS of 75.2% in good risk and 53.5% in poor risk Ph+ ALL, in patients receiving IM with multi agent chemotherapy. In both studies, IM is stopped at end of maintenance. IM as first line in pediatric CML, a French study has clearly shown CCyR and MMR of 61% and 31%, respectively at end of 1 yr. The common toxicities of IM in pediatrics are hematological, hepatotoxicity, rash, edema and bone pains, other most common toxicity are growth retardation and poor bone health, in approximately 73% of patients especially in prepubertal age, which is not seen in adults. Especially in adult CML patients, there is growing evidence of TFR (Treatment Free Remission) in patient attained UMRD (Undetermined Minimal Residual Disease) for 2 yrs, it is now possible to safely stop IM in approx 30-50% of patients. Factors that would predict TFR are low sokal score, prior treatment with interferon, longer length of time on IM, higher NK cells at the time of stopping IM. Most of the recurrence occurred within first 6 months and they do respond well to IM on re-exposure. Monitoring after stopping IM is crucial, monthly once RQ-PCR for one yr and there on bimonthly for next one year. IM and other TKI have long-term toxicities in children, in-patient who attains UMRD for desired length of time is worth considering for stopping IM, if close molecular monitoring is feasible, under strict clinical studies.

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Whole exome sequencing reveals the landscape of clonal evolution from MDS/MPD to sAML progression

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In this study, we performed whole-exome sequencing on 39 patients at the time of MDS/MPD and sAML to dissect the mutational profiles and clonal evolution from MDS/MPD to sAML. Germline and tumor samples at the time of MDS/MPD and sAML were analyzed using whole exome sequencing (Agilent SureSelect v3, HiSeq 2000). Targeted sequencing for selected variants was performed to validate the result. Our extensive analyses reveal the order of gene mutations, inferring the hierarchy of mutated pathways during the progression. Also, our study shows that time series analysis contrasting MDS/MPD and sAML periods provides a much more comprehensive view of clonal structure and evolution.

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