EDITORIAL

Genetics of Acute Myeloid Leukemia – A Paradigm Shift

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It was the spring of 1972 when Janet Rowley noticed that a patient with acute myeloid leukemia (AML) had abnormalities in his chromosomes. She went on to publish her findings in 1973 [1]. Chromosomes 8 and 21 appeared to have some interchange [2]. The bottom of chromosome 21 had broken off and moved to the bottom of chromosome 8, and the bottom of that chromosome 8 had moved to the bottom of that chromosome 21 – an apparently reciprocal exchange, we now know as t(8;21) (q22;q22). Since then many genetic changes have been discovered in patients with AML.

Molecular and cytogenetic abnormalities in AML involve mutations in critical genes of normal cell development, cellular survival, proliferation and maturation. Most of the AML patients have multiple clones of various genes. Genetic and epigenetic configurations of these clones differ in their disease-causing potential. This is the reason why the knowledge of pathobiology of AML has not translated into greater extent in clinical improvements in patient outcomes. However, major advances in understanding the molecular basis of AML in recent times has provided a new platform for various new targeted therapies, which have helped improve outcomes.

The outcomes of AML patients differ significantly according to the underlying cytogenetic abnormalities. Cytogenetics provide the basic framework for risk stratification, but not without some limitations and pitfalls. Sometimes, the cytogenetics fail because of technical difficulties. Also, cryptic gene fusion cannot be identified by conventional cytogenetics [3]. This reinforces the importance of molecular genetics; otherwise, these patients with cryptic gene fusion are assigned to wrong risk groups. Another drawback of conventional cytogenetics is its limited resolution that sometimes fails to pick-up the breakpoints occurring in close proximity [3]. Furthermore, cytogenetics gives no insight to molecular mechanism causing AML in patients with normal cytogenetics. Molecular genetic tests like fluorescence *in situ* hybridization (FISH), genomic hybridization, genomic breakpoint cloning, Sanger sequencing, single nucleotide polymorphism profiling, whole genome sequencing and whole exome sequencing have improved our understanding of the genetic basis of AML [3]. This results in better understanding of the biology of AML, better monitoring of minimal residual disease by clonal biomarkers, better prediction of outcomes, and optimization of treatment regimens.

Disease-specific prognostication based on conventional cytogenetics has guided AML treatment for long. The blueprint of treatment algorithms is now changing. In recent times, high-risk patients are taken for allogeneic hematopoietic stem cell transplantation at the earliest. Thus, better delineation of these risk groups based on their cytogenetic and molecular profiles has a great clinical relevance. AML risk stratification has been done according to underlying genetic abnormalities by European Leukemia Network [4].

The genetic profiles of various human races are usually different. There is only sparse data on incidence of various cytogenetic subgroups in Asian population, especially Indian pediatric patients. This is because of financial constraints and lack of adequate expertise in many centers. Amare, *et al*. [5] had described their experience of cytogenetic profile of leukemia patients, including both adult and pediatric age groups. Out of 7,209 patients, 567 were pediatric AML patients. They found that the incidence of t(8;21) was high in comparison to other Asian countries. Cheng, *et al.* [6] from China had studied cytogenetics of 1432 adult *de-novo* AML patients, and showed t(15;17) to be the commonest cytogenetic abnormality. In this issue of *Indian Pediatrics*, Tyagi, *et al.* [7] have described their experience of cytogenetic profile of 472 pediatric patients of AML from a tertiary care center of India. They have highlighted the increased frequency of t(8;21) and its significant association with chloromas in North Indian children. This study on AML cytogenetics will be of value to those interested and involved in management of pediatric patients with leukemia, and will lay foundation for research for better

therapeutics in Indian children with AML.

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