PAEDIATRIC LEUKAEMIAS

Genetic findings of paediatric leukaemias in Indian patients

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Paediatric tumours are a broad term used to describe a range of cancer types and non-cancerous tumours found in children. The most common types of paediatric cancers include leukaemia, brain and spinal cord tumours, neuroblastoma, Wilms’s tumour and non-Hodgkin lymphoma.

Prevalence

As per the recent updates on cancer burden from World Health Organization (WHO), the leading cause of death in children and adolescents is cancer. Every year, approximately 3,00,000 children aged 0 to 19 years old are diagnosed with cancer, with the most common being leukaemias, brain tumours, lymphomas and solid tumours such as neuroblastoma and Wilms tumour. Of these, around 2,15,000 cancer cases are diagnosed in patients younger than 15 years with around 80,000 deaths every year. While around 80% children with cancer in high-income countries are cured, this number in low and middle-income countries can be as low as 20%. The two most important aspects of improving outcomes for children with cancer is accurate diagnosis followed by effective treatment.

Molecular basis of paediatric cancers

One important area of translational research that could lead to continuous improvements in cancer diagnosis and treatment strategies is the knowledge of the underlying genomic alterations. The functional role of these genes (oncogene or tumour suppressor) and the related mutations acquired in them is important to decide treatment and surveillance management. Oncogenes with actionable driver mutations act as a source of therapeutic target, as demonstrated by the success of imatinib, in ALL patients with BCR-ABL1 gene fusion. The sequencing of childhood cancer specimens in large numbers has led to the identification of the vast majority of recurring mutations in cancer associated genes. While the therapeutic implications of the ‘targetable’ activated oncogenes are straightforward, there has been extensive ongoing research on ‘untargetable’ activated oncogenes. This has been carried out with the idea of discovering new targetable biomarkers affected by untargetable genomic alterations using a medicinal chemistry approach and high-throughput screening methods to identify small molecule inhibitors to block these novel targets.

There are multiple types of paediatric cancers, with leukaemia being the most common subtype.

Juvenile myelomonocytic leukaemia

Juvenile myelomonocytic leukaemia (JMML) is a rare myeloid malignancy that occurs in infants and young children, originating from pluripotent stem cells of the hematopoietic stem cell origin. A disruption of signal transduction through the RAS pathway, resulting in selective hypersensitivity of monocytes to granulocyte-macrophage colony-stimulating factor, is the underlying pathogenesis for the onset of JMML. Another genetic basis of JMML is related to Noonan’s syndrome, which makes the patient predisposed to developing JMML. However, most of these patients have a good prognosis with a wait and watch management approach, except for a few with an aggressive phenotype associated with PTPN11 mutations. On the other hand, if a child develops somatic mutations that cause JMML, it is going to be highly aggressive and requires immediate intervention with allogeneic stem cell transplantation that improves survival. As an early detection approach for clinical intervention, several studies have shown that a molecular genetic workup at the time of the diagnosis of JMML increases the survival outcome in these patients to 80%. The key genes involved in JMML, RAS pathway genes that include NF1, NRAS, KRAS, PTPN11 and CBL, allow for a molecular diagnosis in 85% of patients.

We, at MedGenome, have developed a JMML specific gene panel that covers
all the important genes in the RAS pathway and other rarely mutated genes associated with JMML (CBLC, KRAS, NRAS, HRAS, PTPN11, SETBP1, JAK3, CBL, ASXL1, RUNX1, TET2, JAK2, EZH2). Our experience in the last 4 years on the performance of this panel for many JMML patients, particularly on the diagnostic power of this panel, indicates there is 90% concordance between clinical/phenotype presentation of JMML and the molecular genetic signature associated with the disease. We hereby share a brief summary of our genetic findings in Indian patients with JMML. Patients presented with a varied age group, ranging from 2 months to 8 years, with an average age of 1.9 years. In terms of gender, the disease prevalence was similar in both male and female. Our statistics in terms of the mutational spectrum for RAS pathway mutations were in concordance with global statistics and it was 60%. There were also patients who were on relapse post BMT, wherein we could identify emerging secondary clones which were potential drivers in other pathways such as JAK-STAT, spliceosome and the chromatin remodeling pathway, which are markers of poor prognosis. To summarize, our panel has successfully been adapted by several clinicians for risk stratification of their JMML patients and further management.

Acute lymphoblastic leukaemia

Worldwide, acute lymphoblastic leukaemia (ALL) has been a part of the success story of the management of paediatric cancers; from 1950, when it was considered an incurable disease to the present where over 90% of the children survive 5 years from diagnosis, with most of them cured. However, it remains an important cause of morbidity and mortality not only in children, but in adults as well. Both B-cell and T-cell ALL comprise multiple subtypes based on somatic genetic mutations that arrest the lymphoid cell development and maturation. An identification of the full range of genetic mutations in ALL in an accurate and comprehensive manner is pivotal for prognostication, risk stratification, therapeutic decision and response monitoring. In addition, when there is disease progression under clonal evolution, comprehensive molecular profiling has been shown to add value in understanding the scientific basis of the disease.

MedGenome had developed a multigene NGS panel for ALL molecular profiling (for both B-ALL and T-ALL as well as certain rare markers to indicate biphenotype signature), which includes ABL1, CDKN2A, CREBBP, ETV6, FLT3, IKZF1, JAK2, KDM6A, KRAS, MLL2, NRAS, PTEN and TP53 for B-ALL, and DNMT3A, FBXW7, HRAS, KRAS, NOTCH1, NRAS, PHF6, PTEN and RUNX1 for T-ALL. The choice of genes and the panel design were based on the international consensus recommendation from WHO, ASH, NCCN, ESMO and ELN guidelines. Beyond the NGS based approach, several other biomarker testings that are part of the international recommendation, including standard flow cytometry for immunophenotyping, detection of ALL related translocations by RT-PCR/FISH and conventional karyotyping, are being offered as a comprehensive package for ALL molecular workup. In the last 4 years, more than 100 patients with paediatric ALL were profiled using this panel at baseline presentation, which enabled oncologists to make informed decisions for the treatment planning and management of these patients.
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