Deep Transcriptome Sequencing of Pediatric Acute Myeloid Leukemia Patients at Diagnosis, Remission and Relapse: Experience in 3 Malaysian Children in a Single Center Study

ABSTRACT

Among the many types of leukemia, acute myeloid leukemia (AML) affects 20% of diagnosed hematological malignancies in pediatric patients (Meshinchi and Arceci, 2007; de Rooij et al., 2015). Standard chemotherapy regimen remains as the first line treatment for pediatric AML, however nearly 40% of AML patients may suffer from relapse and eventually die from the disease (de Rooij et al., 2015). Similarly, it has been reported that 50% of the pediatric AML relapsed within 12–18 months of diagnosis and 45% of those relapsed were not expected to survive (Creutzig et al., 2014). Despite advances in cytogenetic analysis through fluorescence in situ hybridization and multiplex PCR, there is still a need for a better and comprehensive molecular profiling. For instance, microarray has long been used to study the gene expression profiles of AML patients. The different profile of gene expression has enabled clinicians to tailor better treatment for patients and predict whether patients have the tendency to relapse (Goswami et al., 2009). In a recent study, Handschuch et al. reported that three genes, ANXA3, S100A9, and WT1 can differentiate between different prognostic types of AML (Handschuh et al., 2018). The study outcome was in agreement with another study conducted by Shimada et al. (2012), where a high expression of WT1 gene showed prognostic impact in pediatric AML (Shimada et al., 2012). Another study by Jo et al. (2015) reported that high expression of EVI1 and MEL1 could predict the prognosis of pediatric AML (Jo et al., 2015). However, none of the biomarkers identified from these studies have been translated into clinical use. Therefore, the search continues for additional promising biomarkers, notably novel transcripts, novel fusion genes and non-coding RNAs which are not represented in the microarray platform. Transcriptome sequencing through next generation sequencing represents an effective approach to discover new genetic information on gene expression which may contribute to tumorigenesis. Notably, several novel and rare fusion transcripts have been identified from AML patients via RNA-sequencing (Padella et al., 2015). A recent study combining whole genome sequencing, whole exome sequencing and RNA sequencing in pediatric cancers has identified 240 pathogenic variants with increased sensitivity (Rusch et al., 2018). Previous studies in relapsed AML have shown that the cells acquired additional genetic mutations that were either different or evolved from subclones of diagnostic blasts cells (Padella et al., 2015; Rusch et al., 2018). Nevertheless, little is known about the genetic changes at the transcriptomic level at diagnostic, remission and relapse stages of the same patients, especially in the Malaysian population.