Epigenetic Gene Mutations Impact on Outcome in Acute Myeloid Leukaemia

Commentary

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Acute myeloid leukaemia (AML) is a heterogeneous clonal disorder arising in the myeloid lineage with an average age of around 62 years at diagnosis. Morphological and cytogenetic analysis has identified a number of sub-types with a wide range of survival outcomes. Some of the more favourable outcomes are associated with patients who harbour balanced reciprocal chromosomal translocations including the t(15;17) translocation resulting in a fusion gene between PML and RARα; this group of patients have acute promyelocytic leukaemia (APL) (Freireich et al., 2014). Over the past few years, next-generation sequencing has assisted in the identification of a spectrum of molecular mutations in many of the other sub-types of AML, particularly in those with an apparent normal karyotype.

Clinical trials have shown that patients with t(15;17) respond very well to All-Trans-Retinoic-Acid (ATRA) or to ATRA with arsenic trioxide (ATO) resulting in some excellent outcomes in which there is an 85–90% 5-year overall survival (Coombs et al., 2015). ATRA has been widely used in the treatment of APL due to its ability to specifically bind to the ligand-binding domain of the RARα portion of the fusion protein, resulting in the terminal differentiation and subsequent apoptosis of the leukaemic promyelocytes. ATO which targets the PML portion has been combined with conventional ATRA therapy resulting in degradation of the fusion protein. Furthermore, with this therapeutic combination, chemotherapy could be omitted for the patients who have low risk APL (Coombs et al., 2015).

Unfortunately, even with the high rates of remission and overall survival, there remains a sub-set of APL patients who do not respond to ATRA/ATO and it is these patients who highlight the need for better survival, there remains a sub-set of APL patients who do not respond to ATRA/ATO. Shen et al. (2015) identified subsets of mutated genes contributing to a previously unnoticed group of APL patients with poorer outcome and provides the opportunity for the development of better targeted therapies to treat high-risk disease. The inclusion of other mutations outside of PML–RARα has opened up the possibility that APL should be regarded as a more complex heterogeneous disease and ultimately may contribute to the improvement of the current stratification regimen currently employed in the clinic.

Future studies, in larger cohorts and in different centres, should address the need to validate the use of other agents in combination with ATRA/ATO.
ATRA/ATO such as epigenetic modifying agents. This has been alluded to in preclinical studies demonstrating the potential capacity for combination with HDAC inhibitors (De et al., 2014). However, a novel stratification model needs to be developed, at the point of diagnosis, to identify those APL patients who are resilient to ATRA/ATO therapy.

Authors’ Contributions

CY, KC and KIM all contributed to the data interpretation and writing aspects of the manuscript. CY and KC should be considered as making an equal and joint contribution as 1st authors.

Conflicts of Interest

The authors declare that they have no conflict of interests in writing this commentary.

References


