Genomic classification of acute myeloid leukaemia: An incessantly evolving concept

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SUMMARY

In this multicentric study, Papaemmanuil *et al*. evaluated genomic changes in 1540 uniformly treated patients with acute myeloid leukaemia (AML) who received intensive therapy in three prospective randomized clinical trials. They aimed to study the driver mutations in 111 cancer genes and their correlation with cytogenetic and other clinical data to define genomic subgroups that may impact the classification and outcome in AML. A total of 5234 driver mutations in 76 genes were identified with at least one driver mutation in 96% and two or more driver mutations in 86% samples. Based on the

integrated evaluation of genetic and clinical data, Papaemmanuil *et al*. defined 11 molecular classes of AML with distinct clinical outcome. In addition to the eight molecular subgroups previously defined by the WHO classification, three more subgroups identified in this study were: (i) chromatin-spliceosome group accounting for 18% of the cohort with mutations in the genes regulating RNA splicing, chromatin and transcription; (ii) TP53 group accounting for 13% of the cohort with mutations in TP53, chromosomal aneuploidies or both; and (iii) AML with IDH^{R172} mutations accounting for 1% of the cohort.

The overall survival in the previously defined subgroups of recurrent chromosomal translocations in this study is reported to be as expected in the literature but the three newly defined groups varied in their clinical outcome. Patients in the chromatin-spliceosome group were older with lower white cell and blast counts, lower rates of response to induction chemotherapy, higher relapse rates, and a poor long-term clinical outcome similar to patients of AML in the adverse/high-risk group. As per the existing guidelines, 84% of these patients fell into the intermediate-risk category. The TP53-aneuploidy subgroup was shown to have a dismal outcome in this study whereas the IDH^{R172} had an outcome similar to NPM-1 mutated AML. Patients with no driver mutations comprised 4% of the cohort and had lower blast and white cell counts and better outcomes.

The authors also addressed the impact of co-occurring mutations on clinical outcome. The overall survival correlated with the number of driver mutations and 11% of the observed variations in genomic classes were attributed to gene–gene interactions. The co-occurrence of NPM1, DNMT3A and FLT^{ITD} mutations seen in 6% of the cohort, the FLT^{TKD} with partial tandem duplication of MLL and; co-occurrence of DNMT3A and $IDH2^{R140}$ mutations resulted in worse prognosis than that observed with either of these mutations alone. Similarly, NPM1-DNMT3A-NRAS genotype was found to be associated with a relatively benign prognosis in line with a favourable outcome reported for NPM1-NRAS combination. Specifically, the outcome for NPM1 mutated subgroup was influenced by the co-occurring mutations in NRAS, IDH, PTPN11, FLT3 and chromatin-spliceosome class.

COMMENT

The landmark discoveries of t(8;21) and t(15;17) by Janet Rowley in a few patients with AML marked a beginning of the era of discovery of novel mutations in AML.[1,2] As more mutations were identified, the classification of AML moved from an essentially morphology-based FAB classification to the WHO 2008 classification which integrated molecular aberrations with morphological features.[3] The 2008 WHO classification identified t(8;21), t(15;17), t(6;9), inv(16)-t(16;16), inv(3)-t(3;3) and MLL fusion genes as 'recurrent genetic abnormalities', the presence of which alone is considered enough to make a diagnosis of AML irrespective of the bone marrow blast count.[3] Clearly, approximately 50% of the AML cases do not possess any of the above recurrent genomic aberrations and were, thus, classified as 'cytogenetic normal' (CN). The discoveries of mutations in the CEBPA and NPM1 genes in CN-AML prompted their inclusion as provisional entities in the 2008 WHO classification of myeloid neoplasm which have now been included as full entities in the revised 2016 WHO classification.[4–6] Nevertheless, the emerging insight provided by the recent studies into the spectrum of molecular aberrations is rapidly changing perspectives of the existing classification of AML.

The slow and arduous route of discovering mutations in the cancer genome was revolutionized by the advent of massively parallel sequencing technology. The whole-genome and whole-exome sequencing studies have highlighted biological variability in the mutational landscape of AML. The presence of multiple driver mutations and clinical impact of the co-occurring mutations as evident from large multicentric studies of AML cohorts has stationed next generation sequencing as a necessary tool in clinical practice. The Cancer Genome Atlas Research Network (TCGA) evaluated 50 whole genomes and 150 exomes of AML and identified an average of 13 mutations per AML genome; frequent mutations in 260 genes of which 23 were most frequently mutated and; when the mutations were classified on the basis of the biological functions of the genes, >99% of the samples in this study had mutations in one of the nine biological functional subgroups known to impact the pathogenesis of AML.[7] Patterns of co-occurrence of FLT3-DNMT3A-NPM1 and mutual exclusivity of PML-RARA, MYH11-CBFB, MLL fusion genes with NPM1 and DNMT3A mutations and; RUNX1 and TP53 with FLT3 and NPM1 mutations were highlighted by this study.[7] The TCGA study provided comprehensive data on cancer genes frequently mutated in AML but lacked information on the clinical impact of these mutations as the study was not adequately powered. This descriptive study formed the framework of subsequent studies on the characterization and prognostic impact of multiple genetic aberrations in AML.

The prognostic impact of integrated genetic profiling in AML was evaluated by Patel *et al*.[8] In this study, 18 genes, which were also common to the 23 genes found to be frequently mutated in the TCGA AML cohort, were analysed in 398 AML patients treated with high-dose or standard-dose daunorubicin.[8] The internal tandem duplication in FLT3 (FLT3-ITD), partial tandem duplication in MLL (MLL-PTD) and mutations in ASXL1 and PHF6 were reported to be associated with reduced overall survival and; the CEBPA and IDH mutations with improved overall survival. Besides, the study also showed the positive impact of type of therapy, i.e. high-dose daunorubicin on improved survival in patients with DNMT3A or NPM1 or MLL translocations opposed to patients with wild-type forms of these genes who did not benefit from high-dose therapy.[8]

Historically, the classification schemes were designed to classify diseases for diagnostic purpose but the availability of targeted therapy for specific genetic aberration and differential response to modified doses of the conventional 7+3 AML therapy, as shown by Patel *et al*., favour a detailed evaluation of the tumour genome.[8] The futuristic approach to the clinical work-up of AML shall be to identify genomic lesions for targeted therapeutics, monitoring of treatment response and minimal residual disease (MRD), inform treatment decisions for intensive therapy, i.e. high-dose daunorubicin or stem cell transplantation, pre-empt chemo-resistance and relapse. The study by Papaemmanuil *et al*. is essentially one step forward in improved understanding of the clinical impact of the genetic subgroups with recurrent mutations, the co-occurring and mutually exclusive mutations in a large cohort of almost uniformly treated patients covering an expanse of 111 genes most frequently mutated in AML. Papaemmanuil *et al*. have validated the findings of the TCGA data on somatic driver mutations in AML and the prognostic impact of specific mutations as exemplified by Patel *et al*. as well. The current study also provides a prognostic paradigm to the utility of genetic lesions and paves the way for intensely genomic-driven classification of AML. Prospective clinical studies on large AML cohorts in the coming years shall be required to further validate the clinical impact of the molecular-based classification schema proposed by Papaemmanuil *et al*.

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