AMLGlobalPortal

DNMT3A, TET2, General AML

ASH 2017 | Clonal hematopoiesis in AML patients receiving allo-HSCT in CR

Anna Bartus Cynthia Umukoro | Jan 08, 2018

Clonal Hematopoiesis of Intermediate Potential (CHIP) is the presence of hematologic malignancy-associated somatic mutations such as *DNMT3A, TET2, ASXL1* in the peripheral blood or bone marrow but absence of diagnostic criteria for hematologic neoplasm and it is a common phenomenon in healthy individuals.

Persistent Clonal Hematopoiesis-Associated Mutations (CH-mutations) in Acute Myeloid Leukemia (AML) patients in Complete Remission (CR) is associated with an increased risk of relapse. The prognostic impact of CH-mutations in AML patients in CR particularly in the setting of Allogenic Hematopoietic Stem Cell transplantation (allo-HSCT) is not fully understood.

At the 59th Annual Meeting & Exposition of the American Society of Hematology (ASH), Juliane Grimm from the University Leipzig, Leipzig, Germany, on behalf of colleagues presented, data from a study which aimed to analyze the biologic implications and prognostic impact of *CH*-mutations present in AML patients in CR or in CR with incomplete peripheral recovery (CRi) prior to allo-HSCT.

Peripheral blood samples collected within 29 days pre-HSCT from 113 AML patients (median age = 63.6 years) who received HSCT after non-myeloablative conditioning in CR (CR1 61.9%, CR2 14.2%) or CRi (23.9%) were analyzed. *CH*-mutations were identified by targeted amplicon sequencing (mean amplicon coverage per sample 7205x).

The key findings of the study were:

- Seventy CH-mutations were identified in 48 AML patients (42.5%) in CR/CRi with a mean VAF of 19.1% (58.6% of mutations with VAF>10%)
- Most frequent mutations include *DNMT3A* (31.4%), *TET2* (28.6%) and *ASXL1* (14.3%)
- Presence of ≥ 1 CH-mutation in CR/CRi did not impact Leukemia Free Survival (LFS), $P = 0.95$ or Overall Survival (OS), $P = 0.37$
- Patients with ≥ 2 *CH*-mutations had longer LFS ($P = 0.02$) and OS ($P = 0.007$) compared to patients with no or 1 *CH*-mutation
- In CR/CRi, *DNMT3A* mutations did not influence LFS ($P = 0.73$) or OS ($P = 0.71$)
- *TET2* mutations in CR/CRi did not impact LFS ($P = 0.25$) but significantly associated with longer OS ($P = 0.06$)
- ASXL1 mutations associated with longer LFS, $P = 0.11$ and OS $P = 0.13$
- Presence of CH-mutations at diagnosis: 83 *CH*-mutations were found in 55/76 patients (29 persistent, 9 new, 45 lost)
- After cytarabine therapy, 35% of diagnostic *CH*-mutations persisted and 11% CH-mutations were newly detected

The presenter concluded that in AML, CH-mutations are frequently present (42.5%) in CR/CRi and show high VAFs (mean 19.1%) thus suggesting the presence of clonal hematopoiesis. The presence of more than one *CH*-mutation does not impact prognosis. Additionally, patients with ≥ 2 CH□mutations had longer LFS & OS, which suggests that there is an "increased immunogenic potential with higher number of CH□mutations leading to potent graft vs leukemia effects in the HSCT context".

References

1. Grimm J. *et al.* Prognostic Impact of Clonal Hematopoiesis in Acute Myeloid Leukemia Patients Receiving Allogeneic Hematopoietic Stem Cell Transplantation in Complete Remission. Oral Abstract 406. ASH 59th Annual Meeting and Exposition, Atlanta, GA.