Multi-omic Precision Medicine including Functional Drug Screening to Optimize Treatment for Acute Myeloid Leukemia

Pamela S. Becker
City of Hope, USA

Acute myeloid leukemia (AML) is tremendously heterogeneous, both in relation to individual patient characteristics (e.g.-cytogenetics, genomics) as well as intra-patient multiplicity of clones and subclones. Historically, despite this conspicuous variation, treatment has consisted of pairs of agents for all patients. Initially, the regimen consisted of cytarabine and anthracycline for fit patients, and later venetoclax combinations for older individuals or those less functionally able to tolerate the toxicity of the intensive regimens. Recent data from a randomized trial suggest that a venetoclax regimen has advantages, such as event-free survival, for all patients [Fathi et al. Blood (2025) 146 (Supplement 1): 6]. Effective targeted inhibitors were then identified, and these were added to the backbone regimens for individual patients with specific mutations, e.g., FLT3, IDH1/IDH2, NPM1, or gene rearrangements, e.g., KMT2A or BCR-ABL, and others. But despite these advances, 5-yr survival is only ~30%, even with allogeneic transplant and immunotherapy. To approach the very poor survival of older patients, with <10% 5 yr survival, and those with adverse risk, secondary or treatment related AML, or relapsed/refractory (R/R) patients (pts), personalized regimens may offer potential advantage. Large studies by lead investigators in Austria (EXALT; Kornauth et al. Cancer Discov. 2021; PMID: 34635570) and in Finland (Malani et al. Cancer Discov 2022; PMID: 34789538) have demonstrated impressive outcomes in precision medicine trials in hematologic malignancies.
We have endeavoured to identify genes for which increased expression (Lee SI et al. Nat Commun 2018; PMID 29298978) or specific co-occurring mutations (Qin et al. Clin Cancer Res 2024; PMID 38619278) are associated with drug sensitivity or resistance. We have conducted precision medicine clinical trials, 1) an initial pilot study of 15 pts with R/R AML treated with individual agents based on high throughput drug screening, then 2) a multi-omic trial of 60 pts with R/R acute leukemia (median of 4 prior regimens) based on genomics and high throughput drug screening [Kongtim et al. Blood (2022) 140 (Suppl 1): 1200–1202]. The latter trial demonstrated improved survival for patients who received assay guided therapy (#35) vs other treatment (#25), median overall survival 135 vs. 34 days ($p<0.001$), including the fraction of those who were post allogeneic transplant relapses (38% of pts) who received assay guided vs. other treatment. Nineteen different regimens were administered as recommended by the study. Treatment recommended by the study decreased risk of death by 83% after adjustment for age, sex, type of leukemia, cytogenetic risk, and number of lines of previous treatment (HR 0.17, 95%CI 0.08-0.35, P <0.001). Those who received at least one drug with drug sensitivity score (DSS) of 20 or higher showed improved survival compared to those who did not receive assay guided therapy. A protocol at City of Hope is now enrolling with CLIA approved genomics (next gen sequencing, fusions, RNAseq) and CLIA approved drug screening for drugs and drug combinations that will provide testing information to the physician who will select treatment, then retrospective correlative analysis will be performed to assess relative accuracy of prediction of outcomes (positive and negative predictive value) by genomics vs functional drug screening. Thus, functional precision medicine has been validated globally and will undoubtedly continue to improve outcomes for our worst risk patients with acute leukemia.