Trio of Studies Yield New Insights Into Acute Myeloid Leukemia Treatment

AML patients who added Rydapt to chemotherapy had improved survival after 10 years of follow-up.

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Dana-Farber Cancer Institute researchers are leading three studies that yield new insights to help improve treatment for patients with acute myelogenous leukemia (AML). The research teams will present their findings at the 66th American Society of Hematology (ASH) Annual Meeting & Exposition in San Diego, Dec. 7 – 10, 2024. ASH is the world's largest and most comprehensive hematology event of the year.

Genetic re-analysis of clinical trial data for CPX-351 reveals survival benefit for patients with AML-MR mutations

Patients who develop acute myeloid leukemia after a diagnosis of myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML), after therapy for another cancer, or who have chromosomal changes related to MDS have very poor outcomes, with many surviving less than a year. In a randomized Phase 3 trial, patients treated with CPX-351 [liposomal cytarabine and daunorubicin] had improved survival compared to standard of care 7+3 chemotherapy, leading to FDA approval of CPX-351 for this patient population.

Recently, molecular genetic features have supplanted the use of clinical features in AML diagnostic guidelines to enable more accurate classification of AML clinical and biological groups. To define which patients benefit most from CPX-351 using these modern genetic categorizations, Dana-Farber researchers performed a post-hoc genetic re-analysis of this pivotal Phase 3 CPX-351 vs. 7+3 trial. Using sequenced diagnostic samples from 184 patients and classified them into 4 groups: TP53 mutations, AML-MR mutations, germline DDX41 mutations, or de novo (all other) mutations.

Only patients in the AML-MR group had a longer survival with CPX-351 than with 7+3. Patients treated with CPX-351 in the TP53, DDX41 and de novo groups had prolonged myelosuppression without improved disease-related outcomes, raising the question of clinical utility of CPX-351 in these patients. Finally, as previous studies show enhanced sensitivity of AML-MR mutations to venetoclax plus HMA, future studies should focus on better understanding the optimal therapy for this patient subgroup.

Study title: AML-MR Mutations Drive the Benefit of CPX-351 over 7+3 in the Pivotal Phase 3 AML Trial
Oral abstract number: 60
Presenting and lead author: Shai Shimony, MD

Phase 1 trial shows early efficacy of an all-oral maintenance regimen post-transplant for high-risk MDS/AML patients

Relapses are more frequent in patients with high-risk MDS/AML despite allogeneic transplantation particularly when there is persistent measurable residual disease (MRD) at the time of transplant. Dana-Farber Cancer Institute researchers are leading an investigator-initiated, Phase 1 clinical trial (NCT03613532) to determine the safety, feasibility, and tolerability of adding venetoclax [Venclexta] to reduced intensity conditioning chemotherapy regimens and adding post-transplant maintenance therapy with combination venetoclax/oral decitabine-cedazuridine at reduced doses in patients with MDS/AML.

Thirty patients were enrolled into the trial, including 60% with prior venetoclax exposure and 63% with a mutation in TP53. Three patients relapsed before maintenance and one patient withdrew due to travel logistics. Among 26 of 30 patients that went on to receive the above described maintenance therapy (every 42-days for up to 8 cycles), they found no treatment-emergent grade 3-4 non-hematologic toxicities but observed expected, brief grade 3-4 hematologic toxicities (neutropenia, thrombocytopenia). There were two episodes of neutropenia complicated by fever (n=1) and sepsis (n=1), but otherwise the side effects were manageable. GVHD rates were low with 6-month grade III acute GVHD rate at 4% and the 1-year moderate-severe chronic GVHD rate at 16%. After a median of 22 months of follow up, 1-year overall survival was 81%, 1-year progression free-survival was 73%, and the cumulative incidence of relapse was 27%. Achievement of donor chimerism was observed while on maintenance. The investigators are encouraged by the safety, feasibility and preliminary outcomes in this high-risk population.

Study title: Feasibility, Safety and Efficacy of Oral Maintenance Therapy with Venetoclax Plus Decitabine/Cedazuridine after Venetoclax Plus FluBu2 for High Risk MDS/AML Undergoing RIC Allo-HCT
Oral abstract number: 1045
Presenting and lead author: Jacqueline S. Garcia, MD

Researchers report ten-year follow-up data on the RATIFY trial

C10603/RATIFY was the first AML trial to show the benefit of adding a targeted agent to intensive chemotherapy for a specific genetically determined subset of patients — those with mutations in FLT3. The addition of the multi-kinase inhibitor midostaurin [Rydapt] to chemotherapy in previously untreated adults with FLT3-mutant AML resulted in superior event-free survival (EFS) and overall survival (OS) compared to placebo and led to the approval of this agent in combination therapy. Now, Dana-Farber Cancer Institute researchers report the EFS and OS data from C10603 using 10 years of follow-up data to determine the persistence of a midostaurin benefit and to

assess the nature of late relapses or toxicity.

The trial enrolled 717 patients (360 on midostaurin and 357 on placebo; median age 47.8 years, range 18-61). From the 10-year follow-up data, the median EFS was 8.2 months on the midostaurin arm compared with 3.0 months for placebo. Among the 420 patients who achieved complete remission (CR) by the protocol specified time of 60 days, 253 have had an event (death in 69 and relapse in 184); these events were relatively equal on each arm. OS, the co-primary endpoint, remained marginally superior for those randomized to midostaurin compared to placebo; the 10-year OS estimate was 43.7% vs 38.6%. Therefore, the EFS benefit of randomization to midostaurin vs placebo when added to chemotherapy was maintained over time, although the benefit for OS was diminished, likely due in part to the natural aging process occurring in patients in both treatment arms.

Study title: 10 Year Follow-up of CALGB 10603/Ratify: Midostaurin Versus Placebo Plus Intensive Chemotherapy in Newly Diagnosed FLT3 Mutant Acute Myeloid Leukemia Patients Aged 18-60 Years
Oral abstract number: 218
Presenting and lead author: Richard M. Stone, MD

These findings are among more than 100 studies presented at ASH that are led by Dana-Farber affiliated researchers.

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