Abstract: P596

Title: HIGH RISK MUTATIONS IN CRITICAL GENES DO NOT AFFECT REMISSION RATES AND MRD CLEARANCE IN ACUTE MYELOID LEUKEMIA PATIENTS RECEIVING CPX-351 INDUCTION

Abstract Type: Poster Presentation

Topic: Acute myeloid leukemia - Clinical

Background:

Papaemmanuil *et al* reported on the negative prognostic impact of critical gene mutations such as *TP53*, *ASXL1*, *SRSF2* and *RUNX1* in acute myeloid leukemia (AML) patients treated with conventional chemotherapy ("3+7"). Furthermore, *TP53*, *RUNX1*, *FLT3-ITD*, *N/KRAS*, *CBL*, and *KIT* mutations have been reported to have negative prognostic value also in patients receiving hypomethylating agents plus Venetoclax (HMA+VEN).

Minimal residual disease (MRD) assessment is a key prognostic factor in AML and recent studies have focused on the impact of adverse genomic profiles on MRD clearance.

CPX-351 has recently been approved for the treatment of AML evolving from a previous myelodysplastic syndrome (s-AML) or secondary to chemotherapy (t-AML), according to the former WHO 2016 classification and adverse risk mutations are particularly common in those contexts. However, the prognostic relevance of highly unfavorable mutational profiles and their correlation with MRD clearance remains unexplored in CPX-351 treated patients.

Aims:

This study aimed to explore the prognostic relevance of specific mutations or mutational patterns linked to high risk of treatment failure with conventional chemotherapy or with HMA-VEN in a cohort of elderly patients with s-AML or t-AML treated with CPX-351.

Methods:

The study involved 80 consecutive patients (median age 70, range 37-77) diagnosed with s-AML or t-AML according to WHO 2016 classification, treated with CPX-351 in our Center. Next-generation sequencing (NGS) utilizing the Myeloid Solution panel by SOPHiA Genetics, encompassing 34 critical gene mutations, was conducted. Samples were processed on an Illumina MiSeq platform, and analysis was performed using SOPHiA DDM® Software. MRD analysis was conducted in all CR patients using multicolor flow cytometry, with a 0.1% threshold.

Results:

Median number of mutations for single patient (mutational burden) by NGS was 5 (range 2-10) and 42 patients had high mutational burden (≥ 4 mutations). Most frequent mutations involved *TET2* (41%), *RUNX1* (39%), *ASXL1* (29%), *DNMT3A* (29%), *SRSF2* (29%), *CBL* (27%) and *TP53* (26%). Fifty patients (62.5%) and 61 (76%) displayed molecular features related to resistance to VEN or 3+7, respectively.

After cycle 1, 64 patients (80%) achieved complete remission (CR) with MFC-MRD negativity in 43/64 responding patients (67%). Four patients died before response assessment, mainly due to infections.

Uni and multivariate analysis showed that CR probability and MRD negativity rate were not affected by any of the high-risk mutation or by the presence of high mutational burden.

After a median follow up of 39.3 months (CI 95%; 41 - 60 months), median OS was 18 months (CI 95% 15.66-19.89).

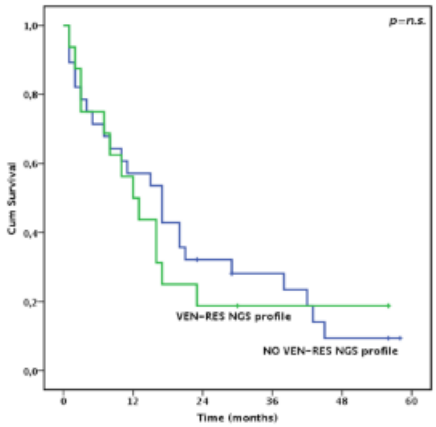
OS was not affected by any mutation, high mutational burden, or by the presence of HMA-VEN resistance profile (median OS 13 vs 14 months in patients without resistance profile, p=n.s., Fig.1). Multivariate OS analysis showed that negative MRD was the strongest independent prognostic factor ($p<0.05$).

In landmark analysis, patients achieving CR and proceeding to allogeneic stem cell transplantation consolidation (HSCT) (n=23) within 3 months from CR (n=8) had a significantly better outcome if compared to CR patients who did not receive HSCT (n=41) or proceeded to transplant later (n=15, $p<0.03$).

Summary/Conclusion:

CPX-351 is able to induce MRD negative CR in a large proportion of elderly s- and t-AML patients, regardless of mutational burden or HMA-VEN resistance profile. While high-risk mutations appear less impactful in patients receiving CPX-351, early HSCT consolidation is the strongest factor in order to achieve long term survival.

Figure 1: OS according to HMA-VEN resistance profile



Keywords: Mutation analysis, Therapy-related AML, Minimal residual disease (MRD), Acute myeloid leukemia