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Blood 142 (2023) 6035–6036

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

The Co-Occurrence of bZIP in-Frame *CEBPA*-Mutation with Unfavorable Genetic Abnormalities Is Associated with a Poor Prognosis in Acute Myeloid Leukemia

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In a previous study (SY Ahn et al, Cancer Res Treat 2023), we reported that the presence of only the basic leucine zipper in-frame mutation (bZIP $^{in-f}$) *CEBPA* is associated with favorable outcomes in patients with *CEBPA*double mutations. However, when bZIP $^{in-f}$ *CEBPA*mutations were accompanied by certain mutations in chromatic/DNA modifiers, cohesion complex, and splicing genes, patients exhibited inferior overall survival (OS). *FLT3*-ITD or additional cytogenetic abnormalities is known to rarely co-occur with *CEBPA* mutation in patients with AML. In cases where both bZIP $^{in-f}$ *CEBPA* and *FLT3*-ITD coexist, there are conflicting aspects in risk stratification, and research on its prognostic significance is limited. Therefore, we aimed to evaluate the prognostic significances of the co-occurrence of bZIP $^{in-f}$ *CEBPA*mutation with unfavorable genetic abnormalities in acute myeloid leukemia.

In 832 patients who were diagnosed with AML excluding acute promyelocytic leukemia and underwent intensive induction therapy, 98 (11.8%) had bZIP $^{in-f}$ *CEBPA*. Among 98 patients with bZIP $^{in-f}$ *CEBPA*, eight cases had *FLT3*-ITD (5 with low allelic ratio, 3 with high allelic ratio), 19 patients had unfavorable genetic mutations according to the 2022 European LeukemiaNet guidelines, and 10 patients had non-favorable cytogenetic abnormalities as detected in diagnostic samples. We observed no clinical differences in features such as age, sex, WBC count, bone marrow blast percentage at diagnosis based on the co-occurrence unfavorable genetic abnormalities (unfavorable-gene). Among the 98 patients with bZIP $^{in-f}$ CEBPA, 30 out of 37 patients with unfavorable-gene achieved complete remission (CR) after induction therapy, and 55 out of 61 without unfavorable genetic abnormalities showed CR (p=0.20). Allogeneic hematopoietic cell transplantation was proceeded at first CR in 21 out of 37 unfavorable-gene group, and 35 out of 61 bZIP $^{in-f}$ *CEBPA*only group (*p*=1.00). In the survival analysis, patients with *FLT3*-ITD, unfavorable genetic co-mutated, or non-favorable cytogenetic abnormalities with bZIP $^{in-f}$ *CEBPA* showed inferior OS (p=0.036) (Fig. A). Due to the limited number of patients for analysis, we classified them into two group: the unfavourable-gene group and bZIP $^{in-f}$ *CEBPA*only group. We observed that the unfavourable-gene group had a poor OS compared to the bZIP $^{in-f}$ *CEBPA*only group (HR 2.71, 95 CI; 1.32-5.55, p=0.007) (Fig.B). On multivariate analysis, unfavorable-gene group was only poorrisk factor for OS. Despite the inclusion of a relatively small number of patients, our study demonstrates that when co-occurrence of bZIP $^{in-f}$ *CEBPA* withunfavourable genetic abnormalities, it results in a poor prognosis. To confirm its clinical significance, further validation with a larger patient population is necessary.

Disclosures Kim: *Novartis:* Consultancy, Honoraria, Research Funding; *BMS:* Research Funding; *Pfizer:* Consultancy, Honoraria, Research Funding; *Paladin:* Consultancy, Honoraria, Research Funding; *Merk:* Consultancy; *Sanofi:* Consultancy, Honoraria.

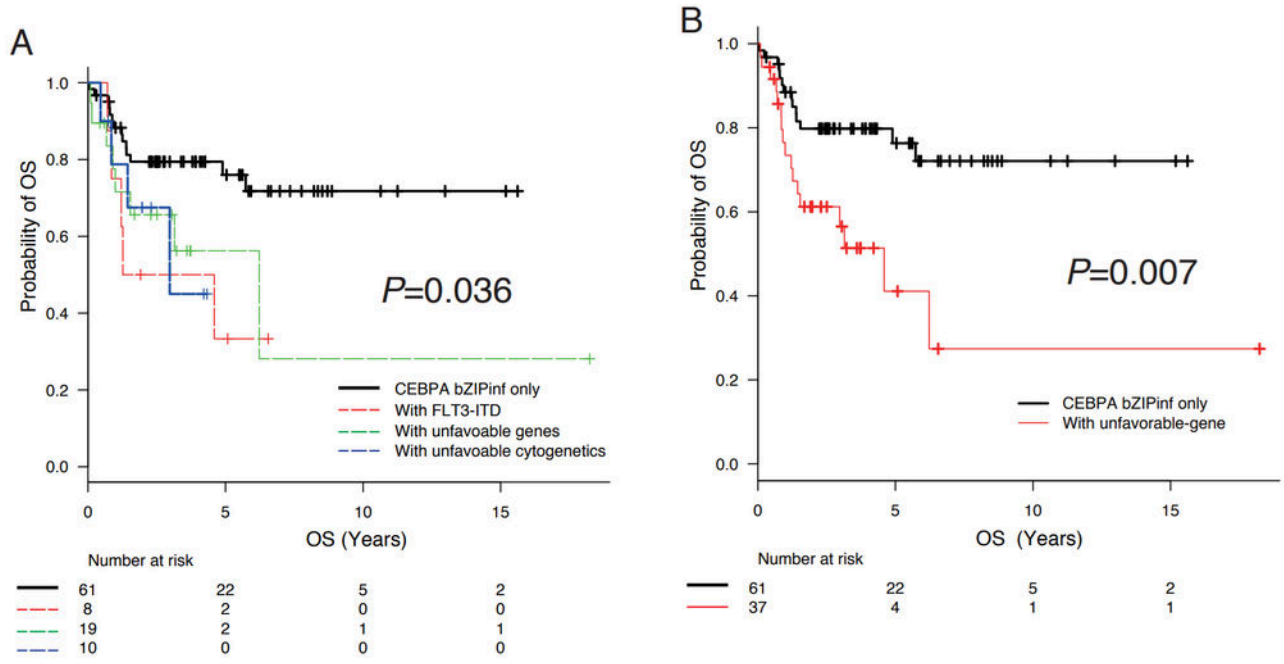

Figure 1

https://doi.org/10.1182/blood-2023-180499