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POSTER ABSTRACTS

509.BONE MARROW FAILURE AND CANCER PREDISPOSITION SYNDROMES: CONGENITAL

Clinical Features and Monitoring of Germline *CEBPA*-Mutated Carriers

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Background: Despite being classified as an independent entity in World Health Organization (WHO) classification in 2016, familial cases of adult acute myeloid leukemia (AML) with germline-mutated CCAAT/enhancer-binding protein-α (CEBPA) gene have been rarely reported due to insufficient knowledge of the clinical features of this entity. Germline *CEBPA*-mutated carriers are at extremely high risk of developing AML but have long been ignored until the onset of AML. We aimed to fully identify the clinical features of the familial cases and healthy carriers for this entity to call for a guideline for its management.
Methods: Whole exome sequencing (WES) data were analyzed in four members from one hereditary AML Chinese family, including two AML patients, one obligated carrier, and one non-consanguineous member. The whole coding region of *CEBPA* was sequenced in 21 members in this family and 6 members in another AML family. Deep sequencing targeting 248 genes related to myeloid malignancies was performed on 2 germline *CEBPA*-mutated carriers. To fully estimate the incidences of AML for each germline *CEBPA* mutation, we performed a thorough literature search for multiple members carrying germline *CEBPA* mutations.
Results: Here, we report two Chinese families with multiple AML cases carrying germline *CEBPA* mutations (c.247C>T; p.Gln83*). One family had 11 cases in four consecutive generations and 5 healthy carriers, and the other had 2 cases in two generations. Together with these two families, we collected clinical data from 57 AML patients in 22 families with germline *CEBPA*-mutation in total. 48 out of 57 AML were confirmed carrying germline *CEBPA* mutations. 58.3% (28/48) of AML harbored double *CEBPA* mutations. The first hit frequently occurred at the N-terminal of CEBP/α (22/28, 78.6%), resulting in an exclusive expression of p30 at the second translation starting site of *CEBPA* (hereafter, *CEBPA* ^{p30}). The second hit normally located at C-terminal of CEBP/α (hereafter, *CEBPA* ^{others}). Germline *CEBPA* ^{p30}-carriershave higher incidences of AML compared to those with germline *CEBPA* ^{others} (80.36% vs 42.86%, P=0.0003). The age at onset is much younger in patients carrying germline *CEBPA* ^{p30} than those carrying *CEBPA* ^{others} (18 vs 38.5, P=0.0093).
Among cases with detailed treatment information, 10/36 did not receive standard chemotherapies according to the NCCN guidelines for AML, and 16/36 received transplantation, nearly half (7/16) of which went through autologous or synergetic (monozygotic twin) transplantation and maintained endurable complete remission. 41.7% (15/36) of AML had at least one episode of relapse, and recurrent relapses occurred in 1/3 (5/15) of the AML patients. Intriguing, despite the high rates of relapse, only 3/15 of AML patients died of relapses. Most familial AML cases with germline *CEBPA* mutations had a favorable overall survival (OS). We found the OS in AML patients with germline *CEBPA* ^{p30} is better than those with *CEBPA* ^{others} (>25 years vs. 11 years, P=0.0125).
There are 27 healthy germline *CEBPA* mutated carriers aged 14 to 88, 20 of which were selected for further analysis due to complete age information, 80% (16/20) are still within the range of age at onset of familial AML with germline *CEBPA* mutations. We detected a pre-leukemia clone harboring a pathogenic IDH2 variant (Arg140Gln) in 1 germline *CEBPA*-mutated carrier, who is currently healthy.
Conclusions: The high penetrance accompanied by early onset in AML with *CEBPA* ^{p30} mutation implies the mutation as a strong genetic risk factor for AML **.** The intensity of chemotherapy should be tailored for familial AML with germline *CEBPA* mutations. Our study is the most extensive clinical data for familial AML cases with germline *CEBPA* mutations and is the first to reveal precise incidences of AML with certain germline *CEBPA* mutations. These data should aid in genetic counsel and the management of AML patients and healthy carriers with germline *CEBPA* mutations.

Disclosures No relevant conflicts of interest to declare.

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