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The relationship between gene mutations and age and gender in patients with first-onset acute myeloid leukemia

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Abstract: AML is a malignant clonal disease whose incidence is proportional to age, with men more likely than women to develop the disease. With the advancement of next-generation sequencing technology, people have become increasingly aware that the clonal evolution of leukemia is a complex, staged, multi-gene mutation process. In the AML diagnosis and treatment guidelines in recent years, gene mutations such as NPM1, FLT3-ITD and C-Kit have been used to assess the prognostic risk of AML. This article will review the previous literature and conduct a summary analysis of the age and gender differences in several common gene mutations in patients with first-episode AML, in order to help unearth the pathogenesis of AML, clinical treatment and prognosis judgment.

1. Introduction

Acute myeloid leukemia is a clonal malignant proliferation disease of immature myeloid precursor cells, which can lead to impaired hematopoiesis and bone marrow failure. The incidence of AML increases with age. As of 2019, SEER data showed that the age-adjusted incidence rate was 19.3 cases per 100,000 person-years for people 65 years or older, and 6.4 cases per 100,000 person-years for people younger than 65 years. The current overall survival rate in children is only 60-70%, and has since gradually declined with age, to less than 5% in those over 65 years old. Meanwhile, men are 1.5 times more likely than women to be diagnosed with AML, with age-adjusted incidence rates of 5.0 and 3.4 cases per 100,000 person-years in men and women, respectively. According to 2000-2020 SEER data, the AML mortality rate is 2.7 per 100,000 person-years (men vs. women: 3.4 vs. 2.1 per 100,000 person-years) (seer.cancer.gov).

With the application of second-generation gene sequencing technology, gene mutations are playing an increasingly important role in the diagnosis, treatment and prognosis of AML. There are many mutated genes associated with AML, but only some types of genes are frequently mutated, and most patients have more than one driver mutation. As the disease evolves, with multiple competing clones coexisting at any time, genetic mutations change. The biology of AML is complex, and further efforts are needed to inform clinical practice.

2. Differences in genetic mutations between children and adults with first-episode AML

The incidence of AML increases with age. Currently, the overall survival rate of children is only

60-70%. For patients over 65 years old, the overall survival rate gradually drops to less than 5% as they age. Children and adults die within 5 years of diagnosis due to recurrence rates as high as 35% and 99% [1]. In children, the vast majority of patients have first-episode AML, and adult AML usually comes from underlying MPN or MDS. This feature becomes increasingly apparent with age [2-3]. Regarding the reason why the incidence of AML in adults is higher than that in children, relevant literature mentions that hematopoietic cells with leukemia somatic mutations may already exist in adults, and somatic mutations will gradually accumulate in hematopoietic stem cells (HSCs) as individuals age. And AML-related mutations can also be acquired accidentally in cells [4]. However, pediatric AML incidence and clonal diversity are not explained by characteristics associated with aging. Therefore, the pathogenesis of AML in children seems to be different from that in adults.

The genetic landscape and mutation load of children and adults are very different, mainly in the following aspects: 1. Only 20% of pediatric patients have normal karyotypes, of which the majority carry chromosomal abnormalities; 2. Somatic cells of pediatric patients The number of mutations is lower than in adult patients (5-6 somatic mutations per pediatric sample [2, 5-6] vs. 10-13 somatic mutations per adult sample [7-8]); 3. In pediatric patients, most Common mutations are FLT3, NPM1, WT1, CEBPA and KIT, the most common are RUNX1, CBFB and KMT2A (also known as MLL) fusions, as well as structural aberrations including trisomy 8 and Y chromosome loss. Compared with adults, the incidence of KMT2A-rearranged AML is much higher in children (38% vs. 2%, respectively), with the highest incidence in infants and young children (77%) [1, 3]. Alterations in the RAS, KIT, and WT1 genes are more common in children than in adults. In contrast, DNMT3A and TP53 mutations common in adults are almost absent in pediatric patients. The most common mutations in adult AML are NPM1, RNA splicing genes (such as SRSF2, DNMT3A, TET2), etc. FLT3 mutations generally occur with similar frequency across all age groups, however, unique and pediatric-specific FLT3 variants have been reported [9].

3. Differences in genetic mutations between male and female patients with first-episode AML

Gender is a key biological factor influencing the development of multiple cancer types, including AML [10]. There are great differences between men and women in the incidence, prognosis and mortality of cancer. These observed complex phenomena can often be attributed to external factors, such as sex-biased social behaviors such as smoking, alcohol consumption, and delayed diagnosis, as well as internal factors including molecular changes in sex chromosomes, hormone levels, and sex bias [10]. The overview of sex-specific mutations in AML has also been described in the relevant literature; FLT3-ITD, NPM1 and DNMT3A mutations are overrepresented in women [11-12], but RUNX1, ASXL1, SRSF2, STAG2, BCOR, U2AF1 in men and EZH2 [10]; it is reported that the proportion of females with DNMT3A, FLT3-ITD and NPM1 mutations in AML patients is higher than that of males [13].

4. Age and gender distribution differences of common genes

4.1 DNMT3A

The DNMT gene located on chromosome 2P23 is a diverse family, which not only includes the four members "DNMT1" "DNMT2" "DNMT3B" and "DNMT3L", but also contains other different genes. A methyltransferase encoded by the DNMT3A gene can methylate specific DNA fragments, thereby triggering significant changes in gene expression [14].

A large number of relevant research reports have proven that the hotspot mutation at the 882 arginine position of the DNMT3A gene is closely related to AML [14]. It has been found that DNMT3A gene mutations mainly occur in patients with first-episode AML. This mutation has not

been found in AML relapse or in AML patients after treatment. Current research shows that the mutation rate of DNMT3A in adult AML is 4.1%~29.0%, the mutation rate in AML-M4 is 13.6%~22.6%, and the mutation rate in AML-M5 is 20.5~50.0%. The DNMT3A mutation rate is very low in pediatric AML patients (0.0%~2.1%), and mutated pediatric AML is accompanied by other molecular mutations [15]. Studies have shown that DNMT3A gene mutations are extremely rare in childhood acute leukemias and that most mutations are associated with other molecules. However, in adult acute leukemia, the incidence of DNMT3A gene mutations is relatively high, especially in elderly patients, especially in patients with adult acute leukemia AML-M4 and M5 [[16]. During the pathogenesis of AML-M4/M5, DNMT3A mutations are likely to be accompanied by FLT3, IDH1, IDH2, NPM1, CEBPA and TET2 mutations, and have certain implications for prognosis.

4.2 FLT3

Mutations in the FLT3 gene have been of great concern, and they occur in different ways. FLT3 can occur in two ways: one is through internal tandem duplication, the other is through point mutations in the active loop of the kinase region, and the latter is more common [17].

In the early days of AML research, FLT3-TKD expression was between 20% and 30%. In elderly cases, this proportion was 34% higher. However, in pediatric studies, AML-positive manifestations only accounted for 10% to 15%. %. There is a significant difference in overall survival between FLT3-ITD positive and negative patients and is an independent prognostic factor for AML. According to a clinical trial of 60 AML patients by the British Medical Research Council [18], it was found that FLT3 gene mutations can better reflect the prognosis of elderly people over 60 years old. Therefore, it may be a key molecule for evaluating the prognosis of AML patients. index. In a study of 1,755 AML patients [18], researchers found widespread differences in sex-related molecules. In women, the mutation rates of FLT3-ITD, NPM1, and DNMT3A are significantly increased, whereas in men, the proportion of these mutations is relatively low, and they are often accompanied by RNA splicing mutations and variations in epigenetic modifying genes. FLT3-mediated regulatory functions are not only in hematopoietic cells but also in tissues characterized by sexual dimorphism such as the gonads, placenta, and brain. This suggests that gender may influence the downstream effects of FLT3 signaling.

4.3 NPM1

NPM1, also known as nucleolar phosphoprotein, usually lives on the long arm of chromosome 5 (5q35) and can span the nucleolus, nucleoplasm and cytoplasm, thus affecting different cell morphologies and effectively promoting The normal metabolism of cells affects the life cycle of cells. NPM1 is significantly expressed in a variety of tissues, including not only tumor cells but also stem cells.

The proliferative activity of cells plays a crucial role in tumor development. NPM1 mutations can occur in all subtypes of AML (except M3), of which M4 and M5 are the most common. In Thiede et al's study [19], NPM1 mutations were 1.5 times more common in females than in males. As patients age, the probability of NPM1 mutations in adults increases [20-21], and the incidence of NPM1 mutations in children and adolescent AML is much lower than in adult AML. The mutated forms of NPM1 differ significantly between children and adults [21], with the proportion of mutant A in children being approximately 43%, while 35% appear to be novel variants not reported in adults, possibly due to their The molecular mechanisms employed differ. NPM1 mutations in children exhibit similar characteristics to adult AML, and the condition is more likely to occur in women. The incidence is also age-related, and NPM1 mutations appear to be more common in older children. However, studies have shown that NPM1 mutations are not found in the M5 type of childhood AML. In pediatric AML, NPM1 mutations are also closely linked to FLT3-ITD

mutations [22]. In addition, foreign studies have also shown that FLT3-ITD mutations have an important impact on the prognosis of AML patients. Although NPM1+/FLT3-ITD may provide favorable prognostic indicators, similar studies have not yet been conducted in children because it does not benefit from allogeneic hematopoietic stem cell transplantation. However, NPM1 mutations may become a new tool for monitoring multidrug resistance (MRD) in adult AML, but its value in monitoring MRD in children with AML requires further study because the incidence of NPM1 mutations in children is low.

4.4 KIT

KIT receptor tyrosine kinase is an important member on chromosome 4q11-12. It can effectively activate C-KIT receptor, thereby promoting the development and reproduction of hematopoietic stem/progenitor cells, and can affect cell development through other mechanisms and division. Mutations in the KIT gene can significantly promote tumor growth and lead to its inhibitory effect on apoptosis.

KIT mutations occur in 25% of pediatric CBF+AML and 20% of adult AML. Pollard et al [23] studied KIT mutations in 203 children with CBF+ AML and found 38 cases (19%), including 20 cases (52.5%) with exon 8 mutations and 17 cases (45%) with exon 17 mutations. Compared with wild-type KIT, patients carrying KIT mutations have a significantly increased recurrence rate and a significantly lower disease-free survival (DFS) rate, ultimately leading to a decrease in overall survival rate. A comprehensive large-scale study from Chinese centers screened 351 patients classified as pediatric t (8;21), adult t (8;21), pediatric inv (16), or adult inv (16), multivariate analysis results indicate that c-KIT mutations have a strong adverse impact on the recurrence and survival of adult t(8;21) AML patients [24].

4.5 ASXL1

ASXL1 encodes a 1084-residue nuclear protein characterized by an N-terminal helix-turn-helix domain HARE-HTH and an unusual C-terminal plant homology domain (PHD) that may bind methylation Lysine. The central part of ASXL1 contains an ASXH globular domain that may interact with polycomb-associated deubiquitinase (DUB). ASXL1 regulates epigenetic marks and transcription by interacting with polycomb complex proteins and various transcriptional activators and repressors[25-26].

The ASXL1 gene is one of the most frequently mutated genes in malignant myeloid diseases. ASXL1 protein belongs to a protein complex involved in epigenetic regulation of gene expression. ASXL1 mutations are found in myeloproliferative neoplasms (MPN), myeloproliferative syndromes (MDS), chronic myelogenous leukemia (CMML), and acute myelogenous leukemia (AML). They are often associated with signs of aggression and poor clinical outcome[27].In some studies, men are more likely to develop ASXL1 mutations than women, but the exact mechanism remains unclear.

5. Conclusion

The gender and age differences in AML are well known. Analyzing the differences in the incidence of AML from a molecular biology perspective can help us better understand and study the reasons behind this common phenomenon.Taken together, we propose that genetic mutation status as a clinical tool should be optimized in an age- and sex-adjusted manner and hypothesize that prognosis, prediction, and development of AML treatment strategies can be improved by incorporating sex-specific considerations.

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