Clinical Treatment Value of Acute Myeloid Leukemia in Different Genotypes

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Abstract: Acute myeloid leukemia (AML), a disease formed by mutations in pluripotent stem cells or mildly differentiated precursor cells, is a clonal malignant disease of the hematopoietic system. In recent years, with the application of immunology, cytogenetics, and molecular biology, a deeper understanding of the biological properties of AML tumor cells has laid the foundation for accurate classification, diagnosis, prognosis, and selection of the optimal treatment for AML. This article reviewed the relevant literature on the difference in clinical diagnosis and treatment value of AML in different genotypes in recent years.

***Keywords*:** acute myeloid leukemia, diagnosis, treatment

1. Introduction

Acute myeloid leukemia (AML) is one of the hematologic malignancies in adults, with 4.3 new cases per 10 0,000 people per year in the United States[1]. In China, the national incidence rate in recent years has been 4.54 cases per 100,000 people[2]and there are relatively few studies on the incidence, mortality and disease burden analysis of leukemia in China. This study aimed to analyze the incidence and mortality rates of leukemia in China from 2005 to 2017 and estimate their age-period-cohort effects, it is an important prerequisite for effective prevention and control of leukemia.\nMETHODS: Leukemia incidence and mortality data from 2005 to 2017 were collected from the Chinese Cancer Registry Annual Report. Joinpoint regression model was used to estimate the average annual percentage change (AAPC. AML was characterized by proliferative clones of the hematopoietic system and infiltration of bone marrow, blood, and other tissues by abnormally differentiated myeloid cells[3]platelets and white blood cells. The disease occurs at all ages, but predominantly occurs in older people (>60 years of age. In 1976, French-American-British (FAB) typing was established and used to classify the subtypes of AML, which meant that doctors could give different traditional cytotoxic chemotherapy regimens according to the different types of FAB. The World Health Organization (WHO) classifies all patients into other risk groups based on age, karyotype, specific genetic mutations, and clinical manifestations (e.g., hyperleukocytosis). Depending on the risk stratification of the WHO classification, doctors can group patients into treatment groups whether they are treated with traditional induction chemotherapy, consolidation chemotherapy, allogeneic hematopoietic stem cell transplantation, or a combination of targeted drug therapy[4].

2. Current status of clinical diagnosis and treatment of AML

2.1 Diagnosis of AML

Diagnosis of acute myeloid leukemia is based on clinical presentation, peripheral blood picture, bone marrow morphology, and examination. The latest classification procedures for AML are currently accomplished through morphological assessment of bone marrow specimens and blood smears, flow cytometry analysis of cell surface markers, routine cytogenetic testing of chromosomes, and molecular genetic lesions[5].

2.2 Clinical treatment of AML

2.2.1 Induction of chemotherapy

Daunorubicin + cytarabine (DA) is a commonly used induction therapy regimen for the treatment of AML patients, which can effectively improve the clinical symptoms of anemia, fever, and bleeding and control the progression of the disease[6]. A study has compared the outcomes of two groups of patients with AML who were treated with different induction regimens. One group received the standard DA3+7 regimen, and the other group received induction chemotherapy with cladribine in addition to the DA3+7 regimen(DAC). Through the analysis of treatment response and survival, the study found that the

response rate in the DAC group was significantly higher than that in the DA3+7 group, and the overall survival in the DAC group was also exceptionally prolonged. This suggested that the addition of cladribine to standard induction chemotherapy regimens could improve response rates and overall survival in patients with AML[7].

2.2.2 Consolidation therapy

Previous studies have shown that 50%~60% of AML patients can obtain complete response (CR) after receiving induction chemotherapy. Although post-CR therapy may benefit some patients, post-CR consolidation therapy is often not possible due to complications or residual toxicity of induction therapy. The standard regimen after CR is 1 or 2 cycles of Ara-C, with or without anthracyclines. It is controversial whether further consolidation therapy should be given to patients who have already acquired CR[8,9]autologous or allogeneic hematopoietic stem cell transplantation is still recognized as the main road toward cure in acute myeloid leukemia (AML.

2.3 Hematopoietic stem cell transplantation

Currently, hematopoietic stem cell transplantation is considered to be the most effective treatment for AML[10], and despite the high remission rate, a significant proportion of AML patients still relapse, and graft-versus-host disease is a major complication after hematopoietic stem cell transplantation(HSCT). Therefore, it is necessary to comprehensively assess the risk factors and individual characteristics of the patient and develop a recommendation based on risk assessment. This approach takes into account the patient's genetic and molecular characteristics, risk of disease recurrence, and risk of non-recurrent death[11]. A recent meta-analysis of 14 randomized controlled trials with a total of 4281 participants, of which 1499 patients received autologous stem cell transplant(ASCT), and 2782 received chemotherapy and continued follow-up, showed that AML patients who received autologous stem cell transplantation had higher disease-free survival (DFS) and relapse-free survival(RFS) and lower recurrence rates than those who received chemotherapy, which means that autologous stem cell transplantation may have a better prognosis[12].

3. Fusion genes in AML

As a malignant blood disease, the occurrence of AML is closely related to chromosomal abnormalities, and many chromosomal abnormalities lead to the formation of fusion genes, which play a very important role in the development of tumors. Fusion genes are mainly caused by chromosomal rearrangements and transcriptional abnormalities, and chromosomal rearrangements are more common than transcriptional abnormalities[13]a considerable number of fusion genes have been detected in leukemia. The majority of them are generated through chromosomal rearrangement or abnormal transcription. With the development of techniques, high-throughput sequencing method makes it possible to detect fusion genes systematically in multiple human cancers. Owing to their biological significance and tumor-specific expression, some of the fusion genes are attractive diagnostic tools and therapeutic targets. Tyrosine kinase inhibitors (TKI.

3.1 MLL (KMT2A)-AF9 (MLLT3)

The MLL (mixed lineage leukemia) gene is located on chromosome 11q23, which can be rearranged to form fusion genes in leukemia, especially AML, and there are many types and numbers, accounting for about 3/5 of AML-related fusion genes[14]particularly chromosome rearrangements generating gene fusion, are associated with clinical characteristics and prognosis in pediatric acute myeloid leukemia (AML. The common fusion partners of MLL are AF4, AF9 and ENL, and MLL-AF9 fusion is the most common, accounting for 2%~5% of all AML patients[15]pediatric, adult, and therapy-induced acute leukemias. So far, about 80 different direct MLL fusions and about 120 reciprocal MLL fusions have been characterized at the molecular level. The common theme in these leukemia-associated genetic rearrangements is the genetic disruption of the MLL gene. This leads to MLL-X fusion proteins that still bind to nuclear factors (e.g., MEN1, LEDGF, t(9; 11)(p22; q23) is found in 86% of M5 AMLs, In addition to chromosome 11q23 abnormalities, AML expressing this type of fusion gene is often accompanied by clinical manifestations such as high white blood cells, multi-organ invasion, remission with conventional chemotherapy, easy recurrence after remission, and short survival[16].

3.2 PML-RAR

The PML-RARα (promyelocytic leukemia/retinoic acid receptor alpha) fusion gene was formed by translocation of the t(15; 17)(q22; q22) chromosome, which is located on the Philadelphia chromosome (Ph). The expression of PML-RARα can interfere with the distribution of RARα in the nucleus and the regulation of cell differentiation, resulting in a large number of cells being arrested in the problastic stage, and about 95% of acute promyelocytic leukemia (APL) have PML-RARα fusion genes, which can become specific molecular markers of APL[17]. In addition, the levels of the fusion protein in the newly diagnosed and relapsed groups of APL were higher than those in the remission group, so the PML-RARα fusion

gene can be used for the observation of the efficacy, prognosis, and recurrence monitoring of APL[18]. At present, most APL patients are sensitive to all-trans retinoic acid (ATRA), which can differentiate immature leukemia promyelocytes into mature granulocytes and is an ideal chemotherapy drug[19].

3.3 AML1 (RUNX1)-ETO (RUNX1T1)

The AML1-ETO (acute myeloblastic leukemia 1-eight twenty-one) fusion gene is formed by t(8; 21)(q22; q22) chromosomal translocation, which occurs in about 15% of AML patients, mostly in M2 leukemia[20]. The fusion protein generated by AML1-ETO expression is a transcriptional repressor that can inhibit normal AML1 protein-mediated functions, alter the self-renewal and maturation process of hematopoietic progenitor cells, and also produce signals to initiate abnormal hematopoietic cell proliferation, causing the growth of leukemia cells[21]and it gives rise to acute myeloid gene 1 (AML1. AML1-ETO transactivates the expression of c-Kit by directly binding to and mediating the long-distance interaction between the promoter and intron enhancer regions of c-Kit (c-kit proto-oncogene protein). Gene expression analysis confirmed that the expression of c-Kit was significantly increased in t(8; 21) AML, and ChIP-3C-qPCR analysis confirmed that AML1-ETO can also mediate the long-distance interaction between the c-Kit promoter and intron enhancer regions to form DNA cycles[21]and it gives rise to acute myeloid gene 1 (AML1.

4. Summary

AML is the most common type of leukemia, accounting for about 30% of pediatric leukemia and 80% of adult acute leukemia, posing a serious threat to human health. The disease is characterized by rapid onset, rapid progression, difficult control, easy recurrence, poor prognosis, and increasing incidence with age. With the progress made in areas such as cytogenetics, immunophenotyping, molecular genetics, and recently developed gene expression profiling analysis, research in recent years has made significant progress in understanding the pathogenesis of AML. Many abnormal molecules involved in AML pathogenesis have been gradually clarified. Therefore, the understanding of the nature of AML is becoming more profound. The most common gene mutations in AML include FLT3, NPM1, RAS, etc. Therefore, continuously exploring the mechanisms and targets of these gene mutations, as well as exploring the differences in proteomics, metabolomics, and other omics in different genotypes of AML, plays an important role in the individualized and targeted treatment of AML.

References

[1] Shallis RM, Wang R, Davidoff A, et al. Epidemiology of acute myeloid leukemia: Recent progress and enduring challenges[J]. *Blood Reviews*, 2019, 36: 70-87.

[2] Lin K, Jia H, Cao M, et al. Epidemiological characteristics of leukemia in China, 2005-2017: a log-linear regression and age-period-cohort analysis[J]. *BMC Public Health*, 2023, 23(1): 1647.

[3] Khwaja A, Bjorkholm M, Gale RE, et al. Acute myeloid leukemia [J]. *Nature Reviews Disease Primers*, 2016, 2(1): 16010.

[4] Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes[J]. *Blood*, 2009, 114(5): 937-951.

[5] Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms[J]. *Leukemia*, 2022, 36(7): 1703-1719.

[6] Solh M, Yohe S, Weisdorf D, et al. Core-binding factor acute myeloid leukemia: Heterogeneity, monitoring, and therapy[J]. *American Journal of Hematology*, 2014, 89(12): 1121-1131.

[7] Anžej Doma S, Škerget M, Pajič T, et al. Improved survival of AML patients by addition of cladribine to standard induction chemotherapy[J]. *Annals of Hematology*, 2020, 99(3): 519-525.

[8] Schlenk RF, Jaramillo S, Müller-Tidow C. What's new in consolidation therapy in AML?[J]. *Seminars in Hematology*, 2019, 56(2): 96-101.

[9] Jimenez-Chillon C, Dillon R, Russell N. Optimal post-remission consolidation therapy in patients with AML[J]. *Acta Haematologica*, 2023.

[10] Shahzad M, Tariq E, Chaudhary SG, et al. Outcomes with allogeneic hematopoietic stem cell transplantation in TP53-mutated acute myeloid leukemia: a systematic review and meta-analysis[J]. *Leukemia & Lymphoma*, 2022, 63(14): 3409-3417.

[11] Cornelissen JJ, Blaise D. Hematopoietic stem cell transplantation for patients with AML in first complete remission[J]. *Blood*, 2016, 127(1): 62-70.

[12] Ge S, Wang J, He Q, et al. Auto-hematopoietic stem cell transplantation or chemotherapy? Meta-analysis of clinical choice for AML[J]. *Annals of Hematology*, 2024.

[13] Wang Y, Wu N, Liu D, et al. Recurrent Fusion Genes in Leukemia: An Attractive Target for Diagnosis and Treatment[J]. *Current Genomics*, 2017, 18(5): 378-384.
[14] Iijima-Yamashita Y, Matsuo H, Yamada M, et al. Multiplex fusion gene testing in pediatric acute myeloid leukemia[J]. *Pediatrics International: Official Journal of the Japan Pediatric Society*, 2018, 60(1): 47-51.
[15] Marschalek R. MLL leukemia and future treatment strategies[J]. *Archiv Der Pharmazie*, 2015, 348(4): 221-228.
[16] Takagi K, Tasaki T, Yamauchi T, et al. Successful Administration of Recombinant Human Soluble Thrombomodulin α (Recomodulin) for Disseminated Intravascular Coagulation during Induction Chemotherapy in an Elderly Patient with Acute Monoblastic Leukemia Involving the t(9;11)(p22;q23) MLL/AF9 Translocation[J]. *Case Reports in Hematology*, 2011, 2011: 273070.
[17] Beez S, Demmer P, Puccetti E. Targeting the acute promyelocytic leukemia-associated fusion proteins PML/RARα and PLZF/RARα with interfering peptides[J]. *PloS One*, 2012, 7(11): e48636.
[18] [The First Switched Time of PML/RARα Fusion Gene in Patients with Acute Promyelocytic Leukemia and Its Clinical Significance] - PubMed[EB/OL]. [2024-01-31]. https://pubmed.ncbi.nlm.nih.gov/26708869/.
[19] De Braekeleer E, Douet-Guilbert N, De Braekeleer M. RARA fusion genes in acute promyelocytic leukemia: a review[J]. *Expert Review of Hematology*, 2014, 7(3): 347-357.
[20] Hatlen MA, Wang L, Nimer SD. AML1-ETO driven acute leukemia: insights into pathogenesis and potential therapeutic approaches[J]. *Frontiers of Medicine*, 2012, 6(3): 248-262.
[21] Fu L, Huang W, Jing Y, et al. AML1-ETO triggers epigenetic activation of early growth response gene l, inducing apoptosis in t(8;21) acute myeloid leukemia[J]. *The FEBS journal*, 2014, 281(4): 1123-1131.