

Personalized Approach to Diagnosis and Treatment of Acute Myeloid Leukemia

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Introduction

Recent advances in disease pathogenesis and modern technologies are gradually transforming conventional medicine into personalized medicine. The personalized approach to diagnosis of leukemic patients consists of comprehensive and individualized evaluation based on characteristics of the tumor cell morphology, immunophenotype, cytogenetic and molecular aberrations as well as the patient's overall genetic make-up. Such a diagnostic approach, in addition to guiding individualized treatment, will help to identify new molecular targets for therapy.

Acute myeloid leukemia (AML) is a type of aggressive neoplasm characterized by clonal expansion of myeloid blasts in the bone marrow, blood, or other tissue. AML is the most common acute leukemia in the USA with an estimated 14,590 new cases and 10,370 deaths in the USA in 2012 [1]. AML is a heterogeneous group of diseases, and can be further divided into multiple subclasses.

Diagnosis and Classification of Acute Myeloid Leukemia

The earlier French-American-British (FAB) classification of AML is mainly based on morphology and cytochemistry [2], and it classifies AML into eight groups, namely AML-M0 to -M7 (Table 1). The most recent WHO classification proposed in 2008 is based on morphology, immunophenotype, genetic abnormalities and clinical history [3]. It divides AML into four major categories with multiple subgroups (Table 2). The inclusion of genetic subgroups has great prognostic and therapeutic significance.

Morphology and immunophenotype

AML is currently defined as a leukemia with 20% or more myeloid blasts in the bone marrow or blood. A myeloblast is an early precursor of myeloid lineage. It typically has immature nuclear features and expresses common myeloid markers such as CD13 or CD33, along with stem cell marker CD34 or early myeloid marker CD117. Further immunophenotyping can identify the cell of origin and the level of differentiation of the blasts, and aid in subclassification of AML into granulocytic, monocytic, erythroid, megakaryocytic, or minimally differentiated AML [3].

Conventional cytogenetics

Certain cytogenetic abnormalities have been frequently observed in AML, and some are distinctively associated with specific subtypes of AML (Table 2). Most importantly, cytogenetic abnormalities are currently recognized as one of the most significant factors in predicting clinical outcomes of AML patients [4-6]. Several cytogenetic risk groups have been proposed [5]. The favorable risk group includes Core-Binding Factor (CBF) abnormalities, t(8; 21) and inv(16)/t(16;16), which are associated with high rate of Complete Remission (CR) and longer survival [7]. The t(15;17) underlies acute promyelocytic leukemia, which is one of the most curable types of leukemia [8]. The unfavorable risk group includes complex cytogenetic abnormalities (≥ 3 cytogenetic aberrations), abnormalities of the long arm of chromosome

3, deletions of the long arm of chromosome 5 and monosomies of chromosomes 5 or 7 [9]. Recent studies have shown that patients with Monosomy Karyotype (MK) have significantly shorter overall survival than patients with non-MK yet unfavorable aberrations. Therefore, it is proposed that MK identifies a distinct subgroup of patients with the most unfavorable clinical outcome [10]. The intermediate risk group includes normal karyotype and abnormalities other than those described in the favorable and unfavorable groups [9].

Molecular genetics

In addition to chromosomal aberrations, gene mutations and duplications are frequently observed in AML patients. Approximately 40-50% of AML patients have a normal karyotype, but have shown a wide range of clinical outcomes [4,5]. Therefore, it is particularly important to identify molecular prognostic factors that can improve risk stratification in this group of patients. It has been shown that 85% of AML patients with a normal karyotype have gene mutations, in particular, NPM1, FLT3 and CEBPA [6]. These mutations have prognostic significance and are being used in diagnosis [9]. Patients with NPM1 mutation without FLT3-ITD have a better CR rate, and improved overall survival and disease-free survival, comparable to those of CBF AML [11,12]. Similarly, patients with biallelic mutations of CEBPA gene have longer overall survival than patients with no or single allelic mutation [13]. On the other hand, FLT3-ITD has negative prognostic influence, resulting in shorter remission duration and poorer survival outcome compared with patients with wild-type FLT3 [14,15]. Prognostic significance of many of the newly identified molecular markers is still unclear. However, continued study may

Type	Name
M0	Minimally differentiated acute myeloblastic leukemia
M1	Acute myeloblastic leukemia, without maturation
M2	Acute myeloblastic leukemia, with granulocytic maturation
M3	Acute Promyelocytic Leukemia (APL)
M4	Acute Myelomonocytic Leukemia, And Acute Myelomonocytic With Eosinophilia (M4eo)
M5	Acute Monoblastic Leukemia (M5a) and Acute Monocytic Leukemia (M5b)
M6	Acute erythroid leukemias
M7	Acute megakaryoblastic leukemia

Table 1: Eight FAB subtypes were proposed in 1976.

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Acute myeloid leukemia with recurrent genetic abnormalities
AML with t(8;21)(q22;q22); (RUNX1;RUNX1T1)
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); (CBFB-MYH11)
APL with t(15;17)(q22;q12); (PML-RARA)
AML with t(9;11)(p22;q23); (MLL3-MLL)
AML with t(6;9)(p23;q34); (DEK-NUP214)
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); (RPN1-EV11)
AML (megakaryoblastic) with t(1;22)(p13;q13); (RBM15-MKL1)
Provisional entity: AML with mutated NPM1
Provisional entity: AML with mutated CEBPA
Acute myeloid leukemia with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia, not otherwise specified
Similar to FAB subgroups

Table 2: 2008 WHO Classification of Acute Myeloid Leukemia.

provide new insight into their importance in clinical outcome and response to certain therapeutic drugs.

Personalized Treatment of Acute Myeloid Leukemia

Therapy of AML includes traditional cytotoxic chemotherapy, targeted therapy, epigenetic therapy, and stem cell transplantation. Risk stratification based on cytogenetics and molecular markers plays a crucial role in guiding personalized treatment.

Traditional treatment adjustment based on specific leukemia characteristics

In AML patients with unfavorable cytogenetic and/or molecular risk, traditional chemotherapy protocol has not produced ideal outcomes. More accurate risk stratification will help better 'targeting' of patients who may benefit from chemotherapy dose adjustment and hematopoietic cell transplantation. In prospectively randomized studies, high-dose daunorubicin compared with standard dose resulted in a higher rate of complete remission and improved overall survival [16,17]. However, intensifying cytarabine has failed to improve clinical outcome [18-20]. Currently, myeloablative allogeneic stem cell transplantation (alloSCT) is recommended for poor-risk but not good-risk AML. AlloSCT, autologous transplant and consolidation chemotherapy are considered of equivalent benefit for intermediate-risk AML [21].

Targeted therapy

Advances in molecular diagnostics have resulted in significant advances in identification of new targets for therapy. Many new therapies are being tested in clinical trials.

Antibody-directed chemotherapy

Monoclonal antibodies target specific antigens expressed on malignant cells and can direct chemotherapy drugs to the targeted cells without affecting normal cells. Gemtuzumab ozogamicin is an immunoconjugate between anti-CD33 antibody and calicheamicin, and has been used as an addition to standard chemotherapy for AML patients. The outcome is controversial. While the Southwest Oncology Group (SWOG) study in 2010 failed to show improvement in CR rate and survival [22], other studies using lower dose gemtuzumab ozogamicin during standard front-line chemotherapy showed survival benefit [23,24].

FLT3 inhibitors

Patients with FLT3 mutations, in particular FLT3-ITD, have

inferior prognosis. Several FLT3 inhibitors, e.g. lestaurtinib (CEP-701), sunitinib (SU-11248), tandutinib (MLN-518), midostaurin (PKC-412), sorafenib (BAY-93006) and anti-FLT3 monoclonal antibody (IMC-EB10), are being evaluated in clinical trials as single agent therapy and in combination with conventional chemotherapy [25]. In a clinical trial of midostaurin combined with standard induction chemotherapy, addition of midostaurin demonstrated higher CR rate and improved overall survival [26].

CXCR4 inhibitor

CXCR4 is a chemokine receptor and serves as the principle regulator of stem cell homing and retention in the bone marrow. Increased CXCR4 expression has been associated with increased risk of relapse and decreased survival in AML. Plerixafor is a small molecule of CXCR4 inhibitor. A phase 1/2 study using Plerixafor in combination with chemotherapy to treat relapsed or refractory AML patients showed improved CR rate [27].

Epigenetic therapy

DNA hypermethylation represses transcription of the promoter regions of tumor suppressor genes. As opposed to conventional cytotoxic chemotherapy, the use of hypomethylating agents, such as azacytidine and decitabine, offer the possibility of disease control, without necessarily achieving CR in AML patients considered unfit for standard chemotherapy [28].

Other new agents, such as an inhibitor of NEDD8 activating enzyme (MLN4924) [29], an antisense oligonucleotide to X-linked inhibitor of apoptosis proteins (AEG 35156) [30], and WT1 tumor antigen-loaded dendritic cells [31], all have shown anti-AML activity and are attractive future options.

Future Directions

New technologies have allowed us to further categorize newly diagnosed AML patients into previously unrecognized biologic and/or prognostic subgroups. Array-based technologies using comparative genome hybridization and single nucleotide polymorphism (SNPs) have been conducted successfully in AML patients and have provided valuable information [32-34]. The development of Next-Generation Sequencing (NGS) methods has revolutionized our ability to diagnose diseases and is now able to analyze disease-associated genetic abnormalities based on the entire genome of an individual patient. Specifically, NGS is now being applied to studies of cancer genomes such as targeted oncogene or tumor-suppressing gene sequencing, exome, transcriptome, methylome, histone-associated genome and whole-genome sequencing [35,36]. Equipped with these new technologies, we are advancing towards an era of disease diagnosis derived not only from population-based genetic information but also tailored from genetic information of an individual patient hence leading to personalized approaches to diagnose and treat a patient. Such an individualized approach will undoubtedly offer more efficient and less toxic therapy to AML in the future.

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