Acute Myeloid Leukemia: A Review

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ABSTRACT

Acute myeloid leukemia (AML) is a malignancy of the stem cell precursors of the myeloid lineage (red blood cells, platelets, and white blood cells other than B and T cells). Like other malignancies, it is due to genetic variations that lead to neoplastic changes and clonal proliferation. AML remains a rare malignancy, accounting for only 1.2% of all new cancer diagnoses in the United States per year, but it accounts for close to one third of all leukemias diagnosed.* For much of the 20th and early 21st century treatment paradigms were unchanged with survival curves remaining stagnant for many decades. Recent changes in our understanding of the genetic variations in the disease have led to some promising new therapies with hopes for improved outcomes in the future. Below we review the definitions, diagnosis and classification of AML and how this affects the evolving treatment paradigm of AML.

KEYWORDS: acute myeloid leukemia, bone marrow, stem cell transplantation

DEFINITION/DIAGNOSIS/CLASSIFICATION

AML is a disease of the bone marrow, a disorder of hematopoietic stem cells due to genetic alterations in blood cell precursors resulting in overproduction of neoplastic clonal myeloid stem cells. While extramedullary manifestations can occur (e.g. myeloid sarcomas, leukemia cutis), the underlying disease is due to abnormalities in hematologic cellular production. A small subset of cases have identified causative factors such as prior chemotherapy or certain chemical exposures, but the large majority are due to genetic alterations, through chromosomal abnormalities or isolated gene mutations, without clear causative agents.[1] Delineating these genetic abnormalities is important in risk stratifying patients and determining appropriate treatment.

Patients with AML will initially present in a myriad of ways. Some cases of disease will be discovered on routine blood work while others may present with symptomatic complications such as infection, bleeding or disseminated intravascular coagulation. Bone marrow examination is paramount for both establishing the diagnosis as well as obtaining tissue for analysis to better classify the AML subtype and prognostic severity.

The World Health Organization in its 2016 updated guidelines distinguishes six groups of AML: (1) AML with recurrent genetic abnormalities, (2) AML with myelodysplasia-related changes, (3) Therapy-related myeloid neoplasms, (4) AML Not Otherwise Specified, (5) Myeloid sarcoma, and (6) Myeloid proliferations related to Down syndrome.[2] The diagnosis is made by the presence of ≥20% blasts in the peripheral blood or in the bone marrow, or through the presence of unique genetic abnormalities found in the bone marrow regardless of blast count [t(8;21), inv(16), or t(15;17)].[3]

AML is further classified into three prognostic risk groups: favorable, intermediate, and adverse [**Table 1**].[3] These are based on both cytogenetics and relatively recent recognition of molecular diseases subsets that are distinct from the

Table 1. Risk Profile Categories as Determined by Molecular and Cytogenetic Abnormalities

Favorable	t(8;21)(q22;q22); RUNX1-RUNX1T1;
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	Mutated NPM1 without FLT3-ITD/low FLT3-ITD
	Biallelic mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD(high)
	Wild-type NPM1 without FLT3-ITD/ low FLT3-ITD (normal karyotype)
	t(9;11)(p21.3;q23.3)MLLT3-KMT2A
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); DEK-NUP214
	t(v;11q23.3); KMT2A rearranged
	t(9;22)(q34.1;q11.2); BCR-ABL1
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)
	-5 or del(5q); -7; -17/abn(17p)
	Complex karyotype
	Monosomal karyotype
	Wild-type NPM1 and high FLT3-ITD
	Mutated RUNX1
	Mutated ASXL1
	Mutated TP53

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contribution of cytogenetic risk. These newly recognized molecular subsets have different responses to standard therapeutics. The prognostic groups predict the response to standard therapy and survival in one large retrospective analysis of patients under the age of 55, the overall survival rate at 5 years was 44%, however when broken down by risk profile the overall survival rates were 64%, 41%, and 11% for favorable, intermediate, and adverse risk respectively.[4] The overall survival decreases when older adults are included but the stratification of survival remains constant.

TREATMENT

The treatment of AML involves initial induction therapy and post-remission therapy. Goal of induction therapy is to achieve complete remission (CR) with preferably no measurable residual disease (MRD). Studies have shown improved survival in patients who achieve CR irrespective of the type of induction therapy.[5] Choice of initial induction treatment depends on functional status of the patient (which is best measured by performance status and comorbidities), biological status of the disease (best measured by prognostic risk groups and recently recognized molecular profile of leukemia cells) and goals of the patient. The two commonly used induction therapies in acute myeloid leukemia include 1) Cytotoxic chemotherapy with or without targeted therapies and 2) Hypomethylating agents with or without targeted therapies.

INDUCTION CHEMOTHERAPY

Favorable and Intermediate Risk Disease

For all patients with AML with the goal of cure and who are medically fit enough to tolerate chemotherapy, the backbone of therapy has not changed for 50 years, with upfront treatment consisting of a continuous infusion of cytarabine over 7 days with the addition of an anthracycline, typically daunorubicin, given daily for the first 3 days. This induction therapy, known colloquially as 7+3, leads to complete disease response in up to 80% of patients with favorable risk disease and 50–60% complete response in those with intermediate adverse risk disease.[6]

The outcomes have improved with addition of various targeted drugs to the traditional 7+3 induction chemotherapy in the favorable and intermediate risk groups. Gemtuzumab ozogomycin (GO) is a monoclonal antibody against CD-33 (a protein that is expressed in myeloid leukemia cells). Addition of GO to standard chemotherapy in patients with favorable and intermediate risk disease decreases the risk of relapse and in some studies improves overall survival (OS). The magnitude of benefit is higher in favorable risk disease than in intermediate risk disease.[7] This has made obtaining early cytogenetic and molecular studies on patients with a new diagnosis of the upmost importance as GO is added to the first day of therapy for patients with favorable risk disease who are CD-33 positive.

Midostaurin is an oral multi-targeted tyrosine kinase inhibitor active in patients with a FLT3 mutation. FLT3 mutations initiate oncogenic signal transduction in about 25–30% of patients with AML. There are 2 types of FLT3 mutation; Internal tandem duplication and tyrosine kinase domain. Addition of midostaurin to standard 7+3 chemotherapy in patients with FLT3 mutation has improved survival, from a median of 25 to 74 months.[8]

Adverse Risk Disease

Adverse risk disease is an unmet need in AML. The outcomes with standard 7+3 chemotherapy remain unsatisfactory. Complete remission (CR) rate is only about 40% and median overall survival is in the range of 12–18 months. Even with allogenic hematopoietic stem cell transplantation (see below), almost half of the patients relapse. Patients are therefore usually referred for clinical trials if there is one available, due to these lower rates of survival. Recently two therapies, CPX351 and venetoclax with a hypomethylating agent, have shown better results than the standard therapy in patients with adverse risk disease.

CPX 351 is a liposomal formulation of cytarabine and daunorubicin at a fixed 5:1 molar ratio of cytarabine and daunorubicin. The liposomal encapsulation leads to prolonged exposure to the two drugs. CPX 351 showed significantly improved response rates and improved survival compared to 7+3 chemotherapy in patients with adverse risk disease (i.e. therapy-related AML, AML with MDS related changes).[9]

Venetoclax is an oral highly selective inhibitor of the anti-apoptotic protein BCL-2. BCL2 is thought to mediate resistance to standard therapy in patients with adverse risk AML. Venetoclax was studied with hypomethylating agents (decitabine and azacitadine) as a backbone in patients with adverse risk disease. Even in elderly patients and patients with poor cytogenetics and adverse molecular mutations, the outcomes were better with venetoclax plus hypomethylating agents than hypomethylating agents alone.[10] Median overall survival in these preliminary studies was approximately 15 months, significantly improved from the historical median survival of approximately 10 months with the use of hypomethylating agents alone.[11]

POST-REMISSION THERAPY

The goal of post-remission therapy is to prevent relapse of the disease. The two commonly employed strategies are additional post remission cytotoxic chemotherapies (such as high or intermediate dose cytarabine) with or without targeted therapies, or allogenic hematopoietic stem cell transplantation (Allo SCT). The choice of therapy is determined by the unique risks and benefits provided by each treatment

arm. The risk of non-relapse mortality (NRM) is high with Allo SCT; however, the risk of disease relapse is reduced. Furthermore, there is increased morbidity with Allo SCT (such as chronic graft vs host disease, secondary malignancies, or infection from chronic immunosuppression).

The absolute decrease in the risk of disease relapse has to be more than the risk of NRM to justify Allo SCT as post-remission therapy. All patients with adverse risk profiles and most of the patients with intermediate risk meet this criteria.[12,13] Patients with favorable risk profiles, however, are able to remain free from relapse at high enough rates with chemotherapy alone such that the risks of Allo SCT are not justified. Therefore, in favorable risk group, induction therapy is followed by definitive consolidation therapy with high dose cytarabine (HiDAC).[14]

FUTURE DIRECTIONS

Over the last decade, there have been significant advancements in the genomic profiling of AML. This has resulted in exciting opportunities to create genomically defined targeted therapies for patients with AML. Some of the therapies like FLT3 inhibitors, Isocitrate dehydrogenase (IDH) 1 and 2 inhibitors have been tested in clinical trials and are now the standard of care in patients who harbor these mutations. There are other targeted agents directed against various mutations seen in AML that are currently being investigated in clinical trials. One ongoing multicenter trial is sponsored by the Leukemia and Lymphoma Society in the United States and is known as the "BEAT AML" trial. Patients are assigned to targeted therapies based on their genomic profile, with the hope that the results of this and several other trials will provide important information regarding the clinical benefits of genomically defined targeted therapies in AML.

CONCLUSION

Acute myeloid leukemia remains a rare but lethal malignancy. Our understanding of the disease has progressed significantly, and new and evolving therapies are providing hope for improved survival and less toxic treatment. Early diagnosis with rapid analysis of cytogenetic and molecular abnormalities (e.g. NPM1, FLT-3) are paramount in tailoring best therapy for patients, especially in light of new treatment modalities that rely on cytogenetic and molecular testing. Chemotherapy remains the backbone of treatment with stem cell transplantation still the best hopes for cure in many patients with adverse cytogenetic risk profiles.

*SEER Cancer Stat Facts: Acute Myeloid Leukemia. National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/statfacts/html/amyl.html

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