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International Journal of Biochemistry & Physiology
ISSN: 2577-4360

Acute Myeloid Leukemia: Review and Current Update

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Research article

Volume 6 Issue 2

Received Date: July 31, 2021

Published Date: October 26, 2021

DOI: 10.23880/ijbp-16000197

Abstract

Acute myeloid leukemia (AML) is a heterogeneous clonal disorder which is characterized by an immature myeloid precursor cell proliferation and bone marrow failure. Acute leukemias comprise few most common malignant disorders. Due to effects of inherited genetic variations and disorders, pre-existing diseases, infectious agents, hobbies, occupations, prior treatments, and other factors have been identified, but not even a single is applicable to all cases. Despite robust advances in the fields of new drug targets and increased understanding of the biology, AML treatment remains same for decades with the majority relapse and dying due to the disease. Allogenic Bone Marrow Tissue transplant remains a best chance for cure for patients with intermediate or high risk disease. Advances in technologies like genomic profiling, including genome-wide gene expression, DNA copy number and single nucleotide polymorphism (SNP) genotype, spread some light on the role of genetics in these disparities. Combination of genetics and infection factors resulting in leukemogenesis. The exact nature, timing, sequence of the events and mechanisms leading to development of leukemia requires further investigations. This review summarizes the genetic studies that have improved outcome prediction and spread some light on the developing novel therapies.

Keywords: Leukemogenesis; Acute Myeloid Leukemia; Single Nucleotide Polymorphism

Abbreviations: AML: Acute Myeloid Leukemia; APL: Acute Promyelocytic Leukemia; ML: Myeloid Leukemia; WHO: World Health Organization; FDA: Food and Drug Administration; HSCT: Hematopoietic Stem Cell Transplant; MRD: Minimal Residual Leukemia; OS: Overall Survival; ATRA: All-Trans Retinoic Acid; DIC: Disseminated Intravascular Coagulation; NSE: Nonspecific Esterases; FISH: Fluorescence in Situ Hybridization; PCR: Polymerase Chain Reaction.

Introduction

Most common acute leukemia in adults is Acute myeloid leukemia (AML), accounting for about 80 percent of cases in group of acute leukemia [1]. The incidence of AML ranges from about 5 cases per 100,000 populations. In 2015, Leukemia covers 20,830 newly diagnosed cases, and over 10,000 mortalities [2]. The incidence of AML increases with age, from ~1.3 per 100 000 populations in patients but 65 years old, to 12.2 cases per 100 000 populations in those over 65 years. Despite of advancement of AML treatment, which led to significant improvements in outcomes for younger patients, prognosis in the elderly still remains poor [3]. Even with current treatments, as much as 26% of patients 65 years or older will die of their disease within 1 year of diagnosis [4].

Sign and Symptoms

The signs and symptoms of AML are related to variety of other, less serious diseases. To feel a loss of well-being due to the underproduction of normal bone marrow cells is common for people with AML. The person may more prone to have shortness of breath while having normal physical activities. AML patients also have, pale complexion from anemia, Signs of bleeding caused by a really low platelet count, including:

- Black-and-blue marks or bruises on the skin
- Looks of pinhead-sized red spots on the skin, called “petechiae”

- Abnormally Prolonged bleeding from minor cuts
- Mild fever
- Swollen gums
- Frequent minor infections, such as perianal sores
- Loss of appetite and weight loss
- Discomfort in bones or joints
- Enlarged spleen and liver etc.

Bleeding: Bleeding causes low platelet count predisposes patients to further bleed. Bleeding within the brain or lung is serious and may be fatal. However, such bleeding is typically preceded by minor bleeding, like nose bleeds, blood within the urine or bruises.

Infection: Severe infection can occur at the time of diagnosis but becomes more common and sometimes more serious during treatment, when the bone marrow is totally suppressed. Because of AML or its treatment, if the Neutrophils cell count becomes or remains low, serious infection most commonly occurs and becomes cause of death from AML.

Myeloid Sarcoma: Very uncommonly, a bunch of AML cells, called a "myeloid sarcoma," originates outside the marrow. A myeloid sarcoma may occur in almost any a part of the body. After the initial myeloid sarcoma diagnosis AML signs might not appear within blood and marrow for few weeks or months. A myeloid sarcoma diagnosis is like a diagnosis of AML, and is treated with chemotherapy instead of local therapy. Treatment can also include allogeneic or autologous somatic cell transplant. "chloroma," "granulocytic sarcoma," "myeloblastoma" or "monocytoma" are other names for myeloid sarcoma.

Pathophysiology of Acute Myeloid Leukemia

It appears as a denovo malignancy in previously healthy individuals in majority of cases. Regardless of various etiologies, pathogenesis of AML involves the abnormal proliferation and differentiation of a clonal population of myeloid stem cells. The formation of chimeric proteins (RUNX1-RUNX1T1 and PML-RARA, respectively) are due to well-characterized chromosomal translocations, such as t (8:21) in core-binding factor AML (CBF-AML) or t (15:17) in acute promyelocytic leukemia (APL), which changes to the abnormal maturation process of myeloid precursor cells. In the development of AML instead of addition to large chromosomal rearrangements, molecular changes have also been implicated. In fact, More than 97% cases represent genetic mutations often in the absence of any large chromosomal abnormality [5].

<table>
<tr><th>Property</th><th>Autonomous Cell Proliferation</th><th>Differention Block</th><th>Escape from Apoptosis</th><th>Increased Self-Renewal</th><th>Loss of Cell Cycle Control</th><th>Dissemi nation</th></tr>
<tr><td rowspan="8">Molecular Lesion</td><td>Activaling mutations Fit3, Ras other 0-FMS. Jake PTPN11 Inactivating mutation- NF1</td><td>Fusion transcription factors</td><td>AKT pathway activation_following RTK activa-_ tonleads to Bad_ deactivation</td><td>B-catenin mutations</td><td>P53 dystunction</td><td>TNF secretion by_leukemic blasts_ stimulates endolhellum.</td></tr>
<tr><td rowspan="7">Jake PTPN11 Inactivating mutation- NF1 Autoone loops (Trk-A upregulation by RUNX1-MTG8)</td><td>Retinoio acd receptor PML -RARa, PLZF-RARm</td><td>P53 mulations in_ AML the elderly</td><td>Activation of Wnt_Catenin pathway by_fusion transcription_ factors</td><td>Loss Rb</td><td rowspan="7">Increased selectin,_ cadherin and integrin_ expression encourage_ adhesion and egreos_ through vessels</td></tr>
<tr><td>Core binding factor_ CBF8-MYH11_RUNK1-EVI1</td><td>P63 dysregulation by_fusion proteins,_ NPM mutation</td><td rowspan="5">Activated RTK_pathways cooperate to induce sell-renewal</td><td rowspan="5">P15, P16 cyclin-_ dependent kinase gene methylation</td></tr>
<tr><td>MLL-Jusions</td><td rowspan="2">Bd2 overexrepsion</td></tr>
<tr><td>Hox gene fusions and_ overexpression</td></tr>
<tr><td>Point mutation of transcrip-_tion factors_ Pui, C/EBPa, RUNK1</td><td rowspan="2">Sunvinin (IAP)_over expression</td></tr>
<tr><td>RTK inhitition of oritical_ractor expression 9 (Fit3_inhbits C/EBPa expres-_sion)</td></tr>
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Table1: The molecular lesions in acute myeloid leukemia (AML) associated with malignant characteristics.

The molecular pathogenesis of AML is complex, but multiple genetic defects are depicted in the (Table 1) which shows the molecular lesions in acute myeloid leukemia (AML) associated with malignant characteristics. There is a different correlation in some cases between the molecular defect and the biological process, while in other cases there may be an undetermined explanation for the molecular basis of the disease. By a more explained understanding of these chemical links we anticipate that more precise and specific therapies for AML can be developed. Whereas by current investigational therapies, the differentiation block and proliferative activity of AML is being targeted, by current investigational therapies we try to restore genomic stability, try to induce specific apoptosis of leukemia cells and try to restore cell cycle checkpoint control, should be given strong consideration in the development of future experimental therapeutic efforts [6].

Classification of Acute Myeloid Leukemia

Acute Myeloid Leukemias are divided by World Health Organization (WHO) [7] and the WHO classification is Table 2 and also FAB French-American-British [8] classification is also there for AML which is in Table 2 below.

Types	Genetic Abnormalities
AML 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 PML-RARA
	AML with t(9;11)(p21.3;q23.3); MLLT3-KMT2A
	ML with t(6;9)(p23;q34.1); DEK-NUP214
	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,
	MECOM
	AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);
	RBM15-MKL1
	AML with BCR-ABL1 (provisional entity)
	AML with mutated NPM1
	AML with biallelic mutations of CEBPA
	AML with mutated RUNX1 (provisional entity)
	AML with minimal differentiation
	AML without maturation
	AML with maturation
	Acute myelomonocytic leukemia
	Acute monoblastic/monocytic leukemia
	Acute erythroid leukemia
	Pure erythroid leukemia
	Acute megakaryoblastic leukemia
	Acute basophilic leukemia
	Acute panmyelosis with myelofibrosis
Myeloid sarcoma	
Myeloid proliferations related to Down syndrome	Transient abnormal myelopoiesis
	ML associated with Down syndrome

Table 2: WHO classification for Acute Myeloid Leukemias.

M0	AML with no Romanowsky or Cytochemical Evidence of Differentiation
M1	Myeloblastic leukemia with little maturation
M2	Myeloblastic leukemia with maturation
M3	Acute promyelocytic leukemia (APL)
M3h	APL, Hypergranular variant
M3v	APL, Microgranular variant
M4	Acute myelomonocytic leukemia (AMML)
M4eo	AMML with dysplastic marrow eosinophils
M5	Acute monoblastic leukemia (AMoL)
M5a	AMoL poorly differentiated
M5b	AMoL, differentiated
M6	Acute erythrocytic leukemia
M6a	AML with erythroid dysplasia
M6b	Erythroleukemia
M7	Acute megakaryoblastic leukemia (AMkL)

Table 3: FAB Classification of Acute Myeloid Leukemias.

Myeloblastic leukaemia with minimal differentiation is difficult to diagnose from the morphology only because the blasts represent both lymphoblastic and Myeloblastic features. They account for only 5% of adult AMLs.

In acute myeloblastic leukaemia without maturation, cells are monomorphic, very commonly with myeloid blasts in peripheral blood and no cells beyond the myeloblast stage of differentiation. Leukocytes are present at diagnosis.

Acute promyelocytic leukaemia is usually presents with low peripheral blood leucocyte levels, which makes difficult to diagnose it. A very characteristic morphology called atypical promyelocytes (hypergranular cells), majority of cells have. The cytogenic change characteristic of AML-M3 is t (15;17), which leads to the fusion of the PML (promyelocytic leukaemic) and retinoic acid receptor-alpha (RAR) genes, resulting in the PML-RAR transcript.

Microgranular variant of AML **(M3)** this accounts for between 15% and 20% of all cases of M3. Prognosis is poorer, and leukocytosis is usually featured. Sparsely granulated leukaemia cells are morphologically is characteristic of it. The cytoplasm is more basophilic, due to a lower concentration of azurophilic granules.

Acute myelomonocytic leukaemia **(M4)** accounts for 20% of AML. Clinically, patients present hyperplasia of gums. This type of leukaemia has a granulocyte component and a monocyte component in varying proportions and different degrees of maturation. Chloroacetate esterase is Cytochemically positive and monocytes are positive for naphthol-AS-d-acetate esterase or -Alfa-naphthyl-butyrate-esterase.

M4Eo variant: about 5% of cells are abnormal eosinophils then M4Eo confirmed, also presenting with monocytic nuclei and atypical granules.

(M5) consumes almost 15% of all cases of AML. Leukaemic cells are of a monocytic lineage (monoblasts and promonocytes), divided into: M5a (acute monoblastic leukaemia), in which monoblasts predominate; and M5b (acute monocytic leukaemia), in which a high proportion of promonocytes and monocytes are found, in addition to monoblasts. Monoblastic form is usually presents with t (9;11), t (6;11) and t (8;16) genetic translocations and 11q23 rearrangements (AML with recurrent genetic abnormalities according to the World Health Organization (WHO).

(M6) erythroid sub-type is a proliferation of dysplastic erythroid elements with a proliferation of blasts of myeloid origin. The WHO classification divides 2 sub-types: erythroleukemia **(M6a)**, described as a mixed proliferation of myeloid and erythroid blasts, and can be secondary to a previous myelodysplastic syndrome. (M6a) accounts for 5-6% of all AMLs. The other subtype is the pure erythroid variant **(M6b)**, which occurs when dyserythropoiesis is prominent.

Diagnostic Tools for Acute Myeloid Leukemia

A diagnosis of AML is accomplished by analyzing the Morphology of the cells by microscopic examination and identifying the blasts cells including their lineage followed by immunophenotyping using blood and/or bone marrow which is also used to diagnose the present of leukemia and differentiate AML from other types of leukemia and also classify the subtype of the disease and then the number and appearance of the chromosomes and mutation in genes is then analyzed using cytogenetic and molecular diagnoses respectively.

The mutations analyses are accomplished by fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR) [9]. Morphology Blood and marrow smears are morphologically examined after staining with May-Grunwald-Giemsa or a WrightGiemsa stain. For making a diagnosis, it is recommended that at least 200 leukocytes on blood smears and 500 nucleated cells on marrow smears be counted, with the latter containing spicules [10]. For diagnosis of AML, it is required that a marrow or blood blast count of 20% or more should be present, except for AML with t(15;17), t(8;21), inv(16) or t(16;16), and some cases of

erythroleukemia [11]. The blast count includes myeloblasts, monoblasts, and megakaryoblasts. Monoblasts and promonocytes, but not abnormal monocytes, are counted as blast equivalents in AML with monocytic or myelomonocytic differentiation. Erythroblasts are not counted as blasts except in the rare instance of pure erythroid leukemia [11]. To identify the lineage, we either use cytochemical stain or immunophenotyping the cytochemical stains used are myeloperoxidase, Sudan black b (SBB), nonspecific esterases (NSE) and periodic acid Schiff [12]. Detection of MPO indicates myeloid differentiation, not detection does not exclude myeloid lineage, because early myeloblasts and monoblasts may not have MPO. SBB is less specific than MPO. NSE stains show diffuse cytoplasmic activity in monoblasts (usually ≥ 80% positive) and monocytes (usually ≥20% positive). In acute erythroid leukemia, a periodicacid-Schiff (PAS) stain may show large globules of PAS positivity (11).

Immunophenotyping

Immunophenotypic analysis of the reactivity of leukaemic cells with monoclonal antibodies has proved useful and nowadays essential in the diagnosis of acute leukaemias [13]. This was first shown to be relevant in the characterization and classification of acute lymphoblastic leukaemias of various cell types as there is no specific and reliable cytochemical marker to recognize lymphoblasts. Subsequently, immunological markers have also been shown to be important in the diagnosis of acute myeloblastic leukaemias, particularly when the nature of the blasts cannot be defined by morphology and cytochemistry [14]. Examples of these "undifferentiated" acute leukaemias include those with poorly differentiated myeloblasts (AML-M0),>5 or those derived from early erythroid and megakaryocyte precursors. Some AMLs with recurrent genetic abnormalities are associated with characteristic immunophenotypic features. For example, AMLs with t (8;21) frequently express the lymphoid markers cluster of differentiation (CD), CD19 or, to a lesser extent, CD7; they may also express CD56. AMLs with Inv16 frequently express the T lineage–associated marker CD214; and AMLs with NPM1 mutation typically have high CD33 but absent or low CD34 expression [14].

- MO- Immunophenotype •CD13 + •CD33 + •CD11b + •CD11c + •CD14 + •CD15 +.
- M1- Immunophenotype •MPO + •CD13 + •CD33 + •CD117+ ••CD34 +/-.
- M2- Immunophenotype •MPO + •CD34 +/- •CD13 + •CD15 + •HLA-DR +/- •Sudan black + •CD117 +/-
- M3- Immunophenotype •CD13 + •CD33 + •HLA-DR - •CD34 -
- M4- Immunophenotype •CD13 + •CD15 + •CD33 + •CD11b + •CD11c + •CD14 + •CD64 + •CD4 +.
- M5- Immunophenotype •CD14 + •CD68 + •CD4 + •CD11c + •HLA-DR + •CD64
- M6- Immunophenotype •CD13 + •CD33 + •CD15 + •Glycophorin A + •Glycophorin C +.
- M7- Immunophenotype •CD41 + •CD61 + •CD42 + •CD13 + •CD33 + •CD34.

Cytogenetics

Cytogenetics has become a compulsory for diagnoses of patient suspected of having AML, because research has shown that approximately 55% of adults having AML have chromosomal abnormality which either falls on the WHO category: "AML with recurrent genetic abnormalities" and "AML with myelodysplasia-related features" [15]. A minimum of 20 metaphase cells analyzed from bone marrow is considered mandatory to establish the diagnosis of a normal karyotype, and recommended to define an abnormal karyotype and may be diagnosed from blood specimens [16].

The following are some of the cytogenetic abnormalities encountered in AML with their genetic consequences due to chromosomal translocation. Cytogenetic abnormalities regardless of blast count:

- AML with t(8;21) (q22; q22); RUNX1-RUNX1T1
- AML with Inv16 (p13.1q22) or t (16;16)(p13.1;q22); CBFB-MYH11 .
- APL with t (15;17) (q24.1; q21.1); PML-RARA. 8;21 translocation in AML.

This balanced translocation t(8;21) (q22; q22); RUNX1-RUNX1T1 has been reported in adult patients that have been newly diagnosed with AML. It is also a very common disorder among children diagnosed with AML [17]. It results from fusion between RUNX1 or core binding factor alpha 2 gene on chromosome 21 with the RUNX1T1 gene on chromosome 8 to form RUNX1-RUNX1T1 chimeric product that regulate the transcription of number genes that are important in hematopoietic stem and progenitor cells growth, differentiation and function [18]. Kozu T, et al. [19] also demonstrates this type of translocation in AML-M2 and AML-M4. Adults with t (8;21) type of AML has a favorable prognosis while in children the prognoses are poor.

Treatments for Acute Myeloid Leukemia

Induction Therapy

Since 1926, the importance of intensive induction chemotherapy remains unchanged. The intensive anthracycline and cytarabine regimen, "7 + 3", induction therapy is the standard of care for young adults and fit elderly patients (harboring NPM1 mutations and CBF leukemia). With seven days of continuous cytarabine infusion (100mg/m2/daily for one week (days 1 through 7) either daunorubicin

(60 or 90mg/m2 on days 1, 2 and 3) or idarubicin (10-12mg/m2 on days 1, 2 and 3) is given. The target of induction chemotherapy is to achieve morphologically complete remission (CR). CR is defined as:

- <5% blast in bone marrow aspirat4e sample with marrow spicules and with a count of ≥200nucleated cells (no blast with Auer rods or persistence of extramedullary disease.
- Absolute Neutrophills Count (ANC) >1000/ul
- Platelets ≥ 100,000/ul.

Using standard induction therapy AML patients less than 60 years of age achieve CR in 65%-73% while only 38%-62% of patients over 60 years of age with AML achieve CR [20-22]. It has been shown in several trials that higher dose of anthracycline (90 versus 45 mg/m2) in both younger and older fit adults (from 60 to 65 yrs.) results in higher CR rates [21,22]. Daunorubicin is highly toxic taking care with it and its wide use of the 60-mg/m2 dose as a newer "standard," boosts up the United Kingdom (UK) National Cancer Research Council (NCRC) to conduct a prospective randomized trial with the goal to compare daunorubicin at 60 vs. 90 mg/m2 in the induction of 1206 AML patients [23]. In this study there was no benefit of using higher dosing (90 mg/m2) over 60mg/m2 across all subgroups [23]. In this trial, however there are some caveats to consider. More precisely, due to multiple courses of anthracycline, the cumulative dose of anthracyclines in the low dose arm (60 mg/m2) was equivalent in the United Kingdom National Cancer Research Institute (UK NCRC) trial to the higher dose (90 mg/m2) of the other clinical trials. Instead of that UK NCRC trial has a shorter follow up period also [24]. Thus, it is clear that 45 mg/m2 of daunorubicin seems insufficient and 60 mg/m2 is not inferior to 90 mg/m2 with less associated toxicity. Midostaurin (FLT3 Inhibitor), added to standard induction therapy to patients found to have a FLT3 mutation [25]. In the adult population characterizing fitness is important when deciding treatment strategy. In particular, appropriate therapy in the elderly AML patient should be determined depending on the "patient-specific fitness" independent of age [26]. The use of hypomethylating agents including decitabine and azacitidine has shown useful in older adults, deemed not fit for intensive induction therapy especially harboring complex karyotype without NPM1 mutations, [26-28]. Both agents have activity in AML as initial induction therapy and in the relapsed setting. Several phase II and III studies using azacitidine and decitabine have been conducted [27-29]. In a study of 82 patients who received azacitidine as part of a compassionate use program showed CR/incomplete CR in 11 of the 35 untreated patients (31%). The median overall response duration was found to be 13 months with the one-year and two-years overall survival rates of 58% and 24%, respectively [29]. With 10 days of low-dose decitabine at 20 mg/m2 intravenous over 1 h, Blum et al. showed an even higher CR rate of 47% and overall response rate of 64% [28]. This treatment was well tolerated with CR achieved in 52% of subjects presenting with CN-AML and also in 50% of those with complex karyotypes [28]. Decitabine usually require a median of two to four cycles of therapy to have an optimal response in older patients for induction. Even before the diagnosis is confirmed, Patients with suspected acute promyelocytic leukemia (APL) should be treated with all-trans retinoic acid (ATRA). Because early use of ATRA decreases the risk coagulopathy, development of disseminated intravascular coagulation (DIC) and mortality. For patients with low-to-intermediate-risk APL with white blood cell count in control outcomes are excellent with the use of ATRA with arsenic (ATO) [29]. The ATO-ATRA combination showed CR rates in all 77 patients (100%) and in 75 of 79 patients (95%) in the ATRA-idarubicin group in non-inferiority study. In the comparison of ATO-ATRA arm with those in the ATRA–chemotherapy arm the two-year event-free survival and Overall Survival (OS) rates were significantly improved [29]. For rapid control of leukocytosis in high-risk patients (Abnormal WBC count), chemotherapy with idarubicin should be initiated once the diagnosis is confirmed in addition to ATO-ATRA therapy. It is highly recommended that WBC, fibrinogen level, prothrombin time and partial thromboplastin time be monitored at least twice daily with aggressive transfusion support during induction treatment. The recommendation of prophylactic steroids are also there, in particular to prevent differentiation syndrome, when using ATRA/ATO combination for induction therapy in patients with high WBC count [29,30].

Consolidation Strategies

To prevent relapse and eradicate minimal residual leukemia (MRD) in the bone marrow after induction consolidation or post-induction therapy is given to achieve cure. Using real-time PCR or Next Generation Sequencing (NGS) techniques assessment of minimal residual disease is increasingly used to track treatment response and has been shown to be superior than morphology alone in predicting impending relapse [31,32]. Generally, for consolidation, there are two main strategies, chemotherapy (including targeted agents) and hematopoietic stem cell transplantation [20]. Out of those, both strategies could be implied or one out of two could be used but most commonly they are used in combination depending on the type of leukemia, the fitness of the patient and the availability of a stem cell donor. Intermediate-dose cytarabine 1.5 g/m2 twice daily on days 1, 3 and 5 given in three to four cycles is an effective and established regimen used post induction chemotherapy, to prolong remission and improve survival in favorable risk young adults (60 year of age). With high dose cytarabine no positive effect was noted and sometimes irreversible

neurotoxicity noted [33], therefore 500-1000 mg/m2 is standardly used. After achieving CR in particular fit patients with intermediate risk or high risk disease, allogeneic hematopoietic stem cell transplantation remains the most effective long term therapy for AML. Instead of that, several patients never become eligible for transplant. It is standard practice to give post induction chemotherapy to maintain CR and keep the leukemia burden low while waiting for transplant. As consolidation therapy increases risk of morbidity and mortality, which may hinder eventual curative transplant so the decisions regarding consolidation rather than moving straight to transplant should be individualized. Age should no longer be used as the sole criteria for transplant eligibility, recent evidence unanimously confirms that [34], On Pre-transplant performance status, co-morbidities and current remission decides the transplant eligibility. Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) is most widely recognized and validated tool for assessing comorbidity for such transplant [34]. The clinical outcome becomes worse with the increase of score.

Based on patient fitness, conditioning regimen should be decided and transplant options given. Instead of a higher risk of relapse, long term outcomes of reduced-intensity allogeneic hematopoietic stem cell transplant in patients who were ineligible for myeloablative transplant are promising. The results of a prospective multicenter phase II trial conducted by the Alliance for Clinical Trials in Oncology (formerly Cancer and Leukemia Group B) and the Blood and Marrow Transplant Clinical trial Network showed reduced intensity conditioning-based hematopoietic stem cell transplant (HSCT) to be an effective strategy for suitable older patients with an available matched donor with a disease-free survival and OS at two years after transplant of 42% and 48%, respectively [35]. Therefore more common and more clinically accepted are reduced intensity transplant.

Relapsed Disease

Of the patients who relapse, only a small fraction achieve successful second remission using salvage chemotherapy followed by allogeneic stem cell transplant with curative intent [20]. Studies examining clonal evolution of relapse show that relapse can occur from expansion of major or minor clones present at diagnosis or through newly acquired mutations over time [36]. So, especially in light of novel targeted therapies clinical trials are the preferred treatment approach. Early relapse (occurring within the first six months after CR1) portends a poor overall survival. Salvage regimes include intermediate dose cytarabine (500-1500 mg/m2 intravenously every 12h on days 1-3); MEC (Mitoxantrone 8 mg/m2 on days 1–5, Etoposide 100 mg/m^2 on days 1-5, and Cytarabine 100 mg/m^2 on days 1-5) or lastly, FLAG-IDA (Fludarabine 30 mg/m^2 , intravenously on days 1-5 (20 mg/m2 in patient >60 years old), Cytarabine 1500 mg/m2 (500–1000 mg/m^2 in patients >60 year) intravenously, 4 h after fludarabine infusion, on days 1-5; Idarubicin 8 mg/m^2 , intravenously, on days 3-5; Granulocyte colony-stimulating factor 5 μg/kg, subcutaneously, from day 6 to white-cell count >1 g/L (FLAG-IDA) [37]. The likelihood of achieving a second CR is best in patients with a long first remission, younger age and in those with favorable cytogenetics, In cases of APL, re-induction with ATO ±ATRA remains the standard therapy. CR rates with single agent ATO are good nearly 85% [38].

Novel Targets

Fms-Like Tyrosine Kinase 3 (FLT3) Inhibitors: At 2015 American Society of Hematology (ASH) Plenary session presented the 'FLT3-mutated AML', the largest randomized, phase III clinical trial showing the benefit of midostaurin added to induction chemotherapy (RATIFY trial) in which patients receiving midostaurin had significantly longer median OS than those receiving placebo: 74.7 versus 25.6 months (p=0.0076) [39]. Quizartinib and Crenolanib are Second generation agents, promising to have better potency and fewer side effects, still undergoing clinical investigation. Better blast count clearance has been shown in one trial, using quizartinib (AC220), also noted the development of secondary resistance. The major challenge in treating patients with a single FLT3 inhibitor is drug resistance. Within the kinase domain of FLT3-ITD point mutations identified which lead to resistance are found N676, F691, and D835 respectively [40].

Isocitrate Dehydrogenase (IDH) Inhibitors: The IDH1 inhibitor AG-120 and the IDH2 inhibitor AG-221 have demonstrated promising response rates in patients with AML in two separate phase I clinical trials [41,42]. On the analysis more interestingly the duration of the responses for AG-221 and AG-120 were more than 15 and 11 months, and still ongoing. The responses lasted longer than six months are about 76%. Based on these Promising figures, for patients with AML, the Food and Drug Administration (FDA) have granted the medication an orphan drug designation.

Nuclear Exporter Inhibitors: The much excitement has brought by the anti-leukemic efficacy of reversible inhibitors of the major nuclear export receptor, chromosome region maintenance 1 (CRM1, also termed XPO1). The export and inactivation of several tumor suppressors such as p53, p73, FOXO1, RB1 and p21 (CDKN1A) among others is maintained by the CRM1 major nuclear exporter protein [43]. The up-regulation of CRM1 has been shown in a range of solid tumors and hematological malignancies, including AML [44]. With novel CRM1 inhibitors (Selinexor), preclinical studies indicate that treatment of AML cell lines, patient samples and AML xenografts induces strong anti-leukemic effects [45]. Phase I/II clinical trials are currently ongoing to assess the safety, tolerability and activity of selinexor in AML patients

based on these studies.

Immune Therapies: So many new strategies for treating leukemias like novel antibody therapies are currently under development, Monoclonal antibodies which include CD33 (Gemtuzumab ozogamicin) and bi specific antibodies for eg:- AMG 330 (anti-CD33 and CD3) [46]. On the majority of AML blasts CD123 has been found to be expressed but also found on normal hematopoietic cells. Preclinical data shows that targeting CD123 via CARTs (chimeric antigen receptor targets) results in rejection of human AML and myeloablation in the mouse models [47].

Conclusion

Sometimes along with a targeted drug therapy the main treatment for most types of AML is chemotherapy. Which might be followed by a stem cell transplant?. To treat people with acute promyelocytic leukemia (APL) other drugs (besides standard chemotherapy drugs) may be used. Surgery and radiation therapy are not major treatments strategies for AML, but they may be used in special circumstances.

- Chemotherapy for Acute Myeloid Leukemia (AML)
- Targeted Therapy Drugs for Acute Myeloid Leukemia (AML)
- Non-Chemo Drugs for Acute Promyelocytic Leukemia (APL)
- Surgery for Acute Myeloid Leukemia (AML)

- Radiation Therapy for Acute Myeloid Leukemia (AML)
- Stem Cell Transplant for Acute Myeloid Leukemia (AML)

Many novel promising drugs or therapeutic approaches are currently under development for this population but poor long-term outcome is still result for most adult AML patients, although, their inclusion into prospective clinical trials should be strongly recommended and encouraged. In addition, strengthening the clinical trials and standardization of trial procedures and properly decision for choosing the control arms would greatly assist comparison of trial results and strengthen future treatment recommendations.

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