Different treatment for acute myeloid leukemia

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Abstract. Leukemia has become one of the major diseases endangering people's health, which is characterized by a low survival rate and high relapse rate. Although the cure rate of leukemia has been increasing year by year with the continuous improvement of medical technology, nearly half of the patients miss the optimal treatment period due to the failure of early detection and ultimately develop difficult-to-treat acute myeloid leukemia (AML). Due to various uncertainties affecting the treatment of the disease, such as age, degree of morbidity, and external environment, AML cannot be regarded as a homogeneous disease, and different treatment protocols need to be tailored to different individuals, which makes the treatment of AML even more difficult. The need to tailor different treatment regimens for different individuals makes the treatment of AML more difficult, so more detailed and in-depth research on AML is necessary. There are also new advances in the treatment of AML, such as the combination of venetoclax with other drugs and targeted drugs. In this article, the treatment of AML with NPM type 1 mutations and AML not targeting specific mutations will be described in detail.

Keywords: Acute myeloid leukemia; treatment; individuals venetoclax targeted drugs.

1. Introduction

At present, Leukemia is divided into two types: acute leukemia and chronic leukemia. Acute leukemia is further divided into acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML). AML is a common lethal bone marrow stem cell carcinoma and its survival rate is 28.3 % in the US from 2009 to 2015 [1]. Without a doubt, it is a difficult disease to cure.

AML is a heterogeneous disease caused by the uncontrolled proliferation of clonal hematopoietic cells [2] and it includes AML with defining genetic abnormalities (DGA) and AML defined by differentiation [3]. Patients diagnosed with AML always show a blast threshold of ≥ 20 % in the bone marrow or blood or >10 % in the presence of genetic abnormalities [4]. The most commonly used methods for detecting acute AML are multi-parameter flow cytometry and quantitative PCR. However, due to the limitations of these techniques and the high biological heterogeneity of AML in diagnosis and disease evolution, more accurate testing techniques such as NGS and digital PCR have been developed [5].

Acute myeloid leukemia is caused by the rapidly proliferating and transforming of progenitors which leads to a block in terminal differentiation and the ability to self-renew [1]. With the unrestricted proliferation of malignant bone marrow stem cells, patients may experience clinical symptoms such as infection, anemia, and bleeding. Acute leukemia is one of the most common cancers in adults. According to statistics, the median age of patients is 68, and the probability of a total survival time of 5 years after diagnosis is about 30 %. The survival rate is influenced by many factors, such as age. For young patients, 50 % of the population can achieve a 5-year survival time, while for those over 60 years old, only 10 % of them can achieve it [2].

The treatment of AML could be divided into three stages, and initial treatment will induce complete remission, followed by consolidation and maintenance treatment to maximize treatment outcomes. However, depending on the individual patient's situation, 10 %-40 % of patients cannot achieve complete remission through intensified chemotherapy. Although some patients can obtain complete remission, nearly half of these patients experience recurrence, which will be used to evaluate treatment response and examples of treatment failure providing data for future research [4]. The outcome of AML treatment is highly dependent on factors related to the patient's body, the presentation of AML at the time of diagnosis, and the genetics of the disease, so, it is important to

choose a treatment that is appropriate for the patient. The traditional cancer therapy is chemotherapy, such as the 7 + 3 regimen with the combination of an anthracycline and infusional cytarabine [1]. But owing to the side effects like killing some healthy cells, hair loss, and leucocyte thrombocytopenia, etc. We keep updating the treatment. The latest treatment method is immunotherapy, which could distinguish cancer cells from healthy ones. Its main focus is to use the host's immune system to eradicate cancer cells [4], so far, we can permanently alleviate acute myeloid leukemia (AML) through "adoptive immunotherapy". There are also some genes with repeated mutations in AML, such as NPM1, FLT3-ITD, IDH1/2, and TP53 which will provide targets for the treatment of AML in the future [1]. To improve the survival rate and even completely cure it in people of different ages and physical conditions in the future, further research on AML is necessary.

2. Treatment of AML

2.1. The introduction of AML

AML is a heterogeneous disease [6], 80 % of acute leukemia in adults [7]. It is characterized by the malignant proliferation of myeloid hematopoietic stem or progenitor cells [8]. AML is a devastating disease that can quickly lead to death if left untreated [9]. The inherent genetic complexity, variability in disease progression, and response to different treatments make AML treatment a difficult and complex challenge [10]. Even patients who achieve complete remission with initial treatment are at risk of relapse. In recent decades, researchers have been experimenting with different therapeutic approaches to treat AML, which include cytotoxic chemotherapy, immunotherapy, hypomethylating agents, and targeted small molecule therapies [11].

2.2. Treatment of NPMI-type AML

There are many types of mutations in AML, of which nuclear phosphoprotein (NPM1) mutations are the most common, and it is a clinically heterogeneous group characterized by the cytoplasmic localization of NPM1 (NPM1c). Approximately 30 % of AML patients carry NPM1 mutations, so finding a treatment for NPM1 mutations is necessary for the treatment of AML.

NPM1 is a multifunctional protein that is contained in ribosome synthesis, cell growth, and stress responses, among others. NPM1, composed of three structural domains, the N-terminal, the central, and the C-terminal, is mainly found in the nucleus and passes freely between the nucleus and the cytoplasm. Mutations often occur in conjunction with other types of mutations to induce leukemia. NPM1 mutations lead to the generation of a C-terminal nuclear export signal (NES) and deletion of tryptophan residues W 288 and W 290, which gives mutant NPM1 a greater capacity for nuclear export ultimately leading to NPM1 cytoplasmic localization. Although NPM1 mutant AML is a type of AML with high survival and complete remission (CR) rates, there has not been a definitive answer on how to treat this type of AML since it was first discovered. Recently, it has been found that vinatocet combined with azacitidine, vinatocet integrated with intensive chemotherapy (IC), vinatocet united with 5+2 (cytarabine + idarubicin), and vinatocet combined with FLAG + IDA (fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin) have all shown promising results in clinical trials. All of them can greatly improve the CR of the patients. Through the clinical drug screening, venetoclax was identified as a selective drug for NPM1-mutant AML, and then by comparing venetoclax plus hypomethylating agent (HMA), HMA, and intensive chemotherapy (IC) in patients with NPM1-mutant AML, the researchers found that the combination of venetoclax with HMA was better than the other two in reducing the risk rate of death in AML and in boosting the CR rate. In addition to these common combinations, a new combination of venetoclax and arsenic trioxide (ATO) is gradually being discovered. However, the treatment approach of venetoclax is not yet applicable to elderly patients on chemotherapy and young patients on standard induction so after that we need more research to expand the audience of this approach. Other treatments for NPM1-mutant AML include XPO1 inhibitors, ATO plus all-trans retinoic acid (ATRA), actinomycin, and immunotherapy, among others [8].

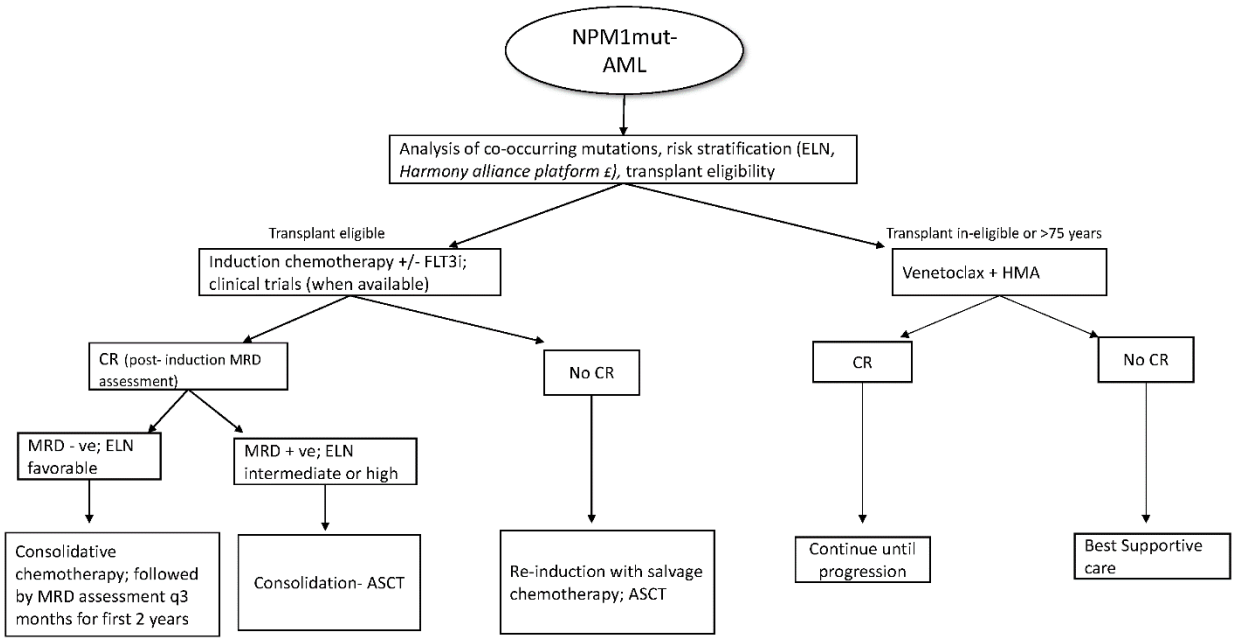

Fig 1. Treatment in NPM1mut-AML; (FLT3i- FLT3 inhibitor; CR- complete response; ASCT- allogenic stem cell transplant; HMA- hypomethylating agents, £- pending clinical validation) [12].

2.3. Treatment that do not target specific AML

In addition to target-specific treatments, some treatments do not target specific mutant AML types.

For AML patients who have achieved a first complete remission with treatment, durable remission can be achieved by combining allogeneic stem cell transplantation (allo-HCT), but this approach is associated with a high relapse rate. Except for Vinetoch, many targeted therapeutic options have been developed to improve the specificity of treatment, [13] One of the best-targeted drugs is the FLT3 inhibitor[13]. The use of FLT3 could be divided into two main classes, the first being first-generation tyrosine kinase inhibitors (TKIs) such as midostaurin, sorafenib, and lestutinib monotherapy, and the second being the first-generation TKI sorafenib combined with intensive chemotherapy [14].

Recently, researchers have further explored the genomes, molecular landscapes, and pathogenesis of AML patients and have made new advances in the development of new drugs with different targets. Currently, the U.S. Food and Drug Administration FDA has also approved these new drugs [6].

Firstly, the BCL-2 inhibitor: venetoclax [6]: venetoclax is an orally active potent small molecule inhibitor that primarily targets B cell lymphoma 2 (BCL-2) BCL-2 is an anti-apoptotic protein that enhances leukemic primitive cell survival by regulating mitochondrial apoptosis[9]. BCL-2 is an anti-apoptotic protein [8] that enhances leukemic primitive cell survival by regulating mitochondrial apoptosis [13].

This is the main gene responsible for the low sensitivity and high relapse rate of AML [14]. The application of venetoclax, as an inhibitor of BCL-2, whose application could promote the apoptotic pathway through the dissociation-mediated pathway thereby increasing the permeability of the outer mitochondrial membrane. However, since the therapeutic effect of venetoclax alone as a therapeutic agent is not satisfactory, in the clinic, it is used in three combinations ways: venetoclax + hypomethylating agent (HMA), or low-dose cytarabine, venetoclax + intensive chemotherapy, and venetoclax + experimental drug or targeted inhibitor [6]. The combination therapy of venetoclax has been clinically proven to be well-tolerated and effective in the treatment of patients with pre-existing or relapsed AML, and the drug has now been approved by the FDA [15].

Table 1. Comparison of randomized prospective studies on venetoclax-based combinations in AML: AZA + venetoclax vs LDCA + venetoclax [6].

Regien	AZA + venetoclax	LDCA + venetoclax
Phase	III VIALE-A trial	III VIALE-C trial
Population	Age > 75 years or unfit for chemotherapy	
Control arm	AZA	LDCA
h/o HMA	No	Yes, allowed (20%)
Patient Number	431 (286 in AZA + venetoclax)	211 (143 in LDCA + venetoclax)
Median age (range), years	76 (49-91)	76 (36-93)
30-day mortality, %	7 %	13 %
cCR (CR) rate, %	66.4 % (36.7 %)	48% (27 %)
MRD negativity, %	N/A	6 %
Time to CR (response)	1.3 months (0.6-9.9)	N/A most response at the end of vycle 2
Median DOR, months	17.5 (13.6 to NR)	NA
Median OS, months	14.7 (11.9-18.7)	8.4 (5.9-10.1)

Table 2. Summary of venetoclax-based combinations in AML [6].

Combination	Phase	Disease status	Patient number	CR/CRi rate, %
FLA-Ida	Retrospective	R/R AML	13	69 %
FLAG-ida	Ib/II	ND AML	27	89 % in ND AML
		R/R AML	35	66 % in R/R AML
CAVEAT (5 + 2)	Ib	ND AML	51	72 % in all 97 % in de novo AML 43 % in secondary AML
DEC 10	II	ND AML	70	86 % in ND AML
		R/R AML	55	42 % in R/R AML
CLIA	II	ND AML	18	88 %
CLAD/LDAC, alternating with AZA	II	ND AML	48	94 %
CPX-351	II	R/R AML	17	37 %
		ND AML	1	
CPX-351 LIT	Ib	ND AML	44 planned	NA
GO	Ib	R/R AML	24 planned	NA

IDH1/2 is another target for the treatment of AML, and similar to the therapeutic regimen of venetoclax, better therapeutic results have also been achieved through the combination of IDH1/2 inhibitors and hypomethylating drugs. Several small molecule inhibitors of IDH1/2 have been developed, such as evonib (AG-120) and enasidenib (AG-221), of which, enasidenib has been approved by the FDA, and it has shown promising results in the treatment of patients with relapsed and refractory AML [15]. Similar to vinblastine-based combination therapy, IDH1/2-based combination therapy has demonstrated robust efficacy and acceptable safety in recent emerging trial results providing a foundation for the treatment of high-risk relapsed/refractory (R/R) AML patients,

followed by open-label, multicenter, dose-escalation phase Ib studies to maximize safety and efficacy of the treatment [6].

In addition to the method mentioned above, immunotherapy can also be used to treat AML and is currently the most widely studied treatment [11]. One type of immunotherapy involves the introduction of antibodies to enhance the body's immune response to cancer cells [6], with CD33 antibodies and PD-1 and PD-L1 antibodies already on the market [8]. CD33 is a bone marrow-expressed transmembrane receptor expressed in the early stages of myeloid cell development [6]. Specific expression of CD33 is found in the primitive cells of almost all AML patients and is mostly associated with adverse features which leads it to a target for certain antibody drug couplers, such as GO [13]. Gituzumab ozogamicin (GO), a CD33-directed immune-coupler, is the only antibody drug currently available for the treatment of myeloid leukemia [6]. It can be used as a drug alone or in combination with other small molecule drugs for the treatment of CD33-positive AML patients. In GO co-administration, on the one hand, kalimycin derivatives are delivered into cells to inhibit DNA synthesis to stop the growth of leukemia cells, and on the other hand, GO binds to CD33 on the surface of the target cells, induces lysosomal internalization, and induces the death of its internalized cells in an acidic environment [9]. Currently, Patients with cytogenetically positive or intermediate-risk AML, as well as elderly individuals who are not suitable candidates for intense chemotherapy or AML that has relapsed or is resistant to treatment, are treated with GO as first-line therapy [6]. Additionally, it has been demonstrated that giving these individuals GO in addition to standard chemotherapy increases their survival [8]. However, in patients with AML who have received allogeneic stem cell transplantation (allo-HCT), GO may result in hemocytopenia and sinusoidal obstruction syndrome (SOS) or hepatic veno-occlusive disease (VOD) [13]. The immunological checkpoint molecules PD-L1 and PD-1, which are implicated in T-cell suppression, are programmed cell death proteins. The primary function of the antibody is to liberate fatigued T cells from inhibition by interfering with the PD-1/PD-L1 connection and enhancing the anti-tumor response, as the PD-1/PD-L1 pathway is primarily involved in tumor metastasis [8].

Lastly, therapy using CAR-T or TCR-T cells: Relay immunotherapy is a novel therapeutic approach for leukemia treatment; however, the lack of genuine AML-specific surface antigens that can cause normal hematopoietic cells to be targeted and killed has made it difficult to treat chimeric antigen receptor (CAR) T cells in myeloid hematological malignancies. Through ongoing research and development, a number of strategies have been developed to date to optimize this therapeutic approach, such as the use of inducible caspase-9 for CAR T cell "suicide switch" control and altering the cells' affinity to target only cells that express a particular antigen at high levels. However, additional experiments are required to ascertain the safety and efficacy of this approach. Other therapeutic approaches are being researched and explored [14].

Other therapeutic approaches regarding AML include microenvironmental targeting such as Uprolon (GMI-1271), cell cycle checkpoint inhibitors such as Aurora kinase inhibitors, Polo-like kinase-1 inhibitors, and other cell cycle inhibitors, bispecific antibodies, CAR-T cell therapy, and so on [13].

3. Summary

This article focuses on treatments for AML with NPM1 type 1 mutations and treatments that do not target specific types of AML. With the continuous development of science and technology, there is more and more information about the causative principles and mechanisms of leukemia, and scientists have updated the guidelines for disease classification, risk stratification, and MRD testing, which will lead to more and more new options for the treatment of AML as well. With the research of many novel drugs and the discovery of more and more causative targets, we are about to enter an era in which we can match the genome and molecular profiles of different AML patients with different therapeutic options. Even though we have made great progress in treatment, it is still far from enough, and combination therapies, especially single or multiple-targeted therapies, play a leading role in the

treatment of AML. We still have a long way to go in the future, and continued recruitment of AML patients into clinical trials and updating of therapeutic regimens will make a complete cure of AML possible.

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