Advances in the drug therapies of acute myeloid leukemia (except acute promyelocytic leukemia)

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Abstract: Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy, characterized by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues. The new drugs used for treating AML are facing a big challenge, and the candidates include cytotoxic drugs, targeted small-molecule inhibitors, and monoclonal antibodies. In recent years, active research has focused on several new agents for including them in the large antileukemic drug family. This review aims to introduce some of these new drugs and highlights new advances made in the old drugs, mainly in the last 5 years.

Keywords: acute myeloid leukemia, new drug therapies, refractory/relapsed AML, 2017 NCCN guideline

Introduction

Acute myeloid leukemia (AML), a heterogeneous hematologic malignancy, is characterized by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues. AML has the highest incidence compared to other acute leukemias (ALs) and also the highest mortality rate among the diseases of the hematologic system. It is estimated that 5,970 people will be newly diagnosed with AML in 2017, and 1,440 patients will die of this disease in the USA.1 Its treatment difficulties are mainly reflected in resistance to drugs, including primary resistance, which exists before the treatment, and secondary resistance, which develops due to the repeated use of some induction chemotherapeutic agents. This directly leads to refractory and/or relapsed AML and reduces the overall survival (OS) of AML patients. There are several approaches to the treatment of AML, which include chemotherapy, targeted therapy, immunotherapy, and hematopoietic stem cell transplantation (HSCT).

For this review, we conducted a literature search of the studies on drug therapies (except HSCT) used for AML, especially those published in the last 5 years.

Chemotherapy

Standard induction regimens from the National Comprehensive Cancer Network (NCCN) guidelines (V3.2017) and their new advances

The NCCN guidelines (V3.2017)2 mainly recommend 5 kinds of induction regimens based on history of prior myelodysplasia or cytotoxic therapy, age, and performance status. First, the standard induction regimen, which is well known as “7+3” induction therapy, used for patients younger than 60 years, has changed a little in the past 25 years. The regimen involves infusion of anthracycline (daunorubicin [Pfizer, USA] 45–60 mg/m² daily or idarubicin [Jian An, China] 12 mg/m² daily) for 3 days, and
cytarabine (Pfizer, USA) for 7 days via continuous infusion (100–200 mg/m² daily), which is still the standard induction therapy for adult patients. In recent years, there is increased focus on the dose of anthracycline. Padron and Fernandez reported a significant increase of complete response (CR) rates (70.6% versus 57.3%, p<0.001) and OS (median 23.7 versus 15.7 months, p=0.003) using daunorubicin 90 mg/m² versus 45 mg/m² in patients younger than 60 years old with favorable- or intermediate-risk cytogenetics. The second standard regimen involves addition of cladribine 5 mg/m² from day 1 to 5 to the “7+3” regimen (cytarabine [Haizheng, China] 200 mg/m², daunorubicin 60 mg/m²). Holowiecki et al conducted a Phase III study, and reported a significant improvement in the CR rate (67.5% versus 56%, p=0.01) and 3-year OS (45%±4% versus 33%±4%). The third regimen recommended by the NCCN guidelines is the “HiDAC regimen” (cytarabine 3 g/m² per 12 hours via 3-hour infusion on days 1, 3, 5, and 7; daunorubicin 60 mg/m² or idarubicin 12 mg/m² on days 1–3), the use of which for induction therapy in younger patients is still controversial. However, its efficacy in patients younger than 46 years old has been proved by Willemze et al. They reported a Gruppo Italiano Malattie Ematologiche dell’Adulto (GIMEMA) and the European Organization for Research and Treatment of Cancer (EORTC) Leukemia Groups randomized trial, concluding that young adults, that is, patients who are younger than 46 years old, can achieve a significant benefit from the regimen (a median 6-year follow-up showed an OS rate of 51.9% versus the standard Decitabine, Cytarabine and G-CSF (DAC) regimen’s 43.3%, p=0.009). However, a new modified HiDAC regimen consisting of cytarabine 2 g/m² for 6 days in combination with daunorubicin 45 mg/m² for 3 days was applied in 59 consecutive patients older than 60 years old who had de novo AML diagnosed between July 1996 and February 2005. The results showed that the modified regimen was well tolerated and 69% of patients achieved CR, and 80% received HiDAC for 3 consolidations. The median OS of patients was 15.3 months, and the relapse-free survival (RFS) was 13.8 months. Survival of patients who achieved CR was 27 months and ranged from 2 to 114 months. New “FLAG-IDA” regimen is the fourth effective induction regimen with a high CR rate introduced by the NCCN guidelines. This consists of infusion of fludarabine 30 mg/m² (Bayer, Germany) on days 2–6; 4 hours after fludarabine, cytarabine 2 g/m² should be infused over 4 hours, idarubicin 8 mg/m² on days 4–6, and granulocyte colony-stimulating factor (G-CSF) daily during days 1–7. Burnett et al indicated that, after receiving 2-course FLAG-IDA (cytarabine 3 or 1.5 g/m²), patients with intermediate risk and favorable risk achieved an 8-year survival of 63% and 95%, respectively. The last regimen is the lower-intensity therapy which is usually used for patients over 60 years old. Specific conditions for the use of these regimens are described below.

New cytotoxic agents

In recent years, several studies have been focusing on a third cytotoxic agent besides cytarabine and anthracycline. Monotherapy using these agents or their combination with other drugs has brought bright prospects in the therapy of AML. According to the research conducted in the last 5 years, these agents have been categorized as follows.

Hypomethylating agents (HMAs)

It has been shown that epigenetic silencing of structurally normal genes by abnormal DNA methylation, which is mediated by DNA-methyltransferase (DNMT) enzymes, leads to the myeloid leukemogenesis, especially in older patients. However, the underlying molecular mechanisms are still unclear. Some articles have reported that a key reason is the reactivation of silenced tumor suppressor genes, while others have indicated that HMAs can induce the expression of tumor antigens, like cancer testis antigens. In older patients, HMAs bring a similar outcome on intensive chemotherapy, but a lower toxicity. Azacitidine (5-azacitidine) (Baxter, Germany) and decitabine (5-aza-2′-deoxycytidine) (Haosen, China) are the 2 main widespread azanucleoside DNMT inhibitors, which are also recommended in the new NCCN guidelines as a lower-intensity therapy for the elderly. Researches indicated that compared with low-dose cytarabine or supportive care, they can effectively prolong the OS of the subgroups. Due to advances in research, a novel second-generation HMA, guadecitabine (BOC Science, USA), has come into our sight. It is a dinucleotide of deoxyguanosine and deoxycytidine and is resistant to degradation by cytidine deaminase. Isa et al assessed the safety and clinical activity of this agent through a multicenter, open-label, Phase I study. The results showed that guadecitabine 60 mg/m² for days 1–5 is the recommended Phase II dose, and further studies are ongoing and preliminary data are awaited.

New nucleoside analogs

Clofarabine (Genzyme, USA), a new second-generation nucleoside analog, has shown significant effect as monotherapy and in combination with multiple drugs in the treatment of AML. A Phase II study used clofarabine monotherapy in newly diagnosed older AML patients (median age 71 years, range 60–88 years), at 30 mg/m² infusion for induction on days 1–5 and 20 mg/m² during reinduction/consolidation, for
totally 6 cycles. As a result, the overall response rate (ORR) was 46% (CR rate 38%), and the median remission duration was 56 weeks.\textsuperscript{19} On the other hand, clofarabine plus low-dose cytarabine (CLDA) is also considered the frontline therapy for elderly patients with high response rate and tolerated toxicity. To test this combination, researchers conducted a propensity score-matched comparison of AML patients aged more than 60 years given CLDA versus idarubicin and cytarabine (IA) for induction therapy. The results showed that CLDA produced significantly fewer grade 3 or worse toxicities (46% for CLDA versus 62% for IA, \textit{p}=0.03) and the median response duration was also longer than that of patients who underwent HSCT (15.9 months for cytarabine versus 7.0 months for IA, \textit{p}=0.033).\textsuperscript{20}

Sapacitabine (Medical Isotopes, USA) is another novel oral cytosine nucleoside analog, which can break the DNA strands causing apoptosis.\textsuperscript{21,22} Kantarjian et al tested the efficacy and toxicity of sapacitabine in a randomized Phase II study. They treated the patients starting with a dose of 200 mg twice a day for 7 days, followed by 300 mg twice a day for 7 days and then 400 mg twice a day for 7 days. The data indicated that the 400 mg dose schedule showed the best efficacy profile.\textsuperscript{23} Regarding clinical effects, Green et al concluded that sapacitabine plus histone deacetylase (HDAC) inhibitors is an effective combination.\textsuperscript{24} However, there is still no sufficient number of trials to prove the efficacy of sapacitabine monotherapy. Further trials on the efficacy of sapacitabine are underway.

**HDAC inhibitors**

Histone acetylation and deacetylation are necessary processes of gene expression regulation. Histone acetylation releases the condensed chromatin and exposes the promoter regions of genes to transcription factors, while deacetylation catalyzed by HDACs causes gene silencing.\textsuperscript{25} In leukemic cells, this balance is disrupted by several mechanisms, and HDAC inhibitors can act as an attractive therapeutic agent to modulate the disease.

Vorinostat (Medchem Express, USA) is a HDAC inhibitor approved in the USA as monotherapy but has limited activity in cutaneous T-cell lymphoma. To assess the safety and efficacy of the combination of vorinostat with the “IA regimen” in the treatment of patients with AML or myelodysplastic syndrome, researchers designed an induction therapy consisting of infusion of vorinostat 500 mg orally 3 times a day for days 1–3, idarubicin 12 mg/m\textsuperscript{2} for days 4–6, and cytarabine 1.5 g/m\textsuperscript{2} for days 4–7. Patients in remission were treated with 5 cycles of consolidation therapy and maintenance therapy with single-agent vorinostat for 12 months. The results showed that 39% were cytogenetically normal, and 15% had FLT3 internal tandem duplication (ITD). At the same time, no excess vorinostat-related toxicity was observed. The event-free survival (EFS) was 47 weeks (range 3–134 weeks), and OS was 82 weeks. ORR was 85%, CR rate was 76%, and CR rate with incomplete platelet recovery was 9%. In diploid patients and patients with FLT3-ITD, ORR was 93% and 100%, respectively. Thus, the combination of vorinostat with “IA regimen” is safe and active in AML.\textsuperscript{26}

Other HDAC inhibitors, including pracinostat (Medchem Express, USA), panobinostat (Medchem Express, USA), and entinostat (Medchem Express, USA), have also shown a great promise in different ways. For example, pracinostat, which is an orally bioavailable HDAC inhibitor, was found to be effective in patients with JAK2 inhibitor (pactrinib [Medchem Express, USA]) in a preclinical study.\textsuperscript{27}

**Proteasome inhibitor**

In recent years, proteasome inhibitors, especially bortezomib (BSP, Italy), have shown promising activity against leukemias.\textsuperscript{28–30} These inhibitors appear to sensitize leukemia cells to cytarabine and anthracyclines.\textsuperscript{31} In AML patients with FLT3-ITD, proteasome inhibitors induce the degradation of leukemic cells through autophagy.\textsuperscript{32}

**Other new cytotoxic agents**

Vosaroxin (Medchem Express, USA) is an anticancer quinolone derivative that inserts into DNA, and like anthracyclines, strongly inhibits DNA topoisomerase II and induces double-stranded DNA breaks. Compared with traditional anthracyclines, it has several advantages. First, vosaroxin is associated with significantly reduced cardiotoxicity because it does not form reactive oxygen species, free radicals, or toxic metabolites. Second, vosaroxin can induce p53-independent apoptosis and is not a substrate of P-glycoprotein.\textsuperscript{33–36} Recently, a Phase III, double-blind, placebo-controlled trial was conducted at 101 international sites. One half of the patients were randomly (by a central interactive voice system with a permuted block procedure stratified by geographical location, age, and disease status) assigned to vosaroxin (90 mg/m\textsuperscript{2} infusion on days 1 and 4 in the first cycle, and 70 mg/m\textsuperscript{2} in subsequent cycles) plus cytarabine (1 g/m\textsuperscript{2} infusion for days 1–5), and other half to placebo plus cytarabine. In the final analysis, median OS was 7.5 months in the vosaroxin plus cytarabine group and 6.1 months in the other group (hazard ratio 0.87, 95% CI 0.73–1.02; unstratified log-rank \textit{p}=0.061; stratified log-rank \textit{p}=0.024). A higher CR rate was indicated in the vosaroxin plus cytarabine group (30% versus 16%, \textit{p}<0.0001).\textsuperscript{37}

In addition, CPX-351 (Jazz, Ireland) is also a nanoscale liposome which has a fixed molar ratio (5:1) of cytarabine

and daunorubicin. This liposome was proved to have an optimal combination, maximizing synergy, and avoiding antagonism. Clinical trials have shown that it has obvious advantage in older patients with secondary AML (sAML, that is, therapy-related AML or AML with a history of antecedent hematologic disorder). A randomized, multicenter, open-label, Phase III study compared first-line CPX-351 (100 U/m²) with daunorubicin (60 mg/m²) plus cytarabine (100 mg/m²) in 309 older patients (60–75 years old) with high-risk sAML. The results indicated that CPX-351 group achieved better OS (median 9.56 versus 5.95 months, \( p<0.005 \)), EFS (\( p=0.021 \)), and composite CR rates (47.7% versus 33.3%, \( p=0.016 \)).

New regimens for the refractory/relapsed AML

HAA regimen

Fan et al tested the efficacy and safety of the HAA regimen (homoharringtonine [Harbin Sanjing, China], cytarabine, and aclacubicin [Biovision, USA]) as salvage chemotherapy in the treatment of refractory/relapsed AML (rrAML). They retrospectively analyzed 64 patients with rrAML who received the HAA regimen as salvage chemotherapy. The overall CR rate was 70.1%, and 67.1% of the patients attained CR after the first induction course. The early death rate was 0%. The median follow-up time was 61 months (range 6–120 months). The estimated 3-year OS rate was 46.8%, and the estimated 3-year RFS rate was 42.8%. The CR rates of patients with favorable-/intermediate-risk and unfavorable-risk cytogenetics were 76.4% and 33.3%, respectively. The 3-year OS rate of favorable-/intermediate-risk and unfavorable-risk group was 53.7% and 10.0%, respectively. The median survival time of unfavorable-risk group was only 8 months. The side effects associated with the HAA regimen were tolerable, among which the most common toxicities were myelosuppression and infection.

FLAG regimen

Alwan et al evaluated the “FLAG regimen” (fludarabine, high-dose cytarabine, and G-CSF) in refractory/relapsed AL (rrAL) patients. A prospective study was conducted at the National Center of Hematology and hematology unit of Baghdad Teaching Hospital from July 2008 to July 2010. Twenty rrAL patients (5 with refractory acute lymphoblastic leukemia [ALL], 4 with relapsed ALL, 8 with refractory AML, and 3 with relapsed AML) received the regimen consisting of fludarabine 30 mg/m² and cytosine arabinoside 2 g/m² for 5 days, and G-CSF 300 mg/d from day 0 till neutrophil recovery (absolute neutrophil count >1.0×10⁹/L). A bone marrow examination was conducted on day 30 post chemotherapy to evaluate the response. The results showed that 45% of patients achieved CR, while 15% died due to post-chemotherapy complications. Major complications encountered were anemia, fever, bleeding, mucositis, and bacterial infections.

FLANG regimen

Mehrzad et al evaluated the mortality and response rate of “FLANG regimen”. They enrolled 25 rrAL patients aged from 15 to 55 years during 2008–2009. Following 1 cycle, they evaluated the responsiveness to treatment using the bone marrow samples from patients, and followed the patients for a year. The results showed that out of the 25 patients, 40% responded to treatment. Among the 10 responders, 5 achieved successful bone marrow transplantation (BMT). On the other hand, 13 (52%) patients who had not achieved CR died during the follow-up.

FCE regimen

Aldoss et al retrospectively analyzed the outcome of 20 consecutive subjects with rrAML (9 refractory and 11 relapsed) treated with “FCE regimen”, consisting of fludarabine, cytarabine, and etoposide (Hengrui, China). Of 20 patients, 75% achieved CR/CRi. The rate of 4- and 8-week treatment-related mortality (TRM) in all patients during reinduction was 0% and 5%, respectively. Fifty-three percent of rrAML patients who successfully achieved CR were able to undergo allo-HSCT with a 0% non-relapse mortality rate. This new regimen also brings a new hope for the salvage treatment of rrAML.

Decitabine combined with DAG regimen

Hao et al also compared the clinical safety and efficacy of different chemotherapeutic regimens in the treatment of rrAML. Sixty-seven rrAML patients were enrolled from September 2008, to April 2013, and the regimen consisted of decitabine combined with DAG regimen, CAG regimen, or “3+7” regimen randomly. The results showed that of 19 members in decitabine group, 5 (26.3%) achieved CR and 4 (21.1%) achieved partial remission (PR) with an ORR of 47.4%. Of 26 patients in CAG regimen group, 8 (30.8%) achieved CR and 1 (3.8%) achieved PR, with an ORR of 34.6%. Among 22 patients in “3+7” regimen group, 4 (18.2%) achieved CR with an ORR of 18.2%. Obviously, the ORR of decitabine group was higher than the other 2 groups (\( p<0.05 \)). It was noticeable that marrow blast counts were lower in CR patients compared with those in non-CR patients (\( p<0.05 \)) in the decitabine group, while this difference was
not observed in “3+7” group and CAG regimen group. Adverse events were similar in the 3 groups, which mainly included myelosuppression, pulmonary infection, nausea, vomiting, and liver dysfunction, and all of them could be well tolerated. The median OS of decitabine group, CAG regimen group, and “3+7” group after relapse was 7.5, 4, and 3 months, while significant difference was observed between decitabine group and “3+7” regimen group (p<0.05). 44

**Targeted therapy**

During the last decade, genomic studies of hematologic malignancies have identified a spectrum of recurrent somatic alterations that contribute to AML initiation and maintenance, and which confer sensitivities to molecularly targeted therapies. 45,46 Some of these new targeted inhibitor drugs have increased the efficacy of the treatment of AML.

**FLT3 inhibitors**

FLT3 is the most frequently (approximately 25%–30%) mutated gene in AML, and leads to poor prognosis because it can mediate resistance to AML cell death through 3 main signaling pathways, including Ras/MAPK, JAK/p-Stat5, and PI3K-Akt. 47-49 The most common activating FLT3 mutation is an ITD in the juxtamembrane domain (FLT3-ITD). 49,50

FLT3 inhibitors can be regarded as the largest family in the targeted agents. These are divided into 2 major categories. First-generation drugs include agents like sorafenib (Bayer, Germany), lestaurtinib (ApexBio, USA), midostaurin (AbMole, USA), sunitinib (ApexBio, USA), and tandutinib (Medchem Express, USA). Sorafenib, which is used widely, has been shown to play an important role in treating rAML with FLT3 mutations. Giri et al conducted a study on older patients with relapsed FLT3-positive AML using the combination of sorafenib with cytarabine and idarubicin, and found that their disease was controlled for up to 7 months. 51 Gu et al also analyzed the efficacy of sorafenib in FLT3-mutated AML patients. 52 Thirty-two cases who were refractory to chemotherapy or relapsed were treated with sorafenib alone or sorafenib in combination with chemotherapy. Ten patients who relapsed after allo-HSCT were retreated with sorafenib alone or sorafenib in combination with donor lymphocyte infusion or chemotherapy. The OS rate was 73.8%; 4 (9.5%) achieved complete molecular remission (CMR), 9 (21.4%) achieved CR, 8 (19%) achieved CR with CRi, 10 (23.8%) achieved PR, and 11 (26.2%) achieved no remission (NR). The response rate of sorafenib alone for 17 patients was 70.6%, and that of sorafenib plus chemotherapy was 66.7% (p=0.555). Among the 13 patients who received allo-HSCT, 6 achieved CMR/CR/CRi, 4 achieved PR, and 3 achieved NR before transplant. Walker et al conducted a Phase I study of the midostaurin with bortezomib alone and in combination with chemotherapy in patients with AML. 53 Patients on dose level (DL) 1 and DL2 received midostaurin 50 mg twice a day orally and escalating doses of bortezomib (from 1 to 1.3 mg/m²), while patients on DL3 or higher received midostaurin combination with bortezomib following chemotherapy with mitoxantrone, etoposide, and cytarabine. The results indicated that none of patients on DL1 and DL2 achieved dose-limiting toxicities (DLTs) or clinical responses. However, among patients enrolled in the DL3 or higher group, DLTs were reflected in peripheral neuropathy, and cardiovascular and digestive system disorders. Overall, a CR rate of 56.5% and an OS rate of 82.5% were observed in the clinical trial. Sunitinib was also added to chemotherapy in older patients with FLT3-mutated AML, and data showed the CR rate was 53% and 71% in patients with FLT3-ITD and FLT3-TKD mutations, respectively. During the follow-up period, 13 patients who achieved CR underwent a consolidated therapy with high-dose cytarabine, and 7 of them received sunitinib maintenance therapy. The median OS in this study was 18.8 months. 54

The second-generation agents, promising to have better potency and cause less side effects, include crenolanib, quizartinib (Selleck, USA), and cabozantinib (Medchem Express, USA). Cooper et al concluded quizartinib (AbMole, USA) (60 mg/m² daily) plus intensive chemotherapy achieved a near-complete inhibition of FLT3 phosphorylation in all patients. 55 However, the major challenge in the use of FLT3 inhibitors is the drug resistance. The point mutations that lead to resistance include N676, F691, and D835, together with FLT3-ITD. 56 The new FLT3 inhibitors, G-749 and ASP2215, have been proved to cause strong inhibition of FLT3 phosphorylation and increase the ability to overcome drug resistance in preclinical trials, but further studies are needed to evaluate their clinical efficacy. 57,58

**Isocitrate dehydrogenase (IDH) inhibitors**

IDH1 and IDH2 mutations occur in up to 20% of AML patients with normal karyotype. The key pharmacological activity of IDH1 and IDH2 is that they can convert isocitrate to α-ketoglutarate (α-KG) as metabolic enzymes. Thus, IDH1 and IDH2 mutations are novel gain-of-function mutations, which carry a neomorphic enzyme to catalyze the conversion of α-KG to the oncometabolite 2-hydroxyglutarate. This process results in the competitive inhibition of α-KG-dependent enzymes, including TET2, impaired hematopoietic differentiation, and hypermethylation of target genes. 59

The IDH1 inhibitor, AG-120 (Selleck, USA), and the IDH2...
inhibitor, AG-221 (Selleck, USA), have been demonstrated to be significantly effective in the treatment of AML in 2 separate clinical trials. In a study of AG-120, it was reported that effective response was found in 16 of 52 (31%) patients, and the CR rate was 16%.60 Similarly, in a Phase I study, 158 patients with IDH2-mutated AML were treated once or twice a day with AG-221 at a dose ranging from 30 to 200 mg. The ORR was 40%, including a CR rate of 16.5%.61 Based on these data and because the drugs are well tolerated, the FDA has approved these medications with an orphan drug designation for treatment of the patients with AML.

Nuclear exporter inhibitors
CRM1/XPO1 (Imgenex, USA) is a key nuclear export protein which shows inhibitory effects on the nuclear accumulation of tumor suppressor proteins and renders cancer cells susceptible to apoptosis. Selinexor is orally bioavailable and belongs to a novel class of small-molecule compounds with activity against a wide variety of cancers.62 Selinexor (Amquara, USA) is currently studied in a Phase I clinical study on hematologic malignancies (ClinicalTrials.gov NCT0167892). In addition, many Phase I/II clinical trials are currently ongoing to assess the safety, tolerability, and activity of selinexor in AML patients.63

Immunotherapy
Novel antibody therapies are new revolutionaries in AML treatment. Some advances in these therapies in the past 5 years are described below.

Gemtuzumab ozogamicin (GO)
GO is a monoclonal antibody (Pfizer, USA) against CD33 cell adhesion molecule, which is differentially expressed during myeloid differentiation. Borthakur et al conducted a study on a new regimen (FLAG-GO) including fludarabine (30 mg/m²), cytarabine (2 g/m²), G-CSF, and low-dose GO (3 mg/m² infusion over 2 hours on day 1) as a preference therapy core binding factor (CBF) AML, in which 45 patients (median age 48 years) were enrolled. The remission rate was 95%, with 5% of induction deaths. The OS and RFS probabilities at 3 years were 78% and 85%, respectively. “FLAG-GO regimen” worked well in CBF-AML patients.64 However, the agent was approved by the FDA in 2000 for the treatment of elderly patients with relapsed CD33-positive AML at a dose of 9 mg/m² for 2 days 2 weeks apart. Almost at once, its safety became a focus, and it was found that the agent triggers a particular liver signal and it was finally withdrawn from practice in 2010. The significant outcome of this agent in the treatment of AML has been recognized by most of the hematologists. In this review, we focus on its safe dose and the balance between its efficacy and side effects. Parigger et al reviewed 14 studies of GO used in AML treatment, and then drew scatter plots and linear regressions to evaluate the relationship between the dose of GO and its toxicity and efficacy. Results showed that a nonsignificant increase in bilirubin level and the incidence of veno-occlusive disease was seen with higher doses of single-agent GO. On the other hand, even a low dose of 3 mg/m² can have an antileukemic effect, but available data do not allow conclusions on its dose dependency. Unfortunately, results of an analysis indicated that higher doses of GO account for more adverse events.65

Other monoclonal antibodies
SGN-33A is a humanized anti-CD33 monoclonal antibody conjugated to a potent DNA-cross-linking toxin, which is a substrate of drug-efflux enzymes. This novel agent carries a pyrrolobenzodiazepine (PBD) dimer. Molecules in the PBD family cause cell death by cross-linking with DNA and interrupting cell division and are being explored clinically for the treatment of human cancers.66–68 Studies69 have showed that the cytotoxic effects of SGN-33A involve DNA damage with ensuing cell cycle arrest and apoptotic cell death. A previous study demonstrated that SGN-33A had more potent antileukemic activity than GO in primary diagnosed patient samples, cell lines, and xenograft model.69 Besides, SGN-33A is currently under investigation as a single agent and in combination with other drugs in several clinical settings (NCT02326584). In a Phase I dose escalation trial, 38 patients with relapsed AML were treated with SGN-33A (range 5–60 μm/kg infusion every 3 weeks), of which 16 (42%) had clearance of marrow blasts and showed good tolerance.70 Clinical trials on other monoclonal antibodies such as AMG 330 (anti-CD33 and CD3), CD45, CD66, and CD123 are underway.71

Chimeric antigen receptor (CAR) T-cell therapy
Among the immunotherapies, CAR T-cell therapy has shown a great promise for the treatment of hematologic malignancies, especially B-cell malignancies, in recent years. CAR T-cells are redirected T-cells that can recognize cancer antigens in a major histocompatibility complex-independent manner. It comprises 2 main functional domains: an extracellular antigen recognition domain, called a single-chain variable fragment, and an intracellular signaling domain.72 However, its efficacy in AML is still not confirmed. Jetani et al proved the efficacy of CAR T-cell therapy in FLT3-mutated AML
patients this year. They engineered CD8+ and CD4+ T-cells expressing an FLT3-specific CAR and demonstrated that the T-cells conferred potent reactivity against AML cell lines and primary AML blasts that expressed either wild-type FLT3 or FLT3-ITD. Also, their data provided the first proof of concept that CAR T-cell immunotherapy and small-molecule inhibition can be used synergistically, as exemplified by superior antileukemic efficacy of FLT3-CAR T-cells in combination with crenolanib.71

Conclusion
AML is a complex disease with high mortality. The drug treatment methods for AML include chemotherapy, targeted therapy, and immunotherapy. Among the different chemotherapies, the standard “7+3” regimen is the primary choice, but researchers have made significant improvements in this regimen based on patients’ conditions. Meanwhile, new drugs are rapidly expanding with increased understanding of the biology and molecular landscape, such as emerging cytokotoxic chemotherapies, targeted small-molecule inhibitors, and monoclonal antibodies. HMAs can be used in older patients due to their low toxicity. New nucleoside analogs, such as clofarabine and sapacitabine, have also been studied. Clofarabine, as monotherapy or in combination with cytarabine, has achieved satisfying outcome in clinical trials, while sapacitabine needs further research for use in clinical treatment. Vorinostat, a new HDAC agent, when combined with “IA regimen,” is safe and active in AML treatment. Vosaroxin, a kind of anticancer quinolone derivative, has showed its superiority to traditional anthracyclines, with respect to cardiotoxicity and induction of p53-independent apoptosis. Other new cytotoxic agents, such as bortezomib and CPX-351, also play a role in AML therapy. With the emergence of resistance to different drugs, researchers have started to search for new regimens for rAML, including HAA, FLAG, FLANG, FEC, and decitabine and DAG, all of which are effective to some extent. There are also improvements made in therapies for patients with different mutations, such as FLT3 and IDH. In FLT3-mutated group, first-generation agents such as sorafenib, lestaurtinib, midostaurin, sunitinib, and tandutinib are used, while in the IDH-mutated group, AG-120 and AG-211 are used. Among immunotherapies, GO, especially the FLAG-GO regimen, plays an important role. Although CAR T-cell therapy is mainly used in B-cell tumor, it also holds promise for FLT3-mutated AML, and FLT3-CAR T-cells in combination with crenolanib have shown superior antileukemic efficacy.

However, a large number of clinical trials are needed to improve the use of these drugs in AML patients with less toxicity and improved efficacy, and more studies should be devoted to better understand the action of these new drugs which will lead to their safe and regular use.

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