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Emerging agents and regimens for treatment of relapsed and refractory acute myeloid leukemia

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Abstract

Relapsed and refractory acute myeloid leukemia (R/R AML) has complicated pathogenesis. Its treatment is complicated, and the prognosis is poor. So far, there is no consensus on what is the optimal treatment strategy. With the deepening of research, new chemotherapy regimens, new small molecule inhibitors, and immunotherapy have been increasingly applied to clinical trials, providing more possibilities for the treatment of R/R AML. The most effective treatment for patients who achieve complete remission after recurrence is still sequential conditioning therapy followed by allogeneic hematopoietic cell transplantation. Finding the best combination of treatments is still an important goal for the future.

Introduction

Acute myeloid leukemia (AML) is a malignant, uncontrolled proliferation of immature myeloid lineage cells that usually reside in the bone marrow [1, 2]. Although 60–80% of adult patients with AML can achieve complete remission (CR) with the first induction chemotherapy, approximately 20% will show primary refractory disease, and more than 50% will relapse [3, 4]. Refractory AML is diagnosed if the patient meets one of the following criteria: (1) failure to achieve CR after two courses of standard induction chemotherapy; (2) recurrence within six months of the first CR; (3) recurrence after six months, but could not reattain CR with the original regimen; (4) two or more recurrences; and

(5) persistence of extramedullary leukemia. Relapsed AML is diagnosed when the blasts were reappeared in the peripheral blood or bone marrow blasts more than 5% or development of extramedullary leukemia after CR.

Some studies had used next generation sequencing to compare the leukemia cell sample at the time of relapse, with the samples taken at the time of initial diagnosis. Several possible causes of recurrence were inferred from these studies (Fig. 1). New genetic mutations could have occurred on the basis of the pre-existing mutation. On the other hand, small subclones might evolve after the predominant clone succumbed to therapy. Furthermore, relapse could result from incomplete treatment. Lastly, previously normal hematopoietic stem cells could gain mutations and become malignant [5].

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Fig. 1 The possible pathogenesis of relapsed and refractory acute myeloid leukemia. **a** New genetic mutations could have occurred on the basis of the pre-existing mutation; **b** small subclones might evolve

after the predominant clone succumbed to therapy; **c** relapse could result from incomplete treatment; **d** previously normal hematopoietic stem cells could gain mutations and become malignant

Information on relapsed/refractory AML (R/R AML) treatment, outcomes, and prognostic factors generates from phase 1 to phase 3 clinical trials (the latter being very scarce), or from collaborative group registrations and protocols. So far, no standard treatment has been established [4, 6–16]. It is widely believed that participation in clinical trials involving new therapies, such as small molecule targeted therapy, immunotherapy, and epigenetic therapy, may be the best option. Unfortunately, the experimental treatments have unclear efficacy and toxicity, not to mention that most R/R AML patients may not meet inclusion criteria for clinical trials [17]. In this review, we discussed new advances in various therapies, with a focus on recently completed clinical trials (Table 1).

Chemotherapy

For patients with R/R AML, reinduction with dose-intensified chemotherapy to achieve deep remission, followed by consolidative allogeneic stem cell transplants (allo-HSCT), may improve long-term survival from <10 to 20–50% [18, 19]. Ideal reinduction chemotherapy needs to have good tolerability to ensure a reasonable performance state for allo-HSCT. Many salvage treatments are based on a combination of fludarabine, cytarabine (Ara-C), and granulocyte stimulating factor, abbreviated FLAG, which has a response rate of 50–60% [20–22]. FLAG combined with idarubicin (FLAG-Ida) is also a widely used regimen. Jonas Westhus et al. analyzed 132 patients with primary

refractory or first relapsed AML who underwent FLAG-Ida protocol. The protocol consisted of fludarabine (30 mg/m²/day, days 1–5) and Ara-C (2 g/m²/day, days 1–5), idarubicin (12 mg/m²/day, days 1–3), G-CSF (days 0–5). The overall CR rate (CR + CRi) was 56%. Median overall survival (OS) was 15 months. The median disease-free survival (DFS) for CR/CRi patients was not reached. The mortality rate on day 30 was 9%, which rose to 16% on day 60. The results showed that the FLAG-Ida protocol was highly effective, and was a reasonable choice for R/R AML patients [23]. In addition to FLAG, CLAG (Cladribine in place of fludarabine) has been recommended by the 2016 National Comprehensive Cancer Network guideline as a first-line treatment for R/R AML [24]. This was based on a prospective cohort study utilizing CLAG in 67 R/R AML patients [25]. CLAG composed of cladribine (5 mg/m²/day, days 1–5), Ara-C (2 g/m²/day, days 1–5), and filgrastim (300 µg/day, days 0–5). Median follow up was 10 months. Of the 57 patients who were evaluable for response, CR rate was 57.9%, and the overall remission rate (ORR) was 77.2%. Median OS was 10 months, with a 1-year OS of 40.3 ± 6.0% and 3-year OS of 16.7 ± 5.7%. In general, CLAG had good efficacy and tolerability profile in R/R AML [25]. To compare CLAG and FLAG, Bao et al. conducted a head-to-head comparison of the two regimens in R/R AML. Fifty-five patients received CLAG, while 48 received FLAG. CR rate and ORR in the CLAG group were 61.7% and 78.7%, respectively. In the FLAG group, they were 48.7% and 69.2%, respectively. Although no

Table 1 Major clinical trials in relapsed and refractory acute myeloid leukemia

Study	N	Age (years)	Major eligibility criteria	Drug (s)	Outcomes
Westhus et al. [23]	132	52 (18–72)	R/R AML	FLAG-Ida	OR: 65.1%; CR: 45%; CRi: 10.1%; CR/CRi: 0.8%
Wang et al. [25]	67	50	R/R AML	CLAG	The median OS: 10.0 months; ORR: 77.2%
Bao et al. [26]	55 (CLAG); 48 (FLAG)	51 (CLAG); 48.8 (FLAG)	R/R AML	CLAG; FLAG	CR: 61.7% (CLAG), 48.7% (FLAG); ORR: 78.7% (CLAG), 69.2% (FLAG)
Aslostovar et al. [28]	13	66 (58–75), 71.6 (67–79), 71 (58–75)	R/R AML	Thiotidazine	Dominant dose: 50 mg/6 h
Stecke et al. [35]	292	56 (17–74)	R/R AML	Melphalan + irradiation + treosulfan	1-, 2-, and 3-year OR: 34%, 29%, and 41%
Wang et al. [36]	36	26.58 (18–59)	R/R AML	CLAG	OS: 69.4 ± 7.7%
Fraccaroli et al. [43]	33	58 (32–71)	R/R AML/MDS	HID-HCT	CR: 97%; 1- and 2-year OS: 56% and 48%;
Usuki et al. [58]	24	NA	R/R AML	Gilteritinib	ORR: 80%
Cortes et al. [63]	76	55 (19–77)	R/R FLT3-ITD ⁺ AML	Quizartinib	Median OS: 20.9/27.3 weeks; ORR: 61%/71%
Stein et al. [80]	239	70 (19–100)	R/R AML	Enasidenib	CR/CRi: 26.6%; ORR: 38.5%; OS: 9.3 months
Aldoss et al. [86]	33	62 (19–81)	R/R AML	Venetoclax + HMA	ORR: 64%; CR: 30%; CRi: 21%
Benton et al. [89]	42	63.5 (20–78), 63.0 (22–80)	R/R AML/MDS	Lurbinectedin	PB/BM reduced: 79%
Mims et al. [93]	17	46 (21–59)	R/R AML	Decitabine	ORR: 35%; CR: 35%
Stahl et al. [99]	655	65 (16–92)	R/R AML	Azacitidine/ Decitabine	CR: 11%; CRi: 5.3%; OS: 6.7 months
Medeiros et al. [102]	50	64 (29–82)	R/R AML	GO + HMA	CR/CRp: 24%
Assi et al. [122]	40	63 (25–75)	R/R AML/MDS	Indisulam	The median OS: 5.2 months; CR: 26%
Pardee et al. [125]	62	60 (21–79)	R/R AML	CPI-613	ORR: 50%; Median survival: 6.7 months; CR/CRi: 46%
Ottmann et al. [127]	88	70 (26–84)	R/R AML	Volasertib	CR/CRi: 18.8% treated with combination therapy and 89% treated with monotherapy
Martínez-Cuadrón et al. [131]	41	52 (18–64)	R/R AML	Plerixafor	CR / CRi: 49%; Median OS: 9.9/13 months

R/R AML relapsed and refractory acute myeloid leukemia, FLAG fludarabine, a combination of cytarabine and granulocyte stimulating factor, *Ida* idarubicin, CLAG claramine and Ara-C, *GO* gemtuzumab ozogamicin, *HMA* hypomethylating agent, *FLT3* Fms-like tyrosine kinase 3, *ITD* internal tandem duplication, *HID-HCT* haploidentical hematopoietic stem cell transplantation, *MDS* myelodysplastic syndrome, *CR* complete remission, *CRi* complete remission with incomplete blood count recovery, *ORR* overall response rate, *OS* overall survival, *CRp* complete remission with incomplete platelet recovery, *NA* not available

difference in OS was observed between the two groups, subgroups analysis was performed to further evaluate difference of outcomes between two therapies. CLAG therapy seemed to achieve better CR rates in patients with second or higher salvage therapy as well as prolonged OS in patients with relapsed disease, poor risk stratification compared to FLAG [26].

Thioridazine (TDZ), a dopamine receptor D2 (DRD2) antagonist, was identified as a potent antileukemia agent in large-scale chemical screening investigating chemicals that could alter the behavior of cancer stem cells. In vitro combination of TDZ with cytarabine resulted in more pronounced inhibition of leukemic clonal formation compared to TDZ alone, highlighting the potential synergistic effect between TDZ and cytarabine [27]. Aslostovar et al. completed a phase 1 dose-escalation trial (NCT02096289) to evaluate the safety of TDZ in combination with cytarabine. Thirteen patients 55 years and older with R/R AML were recruited. Oral TDZ was administered at three dose levels: 25 mg ($n = 6$), 50 mg ($n = 4$), or 100 mg ($n = 3$) every 6 h for 21 days. Intermediate-dose cytarabine was administered on days 6–10. At a dose of 50 mg TDZ, the sum of circulating DRD2 antagonist levels was close to 10 mM, which was selectively active against human AML in vitro. During the 5-day run-in period of TDZ monotherapy, the extent of blast reduction was related to the expression of the putative TDZ target DRD2 in leukemic cells [28].

The network meta-analysis (NMA) is an effective statistical framework for comprehensive comparisons of existing trials and provides valuable clinical references [29, 30]. While some studies are testing new drugs or drug combinations, others have utilized the NMA to analyze existing chemotherapy-related randomized controlled trial data to find out the more effective treatment options for R/R AML. The NMA analyses had pointed out that clofarabine plus Ara-C (CR: 79.05%, ORR: 80.02%) and Ara-C plus vosaroxin (CR: 75.42%, ORR: 73.43%) could be the top two choices to achieve high CR and ORR. CPX-351 (1-year OS: 91.36%), high-dose Ara-C plus MK-8776 (3-year OS: 94.23%), and clofarabine plus Ara-C (1-year EFS: 97.34%) yielded best results in survival analyses [31].

Allogeneic hematopoietic stem cell transplantation

In R/R AML, allo-HSCT remains the only treatment that has curative potential [32–34]. It is debatable what is the optimal conditioning regimen. In a retrospective observational study, high-dose melphalan, followed by a total body irradiation (4×2 Gy)-based or a treosulfan-based dose-adapted conditioning therapy for allo-HSCT was administered to 292 adult patients with primary refractory (144 patients), secondary refractory (97 patients), or relapsed AML (51 patients). The 3-year OS rates were 34%, 29%,

and 41%, respectively. This study illustrated that sequential conditioning chemotherapy based on high-dose melphalan was feasible and capable of achieving long-term remission in R/R AML patients [35]. Wang et al. explored the efficacy and safety of another intensive conditioning regimen. The program consists of CLAG plus modified busulfan (Bu) and cytoxan (Cy) (BuCy). The 1-year leukemia-free survival (LFS) rate and OS rate were $52.9 \pm 8.8\%$ and $69.4 \pm 7.7\%$, respectively. This demonstrated that intensive conditioning regimen of CLAG plus modified BuCy for allo-HSCT may be effective and in R/R AML patients [36].

In the recent decade, the success rate of haploidentical hematopoietic stem cell transplantation (HID-HCT) had been greatly improved, thanks to the development of strong antimicrobials, the reduction of transplant-associated organ damage, leading to less leukemia recurrence [37–39]. One study analyzed the results of 45 adult patients with R/R AML who underwent HID-HCT, and compared it with the result of 53 patients who received HLA-matched related or unrelated donor transplantation (MD-HCT) during the same time period. The 3-year OS, LFS, cumulative incidence of relapse, and nonrelapse mortality rates in the HID-HCT group were similar to the MD-HCT group. Thus, in patients without matched donors, HID-HCT remained a valid alternative treatment strategy to improve long-term survival [40].

More than a decade ago, the Munich team pioneered these sequential therapy to treat patients affected by high-risk AML/myelodysplastic syndrome (MDS) and refractory AML [41, 42]. This salvage approach emphasized on intensified induction therapy and HSCT conditioning, which theoretically improved disease control and promoted graft-versus-leukemia effect—the latter being further enhanced by an additional donor lymphocyte infusion [43]. The original sequential therapy was based on HLA-matched related or unrelated donor HSCT; however a recent study focused on the role of sequential therapy in HID-HCT in high-risk R/R AML/MDS. It analyzed the course of 33 adults with active disease at time of transplantation. Sequential therapy consisted of cytoreductive chemotherapy (FLAMSA $n = 21$; clofarabine $n = 12$) applied shortly prior to reduced intensity conditioning for T-cell-replete haplo-HSCT, and posttransplantation cyclophosphamide for graft-versus-host-disease (GvHD) prophylaxis. No graft rejection was observed. Ninety-seven percent of patients achieved CR on day +30. Relapse rate at 1 and 3 years was 28 and 35%. At a median follow up of 36 months, the estimated 1- and 3-year OS was 56 and 48%. DFS was 49% and 40%, respectively. At 3 years, LFS without chronic GvHD was 24%, while with chronic GvHD was 29%. The results indicated that sequential HID-HCT was also an effective treatment that provided high antileukemia activity, good tolerance, and acceptable toxicity for patients with advanced AML/MDS [43].

Small-molecule targeted therapy

Several genetic lesions and morphological features in AML have been identified as clinically significant prognostic markers. The European Leukemia Network recommends routine screening for mutations in *NPM1*, *CEBPA*, *RUNX1*, *ASXL1*, and *FLT3* at the time of initial diagnosis [3]. *IDH1* and *IDH2* mutations are also frequently tested given their implications in prognosis and treatment [44]. There are a number of small-molecule drugs targeting AML mutations, either in clinical trial or commercial settings, that offer new possibilities for the treatment of R/R AML.

FLT3 inhibitors

Fms-like tyrosine kinase 3 (FLT3), expressed on the surface of the hematopoietic progenitor cells, plays a critical role in the proliferation, survival, and differentiation of multipotent stem cells [45]. In AML, ~30% patients occur activating mutations of it [46–48]. There are two unique activating FLT3 mutations at specific hotspots: internal tandem duplications (FLT3-ITD) in the juxtamembrane domain and secondary point mutations in the tyrosine kinase domain (FLT3-TKD) [49, 50]. FLT3-ITD mutations are strong predictors of rapid relapse and short OS, whereas secondary FLT3-TKD point mutations may confer resistance to FLT3 inhibitors [51–53]. Because *FLT3* mutation is one of the most common recurrent genetic mutations in AML, and a strong negative-prognostic factor, multiple targeted molecules aiming at *FLT3* mutation have been developed [54, 55]. Gilteritinib is a novel, highly specific and potent FLT3/AXL inhibitor. Its antileukemia activity has been demonstrated in R/R AML patients [56]. In a recently published international multicenter phase 1/2 dose-escalation/expansion study of once-daily oral gilteritinib in patients with R/R AML, gilteritinib was well tolerated with a maximum tolerated dose (MTD) of 300 mg/d. Gilteritinib doses ≥ 80 mg/d were associated with consistent and potent FLT3 inhibition and strong antileukemic response, with an ORR of 52% and a median OS duration of 31 weeks [57]. In another open-label phase 1 study (NCT02181660), 24 Japanese patients with R/R AML received once-daily oral gilteritinib in one of six dose-escalation cohorts (20, 40, 80, 120, 200, and 300 mg/d). Gilteritinib was well tolerated. The MTD was 200 mg/d; the recommended dose (RD) was 120 mg/d. In patients with mutated FLT3, the ORR was 80%; in wild-type FLT3, the ORR was only 36.4%. In conclusion, gilteritinib was well tolerated and exhibits antileukemia activity in R/R AML, especially the population that harbored FLT3 mutation (Table 2) [58].

Quizartinib is a highly potent, selective, next-generation oral tyrosine kinase inhibitor against FLT3, and is active against ITD mutants [56, 59, 60]. The clinical experience

accumulated in phase 1 and 2 clinical trials indicated that quizartinib was highly active in R/R AML with FLT3-ITD [61, 62]. The randomized, open-label, phase 2b study (NCT01565668) evaluated the efficacy and safety of two quizartinib monotherapy regimens in FLT3-ITD R/R AML who had previously received transplant or another second-line rescue treatment. Patients ($N = 76$) were randomized to receive single-agent oral quizartinib at a dose of 30 or 60 mg/day (escalated to 60 or 90 mg/day, respectively, if there was a lack/loss of response). Median OS (20.9 and 27.3 weeks), duration of composite CR (4.2 and 9.1 weeks), and bridge to transplant rates (32 and 42%) were better in the 60-mg arm than the 30-mg arm. In the 30-mg and 60-mg arms, 61% and 14% of patients required dose escalation, respectively. This study was consistent with previous reports, showing high clinical activity of quizartinib in FLT3-ITD R/R AML (Table 2) [63].

In addition to the above two new inhibitors, other inhibitors of FLT3 are also under investigation. Midostaurin is a multitargeted kinase inhibitor that has been shown to inhibit wild-type and mutant FLT-3, and also potently inhibit a variety of other molecular targets that are important for the pathogenesis of AML [64]. In a phase 1 study, 11 patients received oral midostaurin, 25 or 50 mg twice daily, in combination with all-trans retinoic acid and CLAG chemotherapy. Two patients (22%) achieved CR and one patient (11%) achieved CR with incomplete count recovery [65]. In another clinical trial, midostaurin was used in combination with bortezomib. As a result, a 56.6% CR rate and a 82.5% CRR rate were achieved [66]. In addition, lestaurtinib [67, 68], sorafenib [69], and SU11248 [70] are also inhibitors of FLT3, and their clinical application continues to be studied (Table 2).

IDH inhibitors

IDH1 and IDH2 are key metabolic enzymes that catalyze the conversion of isocitrate to α -ketoglutarate, while reducing nicotinamide adenine dinucleotide phosphate (NADP) to NADPH [71, 72]. *IDH* mutations occur in ~20% of AML, and are earlier, more stable events [73, 74]. Both IDH isoforms are thought to contribute to leukemogenesis through the overproduction of an oncometabolite, 2-hydroxyglutarate (2-HG), which can cause DNA hypermethylation, leading to impaired cell differentiation [75]. Ivosidenib is an oral, small molecule that targets mutant cytosolic IDH1. It prevents the accumulation of 2-HG. Ivosidenib has been approved in the US for the treatment of *IDH1*-mutated R/R AML [76]. The RD is 500 mg once daily, with or without food, until disease progression or unacceptable toxicity [77]. During preapproval clinical trial (NCT02074839), this dose had achieved a CR rate of 24.0% in R/R AML. Median duration of CR was 10.1 months, and the ORR was 41.9% (Table 3) [78].

Table 2 FLT3 inhibitors in clinical trials

Name	Targets	N	Disease status	Doses	Combination drugs	Reference
Gilteritinib	FLT3/AXL	249	Relapsed/refractory AML	1 of 7 dose-escalation cohorts (20, 40, 80, 120, 200, 300, and 450 mg/d)	NA	[57]
Gilteritinib	FLT3/AXL	24	Relapsed/refractory AML	1 of 6 dose-escalation cohorts (20, 40, 80, 120, 200, and 300 mg/d)	NA	[58]
Quizartinib	FLT3-ITD	76	Relapsed/refractory AML	30 or 60 mg/day (escalated to 60 or 90 mg/day, if there was a lack/loss of response)	NA	[63]
Midostaurin	FLT3	11	Relapsed/refractory AML	25 mg or 50 mg orally twice daily	ATRA + CLAG	[65]
Midostaurin	FLT3	34	Primary refractory, relapsed or relapsed refractory AML	50 mg twice daily in the first three groups; 50 mg PO bid days 8–21 in the last groups	Bortezomib/Bortezomib + MEC	[66]
Lestaurtinib	FLT3	224	First relapsed AML	80 mg twice daily	NA	[67]
Lestaurtinib	FLT3	17	Refractory, relapsed, or poor-risk AML	60 mg twice daily	NA	[68]
Sorafenib	FLT3-ITD	65	Relapsed, chemotherapy-refractory or frail FLT3-ITD AML	The median dose was 600 mg/day in the allo-SCT and 486.5 mg/day in the CT group	NA	[69]
SU11248	FLT3	16	Relapsed/refractory AML	50 mg/day or 75 mg/day for 4 weeks	NA	[70]

AML acute myeloid leukemia, FLT3 Fms-like tyrosine kinase 3, ITD internal tandem duplication, MEC mitoxantrone, etoposide, and cytarabine, ATRA all-trans retinoic acid, CLAG cladribine, cytarabine and granulocyte colony stimulating factor, allo-SCT allogeneic stem cell transplantation, CT conventional therapy cohort, NA not available

Enasidenib is a selective inhibitor of mutant IDH2. This mutation occurs in ~10% of AML patients and also leads to the synthesis of 2-HG [79]. Enasidenib received FDA approval in August 2017 for IDH2-mutant R/R AML at a dose of 100 mg orally once a day, based on the results of two phase 1/2 trials. In the first trial, published in 2017, the approved dose of enasidenib achieved CR/CRi in 26.6% of R/R AML patients. The median duration for the best response was 3.7 months. The median OS was 9.3 months, and the median OS of patients with CR was 19.7 months [80]. In the second trial (NCT01915498) [81], CR rate was 19.6, and 10.3% of all patients proceeded to allo-HSCT. ORR was 38.8%, median OS was 8.8 months. In both trials, enasidenib was well tolerated and induced deep molecular remissions in IDH2-mutant R/R AML patients who failed prior treatments (Table 3).

BCL-2 inhibitors

Venetoclax (ABT-199) is an oral selective BCL2 inhibitor, which is active in various hematological malignancies [82–84]. It also have the potential to sensitize AML cells to hypomethylating agents (HMAs) [85]. And in 2018, based on phase 1 results, the FDA approved it for the treatment of elderly AML patients who are not suitable for strong chemotherapy. One recent trial analyzed 33 patients with R/R AML treated with venetoclax in combination with decitabine or 5-azacitidine. Venetoclax was administered at a daily dose of 400 mg (200 mg if the patient was on azoles). Decitabine dose was given at 20 mg/m²/day and was administered for 5 days ($n = 15$) or 10 days ($n = 16$) based on the decision of the treating physician. 5-azacitidine ($n = 2$) was administered at the dose of 75 mg/m²/day for 7 days. ORR was 64% ($N = 21$); 10 (30%) patients achieved CR. The best response was observed after a median of two cycles (Table 4) [86].

The RhoGTPase pathway inhibitors

Lurbinectedin (PM01183) is one of the next generation minor groove binders that can inhibit genes of the RhoGTPase pathway in monocytic and myeloid leukemic cells. This pathway is involved in signaling events such as actin-cytoskeleton organization and cell motility. Lurbinectedin also demonstrates anti-tumor-associated macrophage activity both in vitro and in vivo, which suppresses leukemia cell growth by changing the tumor microenvironment [87, 88]. In a phase 1 dose-escalation trial, 42 patients with R/R AML/MDS received 1-h intravenous lurbinectedin infusion in a 3 + 3 study design. Two dosing schedules were used: 3.5, 5, 7, or 6 mg on days 1 and 8 versus 2, 3, 1, or 1.5 mg for 3 consecutive days on days 1–3. Overall, peripheral blood or bone marrow blasts were reduced in 33

Table 3 IDH inhibitors in clinical trials

Name	Targets	N	Disease status	Doses	Reference
Ivosidenib	IDH1	179	Relapsed/refractory AML	500 mg/d	[78]
Enasidenib	IDH2	239	Relapsed/refractory AML	1 of 5 dose-escalation cohorts (30, 50, 75, 100, and 150 mg) twice per day; 1 of 8 dose-escalation cohorts (50, 75, 100, 150, 200, 300, 450, and 650 mg) once per day	[80]
Enasidenib	IDH2	214	Relapsed/refractory AML	100 mg/d	[81]

AML acute myeloid leukemia, IDH isocitrate dehydrogenase

patients (79%). One patient achieved a partial response and two patients reached morphologic leukemia-free state. Lurbinectedin was safe and well tolerated in both treatment designs [89].

KMT2A inducers

Another potential target in AML is a partial tandem repeat of the lysine methyltransferase 2A (KMT2A) gene, previously known as mixed lineage leukemia-1 [90]. The mutation causes an epigenetic silence of the gene. It occurs in ~5–10% of AML patients and is associated with poor prognosis. By inducing KMT2A re-expression by either HMAs or histone deacetylase inhibitors, bone marrow blast cells could be sensitized to chemotherapy [91, 92]. A study involving 17 adults with R/R AML treated with decitabine and vorinostat, followed by an escalating dose of cytarabine, six patients achieved CR. In the four patients with KMT2A partial tandem duplication, two achieved CR. The study pointed out that the combination of decitabine, vorinostat, and cytarabine was feasible in younger R/R AML, and further attention should be paid to the KMT2A partial tandem repeat subset [93].

Hypomethylating agents

HMAs promote antitumor immune signaling by upregulating the interferon-gamma pathway genes, increasing HLA class 1 antigens expressions, and activating viral defense pathways [94]. The HMAs concurrently dampen antitumor immunity by increasing the expression of PD-1 and PD-L1 in solid tumors and in MDS/AML [95, 96]. Azacitidine is approved in the US and Europe for patients with MDS, and is approved in Europe and commonly used in the US to treat older patients with newly diagnosed AML [97]. In a single-arm trial, patients with R/R AML were treated with azacitidine 75 mg/m² days 1–7 intravenously or subcutaneously with nivolumab 3 mg/kg intravenously on days 1 and 14, every 4–6 weeks. Seventy patients were treated, and the ORR was 33% including 15 (22%) CR/CRi [98]. Also Stahl et al. used an international multicenter retrospective database to study the effectiveness of HMAs in R/R AML and to evaluate predictors of response and OS. A total of 655

patients from 12 centers received azacitidine (57%) or decitabine (43%), including 290 refractory (44%) and 365 relapsed (56%) patients. The best response to HMAs was CR (11%) or CR with incomplete count recovery (5.3%). In addition, 8.5% of people experienced hematologic improvement. The median OS was 6.7 months. The experimental results indicate that HMA represents a reasonable treatment option for some R/R AML patients [99].

Immunotherapy

Gemtuzumabozogamicin

Gemtuzumabozogamicin (GO, also known as CMA-676) is an antibody-drug conjugate of humanized anti-CD33 monoclonal antibody and N-acetyl gamma calicheamicin. GO binds to the CD33 antigen expressed on the surface of most AML cells and immature myelomonocytic cells. After the binding, GO is internalized and releases calicheamicin, which induces breaks in double-strand DNA and cell death. GO was approved in the US for treatment of CD33-positive R/R AML in patients older than 2 years. Meta-analysis showed that in the treatment of R/R AML, the low-dose “fractional” schedule, i.e., 3 mg/m² on days 1, 4, and 7, was associated with lower rates in early mortality, bleeding, and vaso-occlusive disease, without impairment of the CR rate [100]. Another approach is giving HMA with GO, because the former may enhance GO's cytotoxicity in AML blast cells [101]. In a phase 1/2 study, patients with R/R AML were treated with azacitidine followed by two doses of 6 mg/m² GO. The established MTD was azacitidine 75 mg/m² on days 1–6, and GO 6 mg/m² on days 7 and 21. Of the 50 evaluable patients, 12 (24%) reached CR/CRi. The study confirmed the tolerability and efficacy of HMA-GO sequential combination (Table 5) [102].

CAR-T cells

Novel cell therapies using engineered T cells with chimeric antigen receptors (CAR-T cells) in AML are attracting more attention recently. As early as 2013, it was discovered that LeY is a diglycosylated carbohydrate antigen expressed on a series of proteins including some tumor-associated

Table 4 Small molecule inhibitors with novel mechanisms in clinical development

Name	Targets	N	Disease status	Doses	Combination drugs	Reference
Venetoclax	BCL-2	33	Relapsed/refractory AML	400 mg/d (200 mg if the patient was on azoles)	Decitabine/ 5-azacitidine	[86]
Thioridazine	DRD2	13	Relapsed/refractory AML	1 of 3 dose-escalation cohorts (25, 50, and 100 mg), oral every 6 h for 21 days.	cytarabine	[28]
Lurbinectedin	The RhoGTPase pathway	42	Relapsed/refractory AML/MDS	3 + 3 study design: 3.5, 5, 7, or 6 on days 1 and 8 versus 2, 3, 1, or 1.5 mg for 3 consecutive days on days 1–3.	NA	[89]
Decitabine + vorinostat + cytarabine	KMT2A	17	Relapsed/refractory AML	Decitabine: 20 mg/m ² /day on days 1–10. Vorinostat: 400 mg/day on days 5–10. Cytarabine was intravenously over 2 h every 12 h on days 12, 14, and 16 for 6 doses total.	NA	[93]
Indisulam	Cell-cycle molecules	40	Relapsed/refractory AML and high-risk MDS	400 mg/m ² on days 1 and 8 of a 28-day cycle.	Idarubicin + cytarabine	[122]
CPL-613	PDH and α -KGDH	67	Relapsed/refractory AML	1 of 6 dose-escalation cohorts (1000, 1500, 1750, 2000, 2250, and 2500 mg/m ²)	Cytarabine + mitoxantrone	[125]
Volasertib	PLK1 inhibitor	88	Relapsed/refractory AML	1 of 6 dose-escalation cohorts (150, 200, 250, 300, 350, and 400 mg), 1 h intravenous infusion on days 1 and 15	Ara-C	[127]
Plerixafor	The SDF-1 α -CXCR4 axis	57	Relapsed/refractory AML	1 of 4 dose-escalation cohorts (120, 160, 200, and 240 μ g/kg) twice per day	FLAG-Ida	[131]

AML acute myeloid leukemia, BCL-2 B-cell lymphoma-2, DRD2 dopamine receptor D2, KMT2A the lysine methyltransferase 2A, PDH pyruvate dehydrogenase, α -KGDH α -ketoglutarate dehydrogenase, MDS myelodysplastic syndrome, PLK1 polo-like kinase 1, SDF-1 α -CXCR4 stromal cell-derived factor-1 -CXCR4, FLAG fludarabine, a combination of cytarabine and granulocyte stimulating factor, Ida idarubicin, NA not available

antigens, with high copy number in various malignant tumors including AML, but there was only a limited expression in normal tissues [103–105]. In this phase 1 study of anti-LeY CAR-T, four relapsed patients received up to 1.3×10^9 total T cells, of which 14–38% expressed the CAR. One patient achieved a cytogenetic remission, while another had reduced peripheral blood blasts and a third showed a protracted remission [106]. Wang et. al. pioneered in using anti-CD33 CAR-T without conditioning chemotherapy in one patient with refractory AML. Within two weeks, the patient's bone marrow blast percentage decreased from >50% before infusion to <6% [107]. Larger clinical trials are underway. Natural killer group 2D (NKG2D) is an activating receptor expressed on natural killer (NK) cells and activated CD8+ T cells that triggers cytotoxicity upon recognition of its ligand [108]. NKG2DL expression is reported in AML, and all blast cells express at least one ligand [109, 110]. One R/R AML patient received the NKG2D-based CAR-T therapy and the allo-HSCT was continued after the symptoms continued to improve. As of the time of the report, the patient has maintained a CR 6 months from allo-HSCT and 9 months following initial CAR-T cells infusion [111]. In addition to these experiments, CD123 is another potential target in AML, and respective CAR-T cells are under development (Table 5).

Others

In addition to CAR-T cells, tumor-specific T-cell receptor-gene transduced T cells (TCR-T cells) have also been developed as effective immune cell therapies for refractory tumors [112, 113]. TCR-T cells recognize peptide antigens presented by human leukocyte antigen molecules [114]. Wilms' tumor 1 (WT1) is expressed in most MDS and AML cells, and messenger RNA of WT1 in peripheral blood is monitored as a marker for minimal residual disease in AML and MDS [115]. In one study, a total of eight patients were divided into two groups receiving WT1-specific TCR-T cells. There were no adverse reactions in normal tissues. At the end of the study, four patients survived for more than 12 months [114]. NK cells are also used to treat R/R AML because they mediate direct antitumor effects through their cytotoxicity and cytokine secretion functions [116, 117]. Activated NK cells (aNK) produced by amplification of the human interleukin-2 dependent NK cell line have been shown to mediate strong antileukemia activity [118]. This phase 1 study enrolled seven patients with R/R AML who underwent aNK cell infusion and found that none of them experienced dose-limiting toxicity. No grade 3–4 toxicity associated with aNK cell infusion occurred. This trial demonstrates the safety and feasibility of adopting “off-the-shelf” aNK cells for adoptive cell therapy in R/R AML patients (Table 5) [119].

Table 5 Advanced immunotherapy in relapsed or refractory acute myeloid leukemia

Name	Targets	N	Disease Status	Doses	Reference
GO	CD33	Phase 1 (<i>n</i> = 14); Phase 2 (<i>n</i> = 36)	Relapsed/refractory AML	6 mg/m ² on days 7 and 21	[102]
CAR-T	Le Y	5	Relapsed AML	The median dose of T cells infused was 1.1×10^9 (range 5×10^8 to 1.3×10^9)	[106]
CAR-T	CD33	1	Refractory AML	1.12×10^9 autologous CART-33 cells	[107]
CAR-T	NKG2D	1	Relapsed/refractory AML	3×10^8 cells (flat dose)/injection/2 weeks for three administrations	[111]
TCR-T	WT1	6	Refractory AML and high-risk MDS	1 of 2 cohorts (2×10^8 cells, 1×10^9 cells) on days 0 and 28	[114]
aNK	NA	7	Relapsed/refractory AML	1 of 2 cohorts (1×10^9 cells/m ² , 3×10^9 cells/m ²) on days 1 and 2	[119]

GO Gemtuzumabozogamicin, CAR-T T cells with chimeric antigen receptors, TCR-T tumor-specific T-cell receptor-gene transduced T cells, WT1 Wilms' tumor 1, MDS myelodysplastic syndrome, aNK activated natural killer cells, NKG2D natural killer group 2D, AML acute myeloid leukemia, NA not available

Strategies targeting metabolomics

In addition to drugs that directly inhibit mutation sites, some other drugs target metabolic pathways. Indisulam (a.k.a. E7070) is a sulfonamide derivative inhibiting carbonic anhydrases and cytosolic malate dehydrogenase [120]. The drug inhibits crucial cell-cycle molecules at various checkpoints, including cyclins A, B1, H, and cyclin-dependent kinase 2 [121]. It has synergistic effects with nucleoside analogs and topoisomerase inhibitors. A phase 2 study evaluated the combination of indisulam, idarubicin, and cytarabine in patients with R/R AML and high-risk MDS. In the first stage of the trial, 40 patients received intravenous indisulam 400 mg/m² on days 1 and 8 of a 28-day cycle. If they had no response, they moved on to receive a second cycle of indisulam with the same dose schedule, followed by intravenous idarubicin 8 mg/m² daily for 3 days and cytarabine 1.0 g/m² over 24 h daily on days 9 through 12 (for those <60 years) or days 9 through 11 (for those >60 years). Among the patients who got combination therapy (*N* = 31), 11 (35%) responded with a median duration of 5.3 months. Responders' 1-year OS rate was estimated at 51%, while nonresponders were 8% (*P* < .001). Therefore, in heavily pretreated AML patients, the combination of indisulam with idarubicin and cytarabine might be a very active therapy [122].

CPI-613 is a novel lipoic acid analog with anticancer activity by inhibiting pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase [123, 124]. A phase 1 study tested the efficacy and safety of CPI-613 in combination with high-dose cytarabine and mitoxantrone in R/R AML patients. It enrolled 67 patients, 62 were evaluable. ORR was 50%. Median survival was 6.7 months. In patients over 60 years old, the CR/CRi rate was 47% (15/32) and the median survival was 6.9 months. The CR rate of 46% in

patients with poor-risk cytogenetics was also encouraging. The addition of CPI-613 to chemotherapy was a promising approach for elderly, poor-risk patients [125].

Volasertib is a potent ATP-competitive polo-like kinase 1 inhibitor and might also inhibit PLK2 and PLK3 [126]. Eighty-eight patients received escalating doses of volasertib on days 1 and 15 as monotherapy or in combination with a fixed-dose low-dose Ara-C (2×20 mg/day subcutaneously on days 1–10) of a 28-day cycle. CR/CRi was observed in six patients (18.8%) treated with combination therapy and five patients (8.9%) treated with monotherapy. The event-free survival of the combination and monotherapy groups was 153–392 and 64–566 days, respectively. CR or CRi was achieved after 1–3 treatment cycles in the combination group, or after one treatment cycle in the monotherapy group. Volasertib monotherapy alone or combined with low-dose Ara-C demonstrated antileukemia activity in this early trial [127].

Plerixafor is a small molecule that induces mobilization of AML blasts from the bone marrow niche to the peripheral blood through the stromal cell-derived factor-1-CXCR4 axis blockade. This could make the leukemic cells more vulnerable to the chemotherapy regimens [128–130]. A phase 1/2 trial (NCT01435343) in Spain using FLAG-Ida plus high-dose intravenous plerixafor had enrolled 57 patients, and 41 received plerixafor. Among them, 20 (49%) achieved CR/CRi, but another 3 (7%) died during induction. The primary refractory AML patients have a CR/CRi ratio of 50%. Median overall and DFS were 9.9 and 13 months, respectively. In summary, the combination of plerixafor plus FLAG-Ida resulted in a relatively high CR/CRi rate in adult patients with primary refractory or early relapsed AML, with acceptable toxicity and treatment-associated mortality. It could be a useful bridge to allo-HSCT [131].

Conclusion

Since the early 1970s, intensive cytotoxic treatment has been the standard of care for AML. Despite some limitations, it is still the best choice for achieving remission, prolonging life, and bridging to allo-HSCT for the ultimate cure [132]. Early chemotherapy drugs were mostly anti-metabolites designed to select and damage rapidly dividing leukemia cells rather than the relatively stationary normal cells [133]. In recent years, understanding of the genomic characteristics of AML and the wide availability of next-generation-sequencing of each newly-diagnosed patient have greatly promoted novel and individualized drug development and treatment design. However, our understanding of the new drugs and new pathways remains limited, which mandates caution when combining multiple targeted drugs, or combining targeted therapy with traditional chemotherapy, to treat R/R AML. Cumulative toxicity may occur, some patients may have insensitive mutation, and disease itself may evolve and adapt [134]. There are still many unanswered questions in the mechanism of leukemogenesis, tumor microenvironment, and therapy synergy optimization that may shape the treatment of R/R AML in the near future.

In summary, there is currently no uniform standard to treat R/R AML. In addition to reinduction chemotherapy and targeted therapies, hematopoietic stem cell transplantation remains the primary choice. Immunotherapy and hypomethylation agents are also under rapid development. Despite recent progress in research, R/R AML remains a great challenge for patients and their hematologists.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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