REVIEW

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Relapsed or primary refractory AML: moving past MEC and FLAG-ida

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Purpose of review
Treatment of relapsed and refractory acute myeloid leukemia (AML) is still very challenging, with poor response rates and low chance for cure. This is especially true when treating patients who are elderly, have multiple comorbidities, or who are too unfit for traditional salvage chemotherapy regimens.

Recent findings
Recently, advances in the treatment of relapsed/refractory AML utilizing novel chemotherapy combinations, hypomethylating, and targeted therapies have shown promising results.

Summary
Several early-phase studies with novel targeted therapy combinations have demonstrated encouraging results warranting larger, comparative studies. This has expanded the access of treatment for patients with relapsed/refractory AML who cannot receive traditional salvage chemotherapy. These newer treatments have the potential to outperform traditional chemotherapy as well.

Keywords
hypomethylating agents, relapsed/refractory AML, salvage regimens, targeted therapy

INTRODUCTION

Acute myeloid leukemia (AML) is a biologically heterogeneous disease of the hematopoietic system characterized by clonal accumulation and expansion of immature myeloid cells in the bone marrow. Unfortunately, with current treatment strategies, only approximately 35–40% of patients at least 60 years and 5–15% of patients older than 60 years are cured of this disease [1]. Even with adaptation of cytogenetic and molecular risk-stratified therapies, 10–40% of patients do not achieve a complete remission (CR) after intensive induction therapy and are deemed to have primary refractory disease. Refractory disease is defined by the European LeukemiaNet (ELN) as the inability to attain CR or complete remission with incomplete hematologic recovery (CRi) after two courses of intensive induction treatment. Of note, this definition is not consistent throughout the literature [2]. Although some patients are able to achieve CR, greater than 50% of these patients subsequently experience disease relapse [3]. For patients who relapse, only a small fraction undergo successful salvage treatment with ability to attain a second CR [3]. Additionally, these patients are often not candidates for aggressive treatment (i.e. allogeneic stem cell transplant [alloHSCT]) given comorbid conditions and lack of suitable donors. Therefore, this leaves a large unmet clinical need for treatment of both relapsed and refractory (R/R) AML.

CURRENT STANDARD OF CARE FOR RELAPSED AND REFRACTORY ACUTE MYELOID LEUKEMIA

Traditionally, R/R AML is treated with intensive chemotherapy re-induction (aka. salvage) regimens, typically comprised of a high-dose cytarabine backbone with a variety of anthracycline and alkylating counterparts. Direct comparison of intensive salvage regimens has not been performed; therefore, choice

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KEY POINTS

- Treatment of relapsed and refractory AML is still very challenging, with poor response rates and low chance for cure.
- Recently, advances in the treatment of relapsed/refractory AML utilizing novel chemotherapy combinations, hypomethylating and targeted therapies have shown promising results.
- Several early-phase studies with novel targeted therapy combinations have demonstrated encouraging results warranting larger, comparative studies.
- These newer treatments have the potential to provide treatment to patients who cannot tolerate standard chemotherapy and to eventually outperform traditional chemotherapy.

largely depends on physician preference and patient characteristics. Still, the most common regimens employed in these circumstances have been fludarabine, cytarabine, granulocyte colony stimulating factor, and idarubicin (FLAG-ida) and mitoxantrone, etoposide, cytarabine (MEC) [2,4]. The CR/CRi rate for both FLAG-ida and MEC are approximately 55% [5–7]. Ultimately, the only current chance for cure for patients with R/R AML is an alloHSCT as 3-year overall survival (OS) of these patients without transplant is only 8–18% [2,8].

However, in the past few years, treatment options for R/R AML have expanded, shifting away from intensive chemotherapy. Since 2017, the United States Food and Drug Administration (FDA) has approved multiple regimens for R/R AML: ivosidenib, enasidenib, gilteritinib, and gemtuzumab ozogamicin [8–11]. Ivosidenib and enasidenib are both targeted therapies against the enzymes IDH1 and IDH2, respectively, which are mutated in about 6–12% of patients with AML. In the phase I/II study in R/R *IDH2*-mutated AML, enasidenib showed a CR/CRi rate of 34 and 12%, respectively, with an overall response rate (ORR) of 40.3% leading to FDA approval [12]. In the phase I study, ivosidenib showed a combined CR/CRi rate in *IDH1*-mutated R/R AML of 30.4% (CR rate of 21.6%) with an ORR of 41.6%, which also lead to FDA approval [13].

Gilteritinib is a highly selective FLT3 inhibitor; approximately 30% of patients with AML carry mutations in *FLT3*-ITD or *FLT3*-TKD [14]. In a recent phase III trial in the R/R setting, gilteritinib exhibited a CR/CRh (complete remission with partial hematologic recovery) rate of 34.0%, compared to 15.3% with intensive chemotherapy [15]. The median OS was 9.3 months in the gilteritinib arm, compared to 5.6 months in the chemotherapy arm ($P < 0.001$) [15].

Gemtuzumab ozogamicin (a CD33 antibody–drug conjugate) was initially approved in R/R AML but was pulled from the market in 2010 because of safety concerns including veno-occlusive disease (VOD). However, with a re-vamped dosing schedule, was re-approved in 2017 in both newly diagnosed and R/R AML [11]. Gemtuzumab ozogamicin showed a CR/CRi rate of 26% in patients in their first relapse of CD33-positive AML [16]. Gemtuzumab ozogamicin should still be used with caution in patients planning to receive an alloSCT given the VOD risk.

Ultimately, prognosis is poor for patients with R/R AML if they do not receive an alloHSCT. Ideally, the goal of treatment is for patients to achieve remission prior to undergoing alloHSCT, as outcomes are best in this setting. However, it is reasonable for select patients not in CR to undergo alloHSCT as these patients can still experience long-term survival [17]. In order to select patients with the highest likelihood of long term-survival, the Duval score has been used. This score assesses five variables prior to transplant (first CR duration less than 6 months, circulating blasts, donor other than HLA-identical sibling, Karnofsky or Lansky score less than 90, and poor-risk cytogenetics) to help predict 3-year-CR [18]. Even with recent advances in targeted therapy and expanding access to transplant, there is significant opportunity for improvement in treating patients with R/R AML.

WHAT IS ON THE HORIZON FOR R/R AML TREATMENT

Given the need for more effective treatment options in R/R AML, many promising treatment strategies are under exploration and in development that we will now explore further.

Modifications to allogenic stem cell transplant

As previously discussed, alloHSCT is the only curative treatment for patients with R/R AML, thus, investigations into performing alloHSCT on patients with active disease (>5% blasts in the bone marrow) are underway. A recent phase I study explored utilizing yttrium-90-labeled anti-CD45 antibody, to address residual leukemia disease, followed by a standard reduced intensity conditioning regimen in patients with advanced AML or high-risk MDS [19]. Nine of the 15 enrolled patients had active, refractory disease with bone marrow blasts ranging from 7 to 83.9% prior to transplant. Complete remission was achieved in 13 patients,

and, interestingly, the two patients with persistent disease had the highest blast counts prior to alloHSCT with 70 and 83.9%. The estimated OS was 66% at 1 year and 46% at 2 years (NCT01300572). Although this strategy is still in early-phase trials, it proves a promising concept for the future treatment of patients with R/R AML pursuing alloHSCT.

Improving the efficacy of salvage chemotherapy

Although the strategy of treating patients with AML has begun to move away from intensive chemotherapy regimens, as it stands now, cytotoxic chemotherapy still remains a cornerstone of treatment for R/R AML. However, significant energy and research has been devoted to improve upon their efficacy, ushering a new wave of novel chemotherapy combinations.

Gemtuzumab ozogamicin was investigated in combination with cytarabine 1 g/m^2 twice daily for 5 days (with or without other chemotherapies, including mitoxantrone, daunorubicin, or idarubicin) in patients with primary R/R CD33-positive AML [20]. This study enrolled 58 patients and showed an ORR of 67%, with a median leukemia-free survival of 13.5 months and median OS of 50 months.

Also under investigation is sirolimus, an mTOR inhibitor, combined with MEC [21]. The study evaluated sirolimus combined with MEC in 51 patients with R/R AML, where the ORR was 47% in all-comers, but 71% in the sirolimus sensitive group (compared to 20% in the resistant group) [21].

Ixazomib, a proteasome inhibitor, is FDA approved for multiple myeloma, but was combined with standard salvage regimen MEC in 30 patients with R/R AML [22,23]. This phase I/II trial showed an ORR of 53% (16 patients with complete remission) and a median OS of 4.5 months in all patients, but a median OS of 11.1 months in patients who achieved a CR/CRi [23].

With the availability of newer targeted therapies, there has also been interest in combining these agents to standard intensive salvage chemotherapy. For example, devimistat (CPI-613), a novel lipoate analog that inhibits enzymes in the Krebs cycle, was investigated in combination with cytarabine and mitoxantrone in a phase I dose-escalation study [24]. Sixty-two patients were treated with an ORR of 50% in all-comers and 46% in patients with poor risk cytogenetics. These results were encouraging enough to warrant a phase III study (termed ARMADA 2000), which is currently enrolling patients (NCT03504410) [25].

Cytarabine 1 g/m^2 daily was combined with vosaroxin, a quinolone derivative which intercalates DNA-inhibiting topoisomerase II [26]. This phase III study randomized study compared this combination to cytarabine with placebo in 711 patients. The CR rate was 30 versus 16% with placebo ($P < 0.0001$). Furthermore, vosaroxin/cytarabine showed a survival advantage in patients at least 60 years with refractory or early relapsed disease (<12 months) with a median OS of 6.5 months versus 3.9 months with placebo ($P = 0.0009$).

Attempts for improvement upon intensive salvage regimens with the addition of hypomethylating (HMA) therapy has been evaluated. Decitabine in combination with aclacinomycin and cytarabine (DAC) was prospectively compared to standard FLAG chemotherapy in patients with R/R AML [27▪▪]. Of note, all 35 patients in this study had been treated with the standard induction chemotherapy regimen of cytarabine with anthracycline, and no patient had previously received an alloSCT. In this study, the ORR was 100% ($n = 17$) and 55.6% ($n = 10$) in the DAC and FLAG groups, respectively ($P = 0.002$); 64.7% ($n = 11$) of the patients treated with DAC achieved CR. Furthermore, after 2 years of follow-up, only six patients (35.3%) died in the DAC group compared to 13 patients (72.2%) in the FLAG group ($P = 0.028$).

Decitabine was also explored in combination with vorinostat (a histone deacetylase inhibitor) followed by cytarabine in a phase I study in younger patients (18–59 years) with R/R AML [28,29]. This was tested in 17 patients, of which 15 had received cytarabine in the past. ORR was only 35% (all six of which were complete remissions), and five of these patients relapsed. However, the authors point out that the biology of this treatment regimen warrants further study in patients with AML with *KMT2A* partial tandem duplication, which was unable to be selected for in the small dose-finding phase I study.

Overall, improvements are being attempted to standard salvage intensive chemotherapy regimens, and novel combinations warrant further study. However, at this point lower intensity and single-agent chemotherapy play a limited role in R/R AML treatment.

Improving the efficacy of hypomethlyating agents

HMAs have played an important role in treating patients with R/R AML. HMAs alone can be employed as single agents in R/R disease with a multicenter international retrospective review of 655 patients with a CR/CRi rate of 16% [30]. Multiple trials with novel combinations of HMAs have attempted to improve on these outcomes. Gemtuzumab ozogamicin was investigated in combination with azacitidine

in 50 patients with R/R AML and with a 24% CR/CRi rate [31]. Of note, Gemtuzumab ozogamicin as monotherapy had a CR/CRi rate of 26% in patients in their first relapse, but 24% of patients in this study combining gemtuzumab ozogamicin with azacitidine were in their second or later relapse [16,31]. Azacitidine has also been combined with nivolumab, an anti-PD-1 monoclonal antibody with activity in some solid tumors, in R/R AML in a single-arm phase II study [32,33▪▪]. Seventy patients were treated with this combination and experienced an ORR of 33% with a CR/CRi rate of 22% [33▪▪]. Interestingly, HMA-naïve patients fared far better than patients who had received an HMA in the past with ORRs of 58 and 22%, respectively. Finally, adding lenalidominde to azacitidine in patients with R/R AML and MDS resulted in nine patients progressing during their first treatment cycle, and only four patients experiencing CR/CRi (34/37 patients in this study had AML) [34]. However, 14 patients were able to achieve morphological leukemia free state (MLFS) for an ORR of 49%.

Decitabine in combination has also been recently investigated in combination with selinexor [35]. Selinexor is a selective inhibitor of nuclear export (SINE) compound that inhibits the nuclear transport protein exportin-1 (XPO1), which exports almost all known tumor suppressor proteins out of the nucleus. In AML, XPO1 is overexpressed resulting in aberrant localization of tumor suppressors to the cytoplasm. In the phase I dose-escalation study in 20 patients with R/R AML, there was a CR/CRi/MLFS rate of 30% [35].

These novel HMA combination regimens for R/R AML have shown a broad range of response rates, depending on the treatment and patient population. However, the CR rates in these studies is lower than that of standard chemotherapy, making these options more suitable overall for patients unable to receive chemotherapy regimens.

Small molecule inhibitors

The treatment of AML has advanced as molecular classification of the disease has led to the development of multiple-targeted agents. This field continues to progress as a new generation of targeted inhibitors, and new uses for previously approved agents, are under investigation.

Venetoclax

Though venetoclax (a bcl-2 inhibitor) in combination with HMA therapy has changed the treatment landscape in newly diagnosed AML, outcomes in R/R AML currently have not been as promising [36,37]. Venetoclax monotherapy showed an ORR of 19% in high-risk R/R AML [38]. Venetoclax combined with HMA showed ORR of 64% and CR/CRi rate of 51% [39▪▪]. Venetoclax has also been combined with both high dose cytarabine (in patients 2–22 years old) and low-dose cytarabine (or Actinomycin D plus or minus metformin) showing a CR/CRi rate of 38.9 and 53%, respectively [40,41]. Venetoclax has also been combined with idasanutlin, a mouse double minute 2 (MDM2) inhibitor in a phase Ib study [42]. MDM2 binds to p53, resulting in p53 ubiquination and degradation [43]. This combination demonstrated a 37% CR/CRi/MLFS/PR rate [42]. Finally, the combination venetoclax with FLAG-Ida in both newly diagnosed and patients with R/R AML is currently under investigation in a phase Ib/II clinical trial (NCT03214562).

Tyrosine kinase inhibitors

Pazopanib has multiple kinase targets and is approved for rectal cancer and soft tissue sarcomas. As a single agent in a phase II study that included both newly diagnosed and patients with R/R AML unfit for chemotherapy, the best response was a partial remission (PR) in two of 20 patients (15 of which had R/R disease) [44].

Sorafenib, also a multitarget TKI that also targets FLT3, has been studied in the past in combination with HMA in *FLT3*-ITD-mutated R/R AML with a CR rate of 27–80% [45–47]. More recently, sorafenib was investigated in combination with omacetaxine mepesuccinate, a global messenger RNA translation inhibitor, in a phase II trial with 39 patients with R/R AML. Twenty eight of these patients (72%) achieved CR/CRi [48▪▪].

Quizartinib, which is highly selective for *FLT3*-ITD mutations, has been investigated in *FLT3*-mutated AML [49]. A phase III multicenter, randomized, controlled trial in 367 patients treated with quizartinib versus investigators choice of salvage chemotherapy showed that quizartinib treatment had a survival benefit with 6.2 months median OS (vs. 4.7 months in the chemotherapy group) [49]. Although this trial led to quizartinib's approval for R/R *FLT3-ITD*-mutated AML in Japan, the FDA has yet to approve the drug given concerns that the OS benefit was because of a greater proportion of patients in the quizartinib arm subsequently receiving alloHSCT compared to the chemotherapy arm (32 vs. 11.5%, respectively) and the inclusion of low-intensity chemotherapy (subcutaneous low-dose cytarabine) in the chemotherapy group [50,51].

Crenolanib is also under investigation for R/R AML with *FLT3*-ITD and *FLT3*-TKD mutations. Many earlier trials exhibited a CR/CRi rate of 23–39% in FLT3 TKI naïve patients and 5–16.7% in patients with prior *FLT3* TKI exposure [52,53]. Currently, a randomized phase III study is underway investigating crenolanib with chemotherapy

compared to chemotherapy alone in R/R *FLT3*-mutated AML (NCT03250338).

Mitogen-activated protein kinase Inhibitors

Targeting the Ras/Raf/MAPK growth signaling pathway is not a new concept in AML treatment, but there has yet to be an approved agent in this class of therapies for AML [54]. Recent studies have looked at novel and previously approved MEK inhibitors alone and in combination. The novel, potent MEK1/2 inhibitor binimetinib (MEK162) was studied in 17 patients with R/R AML (and one patient each with R/R MDS and CMML), but unfortunately after a median follow up of 1.8 months, 18 of these 19 patients have died [55]. Trametinib, a MEK1/2 inhibitor with approval in melanoma, non–small cell lung cancer, and thyroid cancer, was combined with a novel AKT inhibitor, GSK2141795, in patients with R/R AML with RAS mutations [56]. In this phase II study of 23 patients, no patient achieved a CR or CRi, and the study was closed early given poor clinical activity. Trametinib was also combined with AMG-232, an MDM2 inhibitor [43]. In this phase I study, 30 patients with R/R AML were treated, 26 with single-agent AMG-232 followed by 10 with the combination. Only one patient achieved a CR (received AMG-232 with trametinib), four patients achieved MLFS (AMG-232 only), and one patient achieved PR (AMG-232 with trametinib).

Hedgehog pathway inhibitors

As with the RAS signaling pathway, inhibiting the hedgehog pathway is promising in the treatment of patients with AML, as shown with glasdegib in combination with low-dose cytarabine in the newly diagnosed setting [49]. Vismodegib is another inhibitor of the hedgehog pathway signaling protein smoothened, and it is approved in basal cell carcinoma [57]. In a phase Ib study, single-agent vismodegib was investigated in 38 patients with R/R AML, but this therapy did not show efficacy in this population with no patients attaining complete remission or MLFS and one patient each attaining CRi and PR, therefore, the study was stopped [57].

Overall, these recent trials with targeted therapies demonstrated little clinical efficacy in R/R AML. The combination of sorafenib with omacetaxine mepesuccinate did show some promise with a 72% CR/CRi rate. However, this is contrasted by the many trials with few to no CRs with the majority of patients succumbing to their disease.

CONCLUSION

As made evidenced by the poor response rates in both approved and investigational therapies, R/R AML is an aggressive disease that is challenging to treat. The current standard of care continues to be salvage intensive chemotherapy regimens in patients that can tolerate this treatment. There are now easier tolerated targeted treatment options available that have demonstrated somewhat comparable, to slightly lower, CR rates than chemotherapy. Even with progress in targeted therapies, the most promising treatment as it stands for R/R AML is novel intensive chemotherapy and HMA combinations. It is important to note that the recent studies explored above are mainly early-phase trials with small sample sizes. It can also be challenging to determine the efficacy of novel agents in the R/R AML setting as it is a difficult disease to treat, even compared to newly diagnosed AML. Therefore, exploration of these treatments in the upfront setting may be the best route to determine clinical activity, prior to disease chemotherapy exposure and clonal evolution, and while patients are still relatively fit. Furthermore, although response rates were not overly promising for most of the investigational agents and combinations above, some therapies did show response; it will be important to determine why certain patients respond, to eventually better predict individual patient responses to certain therapies in the future. Further research in needed to more effectively treat R/R AML with therapies outside of the chemotherapy sphere. Of course, given the poor outcomes of R/R compared to newly diagnosed AML, preventing R/R disease is the goal; to achieve this more effective therapies are needed in the upfront setting.

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Conflicts of interest

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