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REVIEW

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Emerging agents and regimens for AML

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Abstract

Until recently, acute myeloid leukemia (AML) patients used to have limited treatment options, depending solely on cytarabine + anthracycline (7 + 3) intensive chemotherapy and hypomethylating agents. Allogeneic stem cell transplantation (Allo-SCT) played an important role to improve the survival of eligible AML patients in the past several decades. The exploration of the genomic and molecular landscape of AML, identification of mutations associated with the pathogenesis of AML, and the understanding of the mechanisms of resistance to treatment from excellent translational research helped to expand the treatment options of AML quickly in the past few years, resulting in noteworthy breakthroughs and FDA approvals of new therapeutic treatments in AML patients. Targeted therapies and combinations of different classes of therapeutic agents to overcome treatment resistance further expanded the treatment options and improved survival. Immunotherapy, including antibody-based treatment, inhibition of immune negative regulators, and possible CAR T cells might further expand the therapeutic armamentarium for AML. This review is intended to summarize the recent developments in the treatment of AML.

Keywords: AML, Targeted therapy, Novel treatment

Introduction

AML is a heterogeneous disease, defined by a broad spectrum of genomic changes and molecular mutations that influence clinical outcomes and provide potential targets for drug development. The updated 2017 European LeukemiaNet (ELN) risk stratification guidelines combining cytogenetic abnormalities and genetic mutations have been widely used to predict the prognosis of AML patients [1], while others have been exploring to incorporate additional prognostic factors into ELN-2017 guidelines to improve the risk stratification models [2].

Advanced by basic and translational research, especially through large scale genomic analysis to understand the molecular landscape of AML, the development of targeted therapies, such as targeting fms-like tyrosine kinase 3 (FLT3) and isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) mutations, the treatment of AML landscape changed significantly with FDA approvals for several new drugs in the past several years. Even with all these improvements, primary resistance to initial treatment and disease relapse remain huge unmet need in the treatment of AML. The majority of AML patients still eventually succumb to the disease. We still have a long way to further improve the survival of the AML patients, thus many investigational drugs have been explored to target the primary and secondary treatment resistance in AML patients.

This review will provide updates of the emerging therapeutic approaches for the treatment of AML, including combinations with mutation driven targeted treatments, novel immunotherapies in the myeloid disease.

Targeted therapies: alone or combination

BCL-2 inhibitor: venetoclax

BCL-2 is a member of the BCL-2 family of anti- and pro-apoptotic proteins. BCL-2 protects cells against apoptosis. BCL-2 expression in AML has been associated with decreased sensitivity to cytotoxic chemotherapy and a higher rate of relapse [3]. Venetoclax is an orally bioavailable selective inhibitor of BCL-2, promoting intrinsic apoptotic pathway activation resulting in mitochondrial

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outer membrane permeability through dissociation of BCL-2 mediated sequestration of BH3 proteins BIM and BID and effector proteins BAX and BAK. Venetoclax was initially approved by U. S. Food and Drug Administration (FDA) in 2016 to treat individuals with chronic lymphocytic leukemia (CLL) with deletion (17p).

Venetoclax + hypomethylating agents or low dose cytarabine

Early studies using venetoclax as monotherapy in AML demonstrated only modest efficacy in high-risk relapsed/refractory (R/R) AML patients with an overall response rate (ORR) of 38% and complete remission/complete remission with incomplete hematologic recovery (CR/CRi) of 19%. The responses were short lived, with overall survival (OS) of only 4.7 months [4]. Based on promising results from two large Phase 1b/II trials using combination of a hypomethylating agent (HMA) or low-dose cytarabine (LDAC) with venetoclax in untreated older AML patients [5, 6], FDA granted accelerated approval to venetoclax in combination with azacitidine (AZA) or decitabine (DEC) or LDAC for the treatment of newly-diagnosed (ND) AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapies in 2018.

Recently published Phase III randomized studies confirmed the results from these early single arm trials, and demonstrated a significant survival benefit from adding venetoclax to azacitidine and to LDAC [7, 8]. The major findings from the VIALE-A and VIALE-C trials are summarized in Table 1. In summary, the VIALE-A trial included 431 patients without history of exposure to azacitidine. At a median follow-up of 20.5 months, the median OS was 14.7 months in the azacitidine-venetoclax group and 9.6 months in the control group. The incidence of CR and composite complete remission rate (cCR) (CR + CRi) were significantly higher with azacitidine-venetoclax than with the control regimen. However, there were higher rates in key adverse events in the azacitidine-venetoclax group than those in the control group, but they were manageable [7]. The VIALE-C study assigned 211 patients to either venetoclax ($n = 143$) or placebo ($n = 68$) in 28-day cycles, plus LDAC on days 1 to 10. In contrast to VIALE-A trial, 20% enrolled patients had received prior HMA treatments. The planned primary analysis showed a 25% reduction in risk of death with venetoclax plus LDAC *vs* LDAC alone, although this was not statistically significant. Median OS was 7.2 *vs* 4.1 months, respectively. Unplanned analyses with an additional 6-months follow-up demonstrated median OS of 8.4 months for the venetoclax arm (HR, 0.70; 95% CI, 0.50–0.98; $P = 0.04$). CR/CRi rates were 48% and 13% for venetoclax plus LDAC and LDAC alone, respectively. Thus, venetoclax plus LDAC demonstrated clinically meaningful improvement in remission rate and OS *vs* LDAC alone, with a manageable safety profile [8]. Based on these confirmatory data, FDA granted full approval to these venetoclax combinations for treating newly diagnosed AML patients. Both trials established new standard of care for unfit newly diagnosed AML patients. Since VIALE-A trial excluded patients with previous exposure to azacitidine, and 20% patients enrolled on the VIALE-C trial had exposure to HMA, venetoclax plus LDAC might be a preferred consideration for patients who received HMAs in the past.

Table 1 Comparison of randomized prospective studies on venetoclax-based combinations in AML: AZA + venetoclax *vs* LDAC + venetoclax

Regimen	AZA + venetoclax	LDAC + venetoclax
Phase	III VIALE-A trial	III VIALE-C trial
Population	Age > 75 years or unfit for chemotherapy	
Control arm	AZA	LDAC
h/o HMA	No	Yes, allowed (20%)
Patient number	431 (286 in AZA + venetoclax)	211 (143 in LDAC + venetoclax)
Median age (range), years	76 (49–91)	76 (36–93)
30-day mortality, %	7%	13%
cCR (CR) rate, %	66.4% (36.7%)	48% (27%)
MRD negativity, %	N/A	6%
Time to CR (response)	1.3 months (0.6–9.9)	N/A most response at the end of cycle 2
Median DOR, months	17.5 (13.6 to NR)	NA
Median OS, months	14.7 (11.9–18.7)	8.4 (5.9–10.1)
Reference	[7]	[8]

Both trials also identified that patients with NPM1 and IDH1/2 mutations had high CR rates of 91%, and 71%, respectively with HMA + venetoclax [5] and high CR/CRi rates (89% and 72%), respectively, when treated with venetoclax + LDAC [6]. Patients with FLT3 mutations (Internal tandem duplication (ITD) and/or tyrosine kinase domain (TKD) also demonstrated high CR rate of 72% [5]. On the other hand, inhibitors to these mutations have been developed and will be discussed in the following sections. It would be continued debate on how to choose the first line treatment for AML with these mutations: hypomethylating agents with IDH1/2 inhibitors *vs* venetoclax-based combination; how to sequence the treatment options: venetoclax-based combinations first followed by IDH1/2 inhibitors at disease relapse/progression or the other way around; or use three drugs combination with HMA + venetoclax + IDH1/2 inhibitor to get deeper remission. Only randomized clinical trials could eventually answer these important clinical questions.

Venetoclax + intensive chemotherapy

Not surprisingly, venetoclax has been studied in combinations with intensive chemotherapy as well (summarized in Table 2). A retrospective report of 13 patients treated with FLAVIDA salvage therapy (fludarabine, cytarabine, and idarubicin in combination with venetoclax 100 mg daily for 7 days; dose reduced due to concurrent azole administration) compared to a control cohort received FLA-Ida (fludarabine, cytarabine, and idarubicin) reported a higher but not statistically significant CR/CRi rate of 69% compared to 47% in the control cohort [9]. A phase 1b/II trial of medically fit patients with R/R AML receiving FLAG-Ida induction and consolidation in combination with a 14 days course of venetoclax was conducted at MD Anderson. Early results were promising with CRc of 74% in all the patients and an impressive CRc of 91% in newly diagnosed (ND) patients. Consistent with known venetoclax resistance mechanisms, high levels of MCL-1 expression were found in patients who relapsed following FLAG-Ida + venetoclax [10]. The updated data of 62 patients (27 with ND AML and 35 with R/R AML) from the trial was recently presented. The ORR was 84%, with 89% of ND AML and 66% of R/R AML patients achieving a CRc. 83% of patients achieved minimal residual disease (MRD) negative (MRD-) status assessed by flow cytometry. After a median follow up of 11 months, median OS was not reached. The addition of venetoclax to FLAG-ida demonstrated robust efficacy with acceptable safety profile [11].

The CAVEAT study reported data on 51 newly diagnosed patients with AML, either de novo or secondary, who were treated in five venetoclax dose-escalation cohorts (50–600 mg; venetoclax was given over 14 days, day -6 to 7 with induction chemotherapy (cytarabine 100 mg/m^2 days 1–5 and idarubicin 12 mg/m^2 intravenously days 2–3)). The same venetoclax dose and schedule was given for four cycles of consolidation (cytarabine, days 1–2, and idarubicin, day 1), and as maintenance (up to seven 28-day cycles). The overall CR/CRi rate was 72%, but was 97% in the 28 patients with de novo AML and only 43% in secondary AML. [12]. In our center, we have used HiDAC + mitoxantrone + venetoclax for several heavily pretreated patients with R/R acute leukemia to control the disease prior to allogeneic stem cell transplantation (allo-SCT) (personal experience). This combination warrants further study in both newly diagnosed and R/R AML setting.

Table 2 Summary of venetoclax-based combinations in AML

Combination	Phase	Disease status	Patient number	CR/CRi rate, %	References
FLA-Ida	Retrospective	R/R AML	13	69%	[9]
FLAG-ida	Ib/II	ND AML R/R AML	27 35	89% in ND AML 66% in R/R AML	[10, 11]
CAVEAT (5 + 2)	Ib	ND AML	51	72% in all 97% in de novo AML 43% secondary AML	[12]
DEC10	II	ND AML R/R AML	70 55	86% in ND AML 42% in R/R AML	[13]
CLIA	II	ND AML	18	88%	[14]
CLAD/LDAC, alternating with AZA	II	ND AML	48	94%	[15]
CPX-351	II	R/R AML ND AML	17 1	37%	[16]
CPX-351 LIT	Ib	ND AML	44 planned	NA	[17]
GO	Ib	R/R AML	24 planned	NA	[18]

The results of ten-days of decitabine (DEC10) with venetoclax (DEC10-VEN) in AML and high-risk MDS were reported. DEC10-VEN is safe and highly effective in newly diagnosed AML and can serve as an effective bridge to SCT. Median OS in treatment naïve AML patients who subsequently underwent SCT was not reached (1 year OS of 100%). For previously treated AML patients, OS was 22.1 months [13]. In addition, propensity score matched analysis (PSMA) was employed to compare outcomes of 54 younger adult patients with R/R AML treated on the prospective phase 2 trial of 10-day decitabine and venetoclax (DEC10-VEN) with a historical cohort of patients treated with intensive chemotherapy. The analysis demonstrated that DEC10-VEN provided comparable response of CR/CRi, OS, and rate of patient to proceed SCT to non-venetoclax based intensive chemotherapy. Thus, DEC10-VEN represents an appropriate salvage therapy, and provides an appropriate backbone for adding novel therapies in R/R AML patients [19].

The addition of venetoclax to cladribine, idarubicin, and Ara C (CLIA) was safe and effective in ND patients with AML. The combination was not associated with early mortality or prolonged myelosuppression, but did result in high rates of durable MRD negative remissions (NCT02115295) [14]. Addition of venetoclax to a low-intensity backbone of cladribine + LDAC (CLAD/LDAC) alternating with HMA for older patients with newly diagnosed AML provided a CR/CRi rate of 94%; and among the subset of patients who had CR with complete count recovery, the MRD negative rate was 92%. The regimen was well tolerated, with 4-week mortality rates of 0%. With a median follow-up of more than 11 months, the median OS has not been reached (NR), with 12-month OS rates of 70% [15]. Full dose CPX-351 plus 7 days of VEN (300 mg on D2-8) was demonstrated to be tolerable with acceptable toxicities in patients with R/R AML with an ORR of 44%; and ORR was high at 60% in patient without prior VEN exposure, compared to just 17% among those who had prior VEN. 86% of responding patients proceeded to SCT. The median OS overall was 6.4 months; and the median OS was not reached among the responders [16].

Other ongoing trials include open-label, multicenter, 2-part, phase 1b study (NCT04038437) to determine the maximum tolerated dose and evaluate the safety, efficacy, and pharmacokinetics of CPX-351 lower-intensity therapy (LIT) plus venetoclax [17]. Another single arm, open-label, multi-center, dose-escalation phase Ib study is evaluating the combination of venetoclax and gemtuzumab ozogamicin in R/R CD33 + AML patients (NCT04070768) [18].

Venetoclax + experimental drugs or targeted inhibitors

Given the proven synergies of BCL-2 inhibition, multiple combinations with targeted agents, and venetoclax are under investigation. There are many ongoing combinations of therapies targeting BCL-2 and other pathways, including FLT3 inhibitors (gilteritinib) and IDH1 and 2 inhibitors (Ivosidenib and enasidenib) (will be discussed in the later sections), MCL-1 inhibitors (VU661013, A-1210477); MEK1/2 inhibitor (cobimetinib), and MDM2 inhibitor (idasanutlin) (reviewed in [20]), combination with TKI in Ph + acute leukemia [21] and other emerging pre-clinical combinations including small-molecule inhibitors of CDK9 (the orally active A-1592668 and the related analog A-1467729) leading to down-expression of MCL-1 [22]; the Exportin inhibitor, Selinexor, [23]; BET inhibitors, ABBV-075, [24]; SRC family kinases (SFK) and Bruton's tyrosine kinase (BTK) inhibitor, ArQule 531 (ARQ 531), [25]; and it is expecting much more novel combinations to come.

Resistance mechanisms

HMA + venetoclax or LDAC + venetoclax have clearly advanced the treatment of AML for older or unfit AML patients. Unfortunately, these regimens are unlikely to provide cure as most patients have relapsed at the median of 7 cycles of treatment. A retrospective study demonstrated that the outcome of 41 patients who failed to respond to HMA + venetoclax was very poor with the median OS of only 2.4 months despite salvage therapy [26]. To understand the resistance mechanisms, DiNardo CD et al. analyzed 81 patients receiving these venetoclax-based combinations to identify molecular correlates of durable remission, initial response followed by relapse (adaptive resistance), or refractory disease (primary resistance). Acquisition or enrichment of clones with activation of the signaling pathways such as FLT3 or RAS or bi-allelic mutations perturbing TP53 were most commonly identified among primary and adaptive resistance to venetoclax-based combinations. Single-cell studies identified heterogeneous and sometimes divergent interval changes in leukemic clones within a single cycle of therapy, highlighting the dynamic and rapid occurrence of therapeutic selection in AML. In functional studies, gain of FLT3-ITD mutation or loss of TP53 conferred cross-resistance to both venetoclax and cytotoxic-based therapies [27]. These data confirmed the previous findings that TP53 apoptotic network is the primary mediator of resistance to BCL-2 inhibition in AML cells [28]. Interestingly, recent study demonstrated that monocytic AML is intrinsically resistant to venetoclax + AZA due to loss of expression of the venetoclax target of BCL-2, but instead preferentially reliant on MCL-1 for the survival.

Thus, venetoclax + AZA treatment selects monocytic disease at disease relapse, which is derived from pre-existing monocytic subclones [29]. AML patients with monocytic disease or TP53 mutation might have high risk to be resistant to venetoclax-based combinations, and clinical trials targeting TP53 mutation or trials specifically targeting monocytic AML might be considered over venetoclax-based combinations.

Future clinical research will focus on deepening the responses provided by HMA + venetoclax with additional targeted agents, like ivosidenib in IDH1 mutated AML (to be discussed in next section), FLT3 inhibitors, and novel pathways inhibitors to eventually cure a greater fraction of newly diagnosed AML, and to explore new strategies to deal with relapses after venetoclax-based therapies.

IDH1/2 inhibitors

IDH1 and IDH2 are critical enzymes for the oxidative carboxylation of isocitrate. A mutation in one of these genes results in increased concentration of 2-hydroxyglutarate (2-HG). 2-HG causes DNA and histone hypermethylation, leading to blocked cellular differentiation and tumorigenesis. Mutations in IDH1 or IDH2 are present in 5% to 15% and 10% to 15% of patients with newly diagnosed AML, respectively [30]. Oral, small-molecule inhibitors have been developed for both mutant IDH1 (ivosidenib) and IDH2 (enasidenib). In R/R AML, ivosidenib and enasidenib as single agent produced promising responses for the corresponding mutations with ORR of 41.6% (CR: 21.6%) with median OS of 8.8 months [31] and ORR of 40.3% (CR 20.6%) with median OS of 9.3 months [32] respectively. FDA approved ivosidenib and enasidenib for patients with relapsed or refractory IDH1 and IDH2 mutated AML, respectively, in 2018. In the front line setting, both inhibitors have also demonstrated clinical effectiveness [33, 34], leading to FDA approval of ivosidenib for patients with newly diagnosed IDH1 mutated AML based on an ORR of 42% (CR: 30%) with median OS of 12.6 months in older patients not eligible for intensive therapy [34].

The Phase 3 IDHENTIFY study evaluating enasidenib plus best supportive care (BSC) versus conventional care regimens, which included BSC only, azacitidine plus BSC, low-dose cytarabine plus BSC, or intermediate-dose cytarabine plus BSC, did not meet the primary endpoint of OS in patients with R/R AML with an IDH2 mutation. The safety profile of enasidenib was consistent with previously reported findings. IDH inhibitors alone are unlikely to provide cure or durable remission for R/R AML, but they might provide excellent disease control with low toxicity and a bridge to allo-SCT.

IDH inhibitors work in part through induction of differentiation of malignant cells, leading to differentiation syndrome in 10% to 20% of patients. Clinical features are similar to those seen in patients with acute promyelocytic leukemia (APL) treated with ATRA-based regimens [35, 36]. Early studies established a firm association between IDH mutations and serum 2-HG concentration in AML, and confirmed that serum oncometabolite measurements provide useful diagnostic and prognostic information that can improve patient selection for IDH-targeted therapies [37]. However, 2-HG level reduction and clearance of IDH mutation by next generation sequencing (NGS) assay does not correlate with the clinical response. These inhibitors are unlikely to provide cure of the AML due to primary resistance from co-mutations in other pathways especially the NRAS/KRAS, and MAPK pathway effectors PTPN11, NF1, FLT3 and others [38] and secondary resistance from development of second-site IDH2 missense mutations or isoform switching [39, 40].

Since IDH1/2 mutations lead to DNA and histone hypermethylation, HMAs might have synergistic effects in combination of IDH inhibitors. Combination of HMAs with IDH inhibitors has been studied. The combination of ivosidenib and azacitidine was studied in 23 patients with IDH1 mutated AML as front line treatment. The ORR was 78% with CR/CRh rate of 70%, and median time to response of 1.8 months; median response duration was not yet reached. The ivosidenib and azacitidine combination was well tolerated with a safety profile consistent with ivosidenib or AZA monotherapy and with 17% incidence of IDH differentiation syndrome. Clearance of mutated IDH1 was seen in 63% patients with CR/CRh. CR and ORR rates exceeded those expected from AZA alone [41]; 83% CR/CRh patients achieved MRD negativity by flow cytometry [42]. AGILE, a global, double-blind, randomized, placebo-controlled, phase III trial for patients with previously untreated IDH1 mutated AML who are not candidates for intensive therapy (NCT03173248) is actively enrolling patients from 172 study centers across the world [43]. Patients are randomly assigned to AZA + ivosidenib or AZA + placebo.

As for the IDH2 inhibitor of enasidenib, the phase II portion of an open-label, randomized phase I/II study of enasidenib (E) + AZA ("E + A") *vs* AZA monotherapy ("A") in patients with mutated IDH2 (mIDH2) ND AML (NCT02677922) was recently reported [44]. 101 patients with intermediate- or poor-risk cytogenetics were randomized 2:1 to E + A or A in 28-day cycles. ORR (71% *vs* 42%) and CR (53% *vs* 12%) rates were significantly improved with E + A with greater clearance of mIDH2 allele frequency. Time to first response was about 2 months in each arm and the time to CR was 5.5 months

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